A GUIDE to
disease mechanisms
and drug
development

Self evaluation 2003 - 2008
Graduate School GUIDE

Graduate School GUIDE
(as of January 2009, part of the Graduate School of Medical Sciences – GUIDE-UMCG and the Groningen Graduate School of Science – GUIDE-GRIP)

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A GUIDE to disease mechanisms and drug development

Self evaluation 2003 - 2008 Graduate School GUIDE
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Cover illustration: GUIDE covers the entire spectrum of research from DNA to patients. Understanding the biological basis of diseases will lead to the development of novel therapeutic entities.

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# Table of contents

1 Preface

## Chapters

1 **Graduate School GUIDE**

2 Groningen Institute of Kidney diseases

3 Cardiovascular Centre

4 Groningen Research Institute for Asthma and COPD

5 Centre for Liver, Digestive and Metabolic Diseases

6 Transplantation, Immunology and Inflammation

7 Northern Netherlands Oncology Center

8 Biopharmaceuticals: Design, Discovery and Delivery

9 Synthesis & Analysis

### Sections

5 26 46 62 88 104 130 158 180 Objectives and research area

7 27 48 64 89 108 134 163 182 Composition of the research unit

9 30 50 67 91 110 137 165 186 Research environment and embedding

11 32 51 70 92 112 138 166 187 Quality and scientific relevance

12 36 54 74 94 118 145 170 188 Quantity of scientific output

13 37 55 75 95 119 146 171 189 Earning capacity

14 38 56 78 97 121 147 174 191 Academic reputation

15 39 57 79 98 123 149 175 192 Societal relevance

16 41 58 81 99 125 150 177 193 Next generation

22 42 59 82 100 126 152 178 194 Viability, SWOT and Future Strategy

## Addendum GRIP

221 List of Abbreviations

Appendices are provided as separate booklets

Appendix Chapter 2
Appendix Chapter 3
Appendix Chapter 4
Appendix Chapter 5
Appendix Chapter 6
Appendix Chapter 7
Appendix Chapter 8
Appendix Chapter 9
Preface

The present Self Evaluation report, “A GUIDE to disease mechanisms and drug development”, provides a full account of the research and PhD education at the Graduate School GUIDE\(^1\) during the period 2003-2008. This self evaluation report was prepared in compliance with the national Standard Evaluation Protocol 2009-2013 (SEP), published in May 2009 by the VSNU/KNAW/NWO\(^2\).

GUIDE is a Graduate School incorporating research groups from the University Medical Center Groningen (GUIDE-UMCG) and the Groningen Research Institute of Pharmacy (GRIP) of the Faculty of Mathematics and Natural Sciences (GUIDE-GRIP).

In the past, the section GUIDE-UMCG was named GUIDE-FMS. However, in January 2005, the Faculty of Medical Sciences (FMS) merged with the Academic Hospital Groningen (AZG) to form the University Medical Center Groningen (UMCG – for details, see relevant section). Therefore, the name GUIDE-FMS was changed to GUIDE-UMCG.

The previous assessment (conducted by the QANU\(^3\)) covered the period 1997-2002 and was described in the self-evaluation report “GUIDE-FMS – From the pathophysiology of chronic disease to innovative drug treatment”. The site visit by the Peer Review Committee (PRC) took place in March 2004. The QANU report “Medical Sciences RuG: GUIDE/FMS” was released in October 2004.

In the same period, GUIDE-GRIP research covering the period 1996-2001 was assessed. However, in the self-evaluation report “Pharmaceutical research at the University of Groningen: from target to tablet” (2003), both the scientific output and the most important changes of 2002 were included as well. The site visit by the Peer Review Committee took place in December 2003. The QANU report “Assessment of Research Quality - Pharmacy RUG: UCP” was released in October 2004.

Following the previous external research assessment, GUIDE-UMCG performed an internal research evaluation based on the Protocol Kwaliteitszorg Onderzoek RuG. In agreement with the Governing Board (CvB) of the University of Groningen (RuG), and in accordance with the recommendation of the previous PRC, the present external evaluation covers GUIDE as a single entity (i.e. including both GUIDE-UMCG and GUIDE-GRIP).

In closing, I am very grateful to everyone who contributed to this report.

Han Moshage

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\(^1\) The Graduate School GUIDE encompasses the research programmes of the research institute GUIDE supplemented with the educational programmes (research Masters and PhD education). As of January 2008, the Board of the University established Graduate Schools per faculty. As a consequence, PhD students from GUIDE-GRIP belong to the Graduate School of Sciences whereas PhD students of GUIDE-UMCG belong to the Graduate School GUIDE. As of January 2009, the Graduate School GUIDE merged with the other 3 graduate school/research institutes of the UMCG into the Graduate School of Medical Sciences. Most importantly, the facilities and services provided to these PhD students by GUIDE remained unchanged. For the sake of simplicity, throughout this document, the term GUIDE is used both for the educational programmes as well as the research programmes.

\(^2\) VSNU: Association of Universities in the Netherlands; KNAW: Royal Netherlands Academy of Arts and Sciences; NWO: Netherlands Organisation for Scientific Research

\(^3\) QANU: Quality Assurance Netherlands Universities
CHAPTER 1

Documentation regarding the Graduate School GUIDE
Section 1.0: Organisation of research and research institutes

The Dean of the University Medical Center (who is also a member of the Board of the UMCG) is responsible for research and education within the UMCG. The Dean has delegated the research portfolio to the Dean of Research. The Dean of Research is responsible for the four research institutes within the UMCG (GUIDE, BCN, SHARE, and the W.J. Kolff Institute). The Groningen Research Institute of Pharmacy (GRIP) is one of the research institutes of the faculty of Mathematics and Natural Sciences (FMNS) at the University of Groningen. Research in GUIDE is clustered in eight programme-oriented research institutes with the participation of many departments from both GRIP and the UMCG (Fig. 1).

The research institute GUIDE is headed by the director (Prof. A.J. Moshage) and the deputy director from GRIP (Prof. B.H.C. Westerink). The director and deputy director are supported by a support staff consisting of two research coordinators (Dr P.G. Braun from GUIDE-UMCG and Dr H.J. Woerdenbag from GUIDE-GRIP), a PhD student coordinator who is also responsible for financial management (Ms H.M.M. Banus), a coordinator for the research Masters (Dr D.F. Jansen), a part-time management assistant (Ms. M.H. Bansema) and secretarial support (Ms M.T.L. Pekelaer GUIDE-UMCG and Ms H.A. Katerborg; GUIDE-GRIP).

Programme Leaders

Director: Prof. A.J. Moshage (since June 2005)
Deputy Director: Prof. Dr. B.H.C. Westerink (since September 2004)

Director: Prof. L. F.M.H. de Leij (until June 2005)
Deputy Director: Prof. J.H. Teuben (until September 2004)

Prof. A.J. Moshage is professor of Experimental Hepatology and Gastroenterology. He served as secretary for the Dutch Society of Hepatology and was a member of the scientific advisory council of the Dutch Digestive Diseases Foundation. He is a board member of FIGON (Federation of Innovative Drug Research Netherlands) and director of the Topmaster programme Medical and Pharmaceutical Drug Innovation. Since June 2005, he has been the director of the research institute GUIDE, and since January 2009 the director of the Groningen Graduate School of Medical Sciences.

Prof. B.H.C. Westerink is head of the department Biomonitoring and Sensoring. His area of research is in vivo monitoring of endogenous compounds (neurotransmitters, metabolites, modulators) in experimental animals and humans. He has published approximately 200 papers in peer-reviewed journals and is one of the founders of the microdialysis technique. His special interest is the mechanism of action of centrally acting drugs. Since 2004, he has been the director of the Groningen Research Institute of Pharmacy (GRIP). Prof Westerink is the scientific director of the university spin-off company Brains-on-line.

The research at GUIDE is clustered in eight programme-oriented research institutes, composed of research staff from either the disciplinary departments of GRIP (“basis-eenheden”) and/or the departments of UMCG (“discipline groepen”).

Researchers at GUIDE focus mainly on:
1. Lead discovery, development of new drugs, drug delivery and advanced formulation technology.
2. Translational research on the molecular and cellular mechanisms underlying disease (aetiology and pathological physiology) and on research related to treatment of disease, e.g. in the context of clinical trials and by using relevant animal models.

The research programmes of GUIDE are:
1. GIKD Groningen Institute of Kidney diseases – Coordinators: Prof. P.E. de Jong and Prof. D. de Zeeuw
2. CVC Cardiovascular Centre – Coordinators: Prof. W.H. van Gilst and Prof. D.J. van Veldhuisen
3. GRIAC Groningen Research Institute for Asthma and COPD – Coordinators: Prof. W. Timens and Prof. H.M. Boezen
4. CLDS Centre for Liver, Digestive and Metabolic Diseases – Coordinators: Prof. H.J. Verkade and Dr S.C.D van IJzendoorn
5. TRIO Institute on Transplantation, Immunology and Inflammation – Coordinators: Prof. C.G.M. Kallenberg and Prof. J.M. van Dijl
6. NNOC Northern Netherlands Oncology Centre - Coordinators: Prof. E.G.E. de Vries and Prof. H.J. Hoekstra
7. BDDD Biopharmaceuticals: Design, Discovery and Delivery - Coordinators: Prof. W.J. Quax and Prof. H.J. Haisma
8. S&A Synthesis and Analysis – Coordinator: Prof. R. P.H. Bischoff
Figure 1: Research Organisation of GUIDE - The Dean of the University Medical Center (who is also a member of the Board of the UMCG) is responsible for research and education within the UMCG. The Dean has delegated the research portfolio to the Dean of Research. The Dean of Research is responsible for the four research institutes within the UMCG (GUIDE, BCN, SHARE, and the Kolff Institute). The Groningen Research Institute of Pharmacy (GRIP) is one of the research institutes of the faculty of Mathematics and Natural Sciences (FMNS) at the University of Groningen.

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Researchers at GUIDE focus mainly on

IX. lead discovery, development of new drugs, drug delivery and advanced formulation technology.

X. Translational research on the molecular and cellular mechanisms underlying disease (aetiology and pathophysiology) and on research related to treatment of disease, e.g. in the context of clinical trials and by using relevant animal models.

The research institutes of GUIDE are

I. GIKD  Groningen Institute of Kidney diseases – Coordinators: Prof. P.E. de Jong and Prof. D. de Zeeuw

II. CVC  Cardiovascular Centre – Coordinators: Prof. W.H. van Gilst and Prof. D.J. van Veldhuisen

III. GRIAC  Groningen Research Institute for Asthma and COPD – Coordinators: Prof. W. Timens and Prof. H.M. Boezen

IV. CLDS  Centre for Liver, Digestive and Metabolic Diseases – Coordinators: Prof. W. Timens and Dr. S.C.D. van IJzendoorn

V. TRIO  Institute on Transplantation, Immunology and Inflammation – Coordinators: Prof. C.G.M. Kallenberg and Prof. J.M. van Dijl

VI. NNOC  Northern Netherlands Oncology Centre - Coordinators: Prof. E.G.E. de Vries and Prof. H.J. Hoekstra

VII. S&A  Synthesis and Analysis – Coordinator: Prof. R.P.H. Bischoff

VIII. BDDD  Biopharmaceuticals: Design, Discovery and Delivery - Coordinators: Prof. W.J. Quax and Prof. H.J. Haisma
Section 1.1: Objectives and Research Area

Research area
The most important event over the past decade has been the establishment of the University Medical Center Groningen (UMCG), which was formed in January 2005 by the merger of the Academic Hospital Groningen and the Faculty of Medical Sciences of the University of Groningen. This new organisation combines the best of both worlds, allowing the development of integral policy measures covering care, research, education and training. This is reflected by the mission of the UMCG: Building the Future of Health. Researchers within GUIDE have a strong clinical position: via the UMCG they have access to a catchment area of 3 million people. Together with the stability of the population in the northern part of the Netherlands (founder population) this will facilitate large-scale longitudinal studies (e.g. LifeLines) and the study of complex, multifactorial diseases.

All the excellent research performed at the UMCG is organised within the Graduate Schools. These Graduate Schools cover Chronic Diseases and Drug Exploration (GUIDE), Biomaterials (Kolff Institute), Neurosciences (BCN-BRAIN) and Health Research (SHARE). For the future, the UMCG has selected Healthy Ageing as its main theme within the framework of its mission. This covers healthcare, research, education and training.

Mission and objectives
The mission of GUIDE is to facilitate and strengthen excellent research and to train and educate the excellent researchers of the future. The ultimate goal is to rank among the top 50 large research universities in the world (according to leading international rankings). To achieve these goals, GUIDE performs and stimulates translational, innovative drug-oriented research on a selected number of diseases and chronic diseases in an inter-disciplinary setting. In addition, it educates and trains the excellent researchers of the future by means of a selective international research Masters programme and PhD education and training programme.

Strategy and Policy
The strategy for achieving this mission and these objectives is to perform research and educate researchers in an inter-disciplinary setting and to employ a quality-driven policy of ‘Focus and Mass’ (Quality and Quantity). This strategy has been formulated in cooperation with the Board of the UMCG and the other Graduate Schools linked to the UMCG.

Broader Perspective
To enhance the optimal positioning and performance of the research groups within the research institutes, two important changes were made:

- Because the research programme Pharmacoepidemiology and Drug Policy (PEDP) was no longer appropriate within the research scope of GUIDE in view of scientific content and methodology, in line with the recommendations of the previous PRC, the PEDP programme (both PEDP-GRIP and PEDP-UMCG) was transferred to the research institute SHARE. The prominent participation of the Dept. of Clinical Epidemiology within SHARE will allow for a substantial strengthening of the research programme PEDP.
- Because the Dept. of Molecular Pharmacology (GRIP) is best situated within the research programme on Asthma and Chronic Obstructive Pulmonary Diseases (GRIAC) it will therefore be evaluated within the research institute GRIAC.

Synergy between GUIDE-UMCG and GUIDE-GRIP
The ultimate goal of the synergy between GUIDE-UMCG and GUIDE-GRIP is to promote the interdisciplinarity of both research and education. An active policy to promote this synergy is being implemented. This policy includes:

- Researchers and PhD students from both entities having equal facilities and support within GUIDE. This 2003-2008 evaluation is the first combined and synchronised evaluation of GUIDE-GRIP and GUIDE-UMCG.
- A joint research Masters programme (Topmaster Medical and Pharmaceutical Drug Innovation), in which pharmacy and medicine staff members participate and in which selected Masters students are trained to perform research at the interface of medicine, pharmacy and biomedical sciences.
- Collaboration in the joint applications for large-scale initiatives (e.g. Top Institute Pharma (TI Pharma), Top Institute Food & Nutrition (TIFN), SmartMix, Parel snoer and the Centre for Translational and Molecular Medicine (CTMM)). For TI Pharma and TIFN in particular, a number of collaborative proposals were approved and funded, resulting in several shared PhD students and postdocs.
- A seminar series has been initiated to identify potential areas of mutual interest between Medicine, Pharmacy and Material Sciences (‘Crossing Borders’ seminars).
- Within the framework of the internationalisation programme of the RUG, a collaborative programme with the University of Uppsala (Sweden) has been initiated, involving groups of both GUIDE-UMCG and GUIDE-GRIP. This is a coherent programme on the theme ‘Mechanisms of Chronic Diseases’. Furthermore, staff members of GUIDE-GRIP have recently started to participate in the Graduierten Kolleg GRK880 Vascular Medicine programme with Mannheim/Heidelberg.
Instruments to stimulate excellence of the research

- GUIDE resources will only be invested in principal investigators (PI) who fulfil minimal (UMCG-broad) quality criteria. A definition of a principal investigator (PI) has been established employing several criteria, e.g. an average of 6 publications over a period of 3 years and ranking in the top 30% of a relevant ISI subject area.
- An active policy for retaining talented researchers within the Graduate School (Tenure Track programme, Rosalind Franklin programme, Pre-tenure Track programme, Topmaster programme, MD-PhD programme). These talented researchers are also eligible for the specific support programmes of the UMCG/RUG in order to acquire career development grants like VENI, VIDI, VICI, ERC, Clinical fellow and AGIKO (Ruggesteun programme).
- Scouting promising PhD students. These PhD students will be encouraged and supported to spend a period abroad and to apply for a postdoc/VENI grant. The agreement with the University of Pennsylvania for ‘preferred positioning’ of postdocs from the UMCG will facilitate this process. To initiate international contacts, GUIDE actively supports PhD students to spend some time abroad during their PhD period. This process takes place within the Project Management Course of the GUIDE education programme.
- Top researchers outside the UMCG have been successfully recruited to strategic positions in key areas of expertise (see section 1.2 for details).

Internationalisation policy

The aim of the internationalisation policy is twofold: i) to form strategic alliances with selected institutes/countries to recruit talented Masters and PhD students and ii) to form strategic alliances with selected institutes based on common research interests in order to improve the international network and status of the partners involved. Some of these strategic alliances include:

- A collaborative programme with the Medical Faculty at Mannheim of the Karl-Ruprecht University at Heidelberg has been operative since 2003 within the framework of GRK880 on the common theme ‘Vascular Medicine’. This collaborative programme has been funded in three successive rounds by the NWO and the DFG and will last in total for nine years (20 shared projects, 5 PhD thesis defences in Groningen to date).
- Collaboration with the University of Uppsala (Sweden; 2 shared projects to date) has been initiated on the joint theme ‘Mechanisms of Chronic Diseases’ and will be extended to include the Universities of Ghent (Belgium) and Göttingen (Germany).
- Collaboration exists with the Mario Negri Institute in Bergamo (Italy) on the common theme ‘Chronic Kidney Diseases’.
- Agreements have been reached between the UMCG and universities in Beijing and Shanghai (Fudan) to initiate customised programmes (Bernoulli bursaries; 29 PhD positions to date).
- A PhD bursary programme based on mutual research interests is being initiated with several Latin American universities (Mexico, Brazil, Chile). An active internationalisation policy also serves to recruit talented Masters and PhD students. Focus areas for these initiatives include Latin America, Eastern Europe and several Asian countries. These alliances also serve to attract more Masters and PhD students funded by local programmes in collaboration with NUFFIC.

Instruments for performing and stimulating translational, innovative drug-oriented research

- Fostering public-private consortia such as TI Pharma. This includes ad hoc support for patent filing.
- Stimulation of the establishment of start-up companies and biotechnology start-up companies, e.g. by the establishment of the Incubator Facility.
- GUIDE provides the PhD course ‘Science to the Market’, which was developed in house to provide selected PhD students with entrepreneurial skills (e.g. development of a business plan and knowledge about intellectual property rights).
- Other initiatives for promoting public-private activities that are driven by research findings within GUIDE include the KOPII programme and the Casimir programme. These programmes are initiated and supported by the GUIDE management.
Section 1.2: Composition of the Research Unit

Description of the research unit
The research input of staff (in FTE or ‘full time equivalent’) is defined as the actually realised research input. The research input is calculated in proportion to the size of the appointment (as expressed in % of FTE) of the researcher involved.

Tables 1.1 and 1.2 show that a steady increase in research staff has occurred over the last six years. This is true for both tenured staff, non-tenured staff (PhD students and postdoctoral fellows) and their funding. The increase in tenured staff is best explained by the inclusion of tenured staff members who qualify as principal investigators. Some of these new PIs acquired grants and corresponding PhD students, raising the number of PhD students (c.f. Table 1.1 and Section 5). The ratio of PhD students to tenured staff members has remained stable (see Section 6), which indicates a constant fund-raising capacity per tenured staff member.

The increase in the total amount of research FTE lags behind the observed increase in staff members. This is due to the introduction of non-employed PhD students who have a student status and therefore do not represent research FTE.

Strategy and policy
The strategy and policy instruments outlined in section 1.1 have contributed to the trends observed in Tables 1.1 and 1.2. In short, the introduction of principal investigators and the tenure track system has led to an increase in the number of tenured staff members. Furthermore, the synergy between GUIDE-GRIP and GUIDE-UMCG has led to a very good participation in large public-private consortia (e.g. TI Pharma and CTMM). As a result, the number of PhD students and acquired funds have both increased.

Overview of Research Staff

Table 1.1  Overview of research staff at the level of GUIDE

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
</tr>
<tr>
<td></td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>Tenured staff</td>
<td>46.44</td>
<td>48.34</td>
<td>50.85</td>
<td>53.57</td>
<td>57.72</td>
<td>60.95</td>
</tr>
<tr>
<td>(141)</td>
<td>(147)</td>
<td>(153)</td>
<td>(163)</td>
<td>(177)</td>
<td>(185)</td>
<td></td>
</tr>
<tr>
<td>Full professors</td>
<td>17.19</td>
<td>18.74</td>
<td>21.65</td>
<td>23.67</td>
<td>26.17</td>
<td>28.80</td>
</tr>
<tr>
<td>(54)</td>
<td>(58)</td>
<td>(68)</td>
<td>(74)</td>
<td>(81)</td>
<td>(89)</td>
<td></td>
</tr>
<tr>
<td>Associate professors</td>
<td>14.37</td>
<td>14.50</td>
<td>13.40</td>
<td>13.50</td>
<td>15.30</td>
<td>13.95</td>
</tr>
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<td>(43)</td>
<td>(42)</td>
<td>(38)</td>
<td>(39)</td>
<td>(45)</td>
<td>(42)</td>
<td></td>
</tr>
<tr>
<td>Assistant professors</td>
<td>7.80</td>
<td>8.00</td>
<td>8.00</td>
<td>8.10</td>
<td>8.30</td>
<td>8.20</td>
</tr>
<tr>
<td>(23)</td>
<td>(23)</td>
<td>(22)</td>
<td>(24)</td>
<td>(25)</td>
<td>(23)</td>
<td></td>
</tr>
<tr>
<td>Other senior staff</td>
<td>6.73</td>
<td>7.10</td>
<td>7.80</td>
<td>8.30</td>
<td>7.95</td>
<td>10.00</td>
</tr>
<tr>
<td>(21)</td>
<td>(24)</td>
<td>(25)</td>
<td>(26)</td>
<td>(26)</td>
<td>(31)</td>
<td></td>
</tr>
<tr>
<td>Non-tenured staff</td>
<td>36.99</td>
<td>34.32</td>
<td>28.35</td>
<td>28.72</td>
<td>29.93</td>
<td>37.91</td>
</tr>
<tr>
<td>(50)</td>
<td>(49)</td>
<td>(39)</td>
<td>(39)</td>
<td>(42)</td>
<td>(49)</td>
<td></td>
</tr>
<tr>
<td>PhD students</td>
<td>155.60</td>
<td>177.13</td>
<td>168.54</td>
<td>168.44</td>
<td>157.15</td>
<td>158.20</td>
</tr>
<tr>
<td>(279)</td>
<td>(313)</td>
<td>(342)</td>
<td>(355)</td>
<td>(369)</td>
<td>(400)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>155.60</td>
<td>177.13</td>
<td>168.54</td>
<td>168.44</td>
<td>157.15</td>
<td>158.20</td>
</tr>
<tr>
<td>(250)</td>
<td>(281)</td>
<td>(285)</td>
<td>(274)</td>
<td>(268)</td>
<td>(272)</td>
<td></td>
</tr>
<tr>
<td>Non employed</td>
<td>.....</td>
<td>.....</td>
<td>.....</td>
<td>.....</td>
<td>.....</td>
<td>.....</td>
</tr>
<tr>
<td>(29/10.39%)</td>
<td>(32/10.22%)</td>
<td>(57/16.67%)</td>
<td>(81/22.82%)</td>
<td>(101/27.37%)</td>
<td>(128/32.00%)</td>
<td></td>
</tr>
<tr>
<td>Total research staff</td>
<td>239.03</td>
<td>259.79</td>
<td>247.74</td>
<td>250.73</td>
<td>244.80</td>
<td>257.05</td>
</tr>
<tr>
<td>(470)</td>
<td>(509)</td>
<td>(534)</td>
<td>(557)</td>
<td>(588)</td>
<td>(634)</td>
<td></td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers also have obligations for patient care. For the sake of simplicity a normative approach has been taken to establish input figures. Accordingly, the research input of tenured researchers at GUIDE is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD students with an employment contract. For non-employed PhD students (student status), expression as FTE is not appropriate.
## Research Funding

### Table 1.2 Overview of the research funding at the level of GUIDE

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE (FTE)</td>
<td>114.00</td>
<td>130.29</td>
<td>123.19</td>
<td>125.78</td>
<td>123.99</td>
<td>120.75</td>
</tr>
<tr>
<td>Direct funding (1)</td>
<td>(47.69%)</td>
<td>(50.15%)</td>
<td>(49.73%)</td>
<td>(50.17%)</td>
<td>(50.65%)</td>
<td>(46.97%)</td>
</tr>
<tr>
<td>Research grants (2)</td>
<td>32.75</td>
<td>30.98</td>
<td>27.20</td>
<td>25.68</td>
<td>26.94</td>
<td>33.06</td>
</tr>
<tr>
<td>Contract research (3)</td>
<td>92.29</td>
<td>98.52</td>
<td>97.35</td>
<td>99.27</td>
<td>93.87</td>
<td>103.25</td>
</tr>
<tr>
<td>(13.70%)</td>
<td>(38.61%)</td>
<td>(37.92%)</td>
<td>(39.30%)</td>
<td>(39.59%)</td>
<td>(38.35%)</td>
<td>(40.17%)</td>
</tr>
<tr>
<td><strong>Total funding</strong></td>
<td>239.04</td>
<td>259.79</td>
<td>247.74</td>
<td>250.72</td>
<td>244.80</td>
<td>257.05</td>
</tr>
<tr>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
</tr>
</tbody>
</table>

### Expenditure (k€)

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel costs (k€)</td>
<td>11,120.1</td>
<td>12,602.3</td>
<td>13,108.0</td>
<td>13,356.3</td>
<td>13,959.6</td>
<td>15,360.8</td>
</tr>
<tr>
<td>Other costs personnel (k€)</td>
<td>4,281.7</td>
<td>4,852.4</td>
<td>5,047.1</td>
<td>5,142.8</td>
<td>5,375.1</td>
<td>5,914.5</td>
</tr>
<tr>
<td>Costs non-employed PhD students (k€)</td>
<td>454.4</td>
<td>506.9</td>
<td>738.1</td>
<td>1,074.4</td>
<td>1,271.3</td>
<td>2,046.8</td>
</tr>
<tr>
<td>Other costs non-employed PhD students (k€)</td>
<td>242.3</td>
<td>263.5</td>
<td>376.1</td>
<td>544.0</td>
<td>633.3</td>
<td>915.9</td>
</tr>
<tr>
<td><strong>Total expenditure</strong></td>
<td>k€ 16,098.5</td>
<td>k€ 18,225.1</td>
<td>k€ 19,289.3</td>
<td>k€ 20,117.5</td>
<td>k€ 21,39.2</td>
<td>k€ 24,238.0</td>
</tr>
</tbody>
</table>

Explanation: The expenses for research include both personnel and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security premiums, the transfer to the provision for ‘wachtgelden’ (i.e. the obligation to provide personnel with reduced pay in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff and other costs such as allowances for child care, and commuter traffic. Although non-employed PhD students do not represent research FTE, the costs of these PhD students have been included. Other costs include operating costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

1. Direct funding by the university;
2. Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programmes ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3. Funding for specific research projects obtained from external organisations, such as industry, governmental ministries, European Commission (Framework programmes) and charity organizations.
Section 1.3: Research Environment and Embedding

Position, reputation, strategy and policy

Inter-disciplinarity
Research in the Netherlands is largely organised into research schools and/or institutes. Most of these research schools and/or institutes deal with only one type of disease, organ or biomedical concept. The research institute GUIDE distinguishes itself from other institutes/schools by organising its research into inter-disciplinary programmes, focusing on a selection of chronic diseases and expertises (pharmaceutical and otherwise). The GUIDE staff is almost equally divided between clinical, biomedical and pharmaceutical researchers, all sharing a common research mission. In this respect GUIDE can be considered to be an example of a successful interdisciplinary integration of fields of research that were formerly largely separated. Furthermore, the presence of patient care, clinical research, pre-clinical research and pharmaceutical research in a single complex is unique in the Netherlands. The organisation of the research institute GUIDE benefits optimally from this unique setting.

Embedding

Staff members of GUIDE are often members of committees or boards of policy-making organisations and scientific associations. In addition, they participate in collaborative scientific networks and have relations with companies and non-profit organisations (charity foundations), both at the national and international levels. This is best described in the various chapters of the research institutes. A selective summary is presented below.

The research projects funded through the NWO and STW are collectively called ‘Direct government funding/Research grants’ (see Table 1.2), and are obtained in a national competition following peer review. The career development programme Vernieuwingimpuls (VENI, VIDI, VICI) is also implemented by the NWO (VENI for young researchers, VIDI for more experienced researchers and VICI for senior researchers). Staff members of GUIDE are often members of committees or boards that are involved in the policy-making process or participate in the peer review committees of these programmes.

Staff members of GUIDE are well represented in the governing boards and/or scientific advisory councils of charity foundations. The charity foundations that are most important for GUIDE are: the Dutch Kidney Foundation (Nierstichting Nederland), the Netherlands Heart Foundation (Nederlandse Hartstichting), the Dutch Asthma Foundation (Nederlands Astmafonds), the Netherlands Diabetes Foundation (Diabetes Fonds), the Netherlands Digestive Diseases Foundation (Maag Lever, Darmstichting), the Dutch Cancer Society (Kankerbestrijding) and the Dutch Rheumatism Association (Nationaal Reumafonds).

Internationalisation

Funding from European Community framework programmes is becoming increasingly important. This type of funding is largely concentrated in the Framework Programmes (FPs). An active policy is being pursued to increase participation in these programmes. This policy includes:

- preparation of research proposals in close collaboration with establishing contacts with national agencies such as Senter or local, RUG-affiliated agencies such as the Transfer and Liaison Group (TLG);
- informing staff members of GUIDE about relevant work programme topics;
- establishing and strengthening strategic collaborations;
- supporting European grant applications.

During the 6th Framework Programme, GUIDE researchers, and in particularly GUIDE-GRIP investigators, were successful in acquiring research grants. The 7th Framework Programme started in 2007, and GUIDE researchers have acquired substantial funding. Currently (October 2009), 23 projects have been funded. GUIDE researchers participate in 21 GUIDE-UMCG projects and 2 GUIDE-GRIP projects.

GUIDE staff members are actively involved in the peer-review panels of the FPs. In addition, the UMCG has a liaison officer located in Brussels (NethER: Netherlands House of Education and Research) who monitors and communicates developments concerning the European science policy to GUIDE. At the same time, this liaison officer can communicate specific UMCG/GUIDE research interests to the relevant policy makers in Brussels.

A number of other programmes promote cooperation between countries, such as the funding of European Graduate Colleges by the NWO and the DFG (GRK880 Vascular Medicine) and the Erasmus Mundus Mobility programmes.

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5 Senter is an agency of the Ministry of Economic Affairs which implements government policy in the fields of technology, energy, environment, exports and international cooperation. Its objective is to make an enduring contribution to the position of the business sector and knowledge institutions in the Netherlands. It also assists with establishing EU contracts. URL: [http://www.senter.nl/](http://www.senter.nl/)

6 The Transfer and Liaison Group (TLG) is part of the university bureau and aims at supporting the acquiring of contract research within the RUG. It is also involved in establishing EU contracts. URL: [http://www.rug.nl/bureau/expertisecentra/tlg/](http://www.rug.nl/bureau/expertisecentra/tlg/)
The University of Groningen and the University Medical Centre Groningen have several formal agreements for collaboration with high-ranking international universities (e.g. UNAM in Mexico, USP and UNIFESP in Brazil, University of Osaka in Japan, University of Pennsylvania in the USA, University of Uppsala in Sweden, etc.). Through these formal agreements, GUIDE is well positioned to start research collaborations with these institutions.

Recently, the University of Groningen was given a top ranking in several prestigious international ranking systems (THES – position 138 in 2009, and ARWU (Shanghai Jiao Tong ranking) – position 101 in 2008). These rankings increase the visibility and attractiveness of the University of Groningen, and consequently make GUIDE an attractive partner for collaboration and an attractive host institute for Masters or PhD education.

A detailed description of our internationalisation policy is given in Section 1.1.

**Guest lecturers**

GUIDE has both an active policy and the financial means to invite distinguished guest scientists to come and lecture about their research, enter into scientific discourse with colleagues, build up national and international networks, participate in Masters classes and participate in thesis defences. An numerical overview is given in the table below (number of guest lectures per year per programme). In addition, during the annual GUIDE scientific meeting, guest scientists lecture for the GUIDE community (PhD students and staff members). Guest speakers at these meetings include several Nobel Prize Laureates (e.g. Prof. Gunther Blobel, Prof. Robin Warren).

<table>
<thead>
<tr>
<th>Programme</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIKD</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>3</td>
<td>11</td>
<td></td>
<td>35</td>
</tr>
<tr>
<td>CVC</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>GRIAC</td>
<td>5</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>4</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td>CLDS</td>
<td>7</td>
<td>12*</td>
<td>7</td>
<td>4</td>
<td>8</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>TRIO</td>
<td>2</td>
<td>14*</td>
<td>9</td>
<td>15</td>
<td>13</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>NNOC</td>
<td>12</td>
<td>8</td>
<td>28</td>
<td>22</td>
<td>21</td>
<td>21</td>
<td>112</td>
</tr>
<tr>
<td>BDDD</td>
<td>1</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>1</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>S&amp;A</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>2</td>
<td>5</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>GUIDE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>35</strong></td>
<td><strong>30</strong></td>
<td><strong>73</strong></td>
<td><strong>58</strong></td>
<td><strong>57</strong></td>
<td><strong>75</strong></td>
<td><strong>328</strong></td>
</tr>
</tbody>
</table>

* 18 combined lectures; noted 9 lectures each.
Section 1.4: Quality and Scientific Relevance

Strategy and policy
Our objective is to be ranked among the top 50 large research universities in the world. To achieve this goal, a policy has been implemented for promoting publication in leading scientific journals. This policy is expected to yield more citations per paper (CPP/FCSm). Therefore, in 2007, the status of principal investigator (PI) was introduced. Only PIs benefit from the resources and support of the research institute/UMCG. At least six publications over a period of three years, ranking in the top 30% of the relevant ISI subject area, are required to qualify as a PI.

Outcome
This policy has led to an increased awareness of the importance of publishing in high-ranking journals. This is best illustrated by the increased number of current UMCG researchers who have qualified for PI status in the research institute GUIDE. This policy served as a wake-up call for those staff members who did not qualify for PI status, making them aware that they should improve their publication standard.

Number of high quality publications
Table 1.3 demonstrates that the publication standard of GUIDE researchers is high. Approximately, 71% of the publications were published in the top 30% of journals and approx. 34% of the publications were in the top 10% of journals.

Table 1.3 Number of articles in the top 10% and 30% of relevant disciplines

<table>
<thead>
<tr>
<th>GUIDE</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td></td>
</tr>
<tr>
<td>Belongs to the best 10%</td>
<td>36%</td>
<td>36%</td>
<td>34%</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>of a relevant subject area</td>
<td>(208)</td>
<td>(244)</td>
<td>(256)</td>
<td>(250)</td>
<td>(254)</td>
</tr>
<tr>
<td>Belongs to the best 30%</td>
<td>71%</td>
<td>71%</td>
<td>71%</td>
<td>70%</td>
<td>70%</td>
</tr>
<tr>
<td>of a relevant subject area</td>
<td>(409)</td>
<td>(477)</td>
<td>(539)</td>
<td>(558)</td>
<td>(549)</td>
</tr>
</tbody>
</table>

Explanation: A ranking for publications present in the on-line database ‘ISI Web of Knowledge’, sub-database ‘Web of Science’ can be calculated and is presented here. Papers are categorised based on the journal in which they appear. Approximately 175 subject areas have been designated (ISI-fields). The percentages are calculated based on the number of journal titles in the subject area. Papers published in subject areas relevant to the research programme are included in this analysis. According to the methodology of bibliometric analysis, only papers of the reference types ‘Article’, ‘Note’, ‘Letter’, ‘Review’; and ‘Proceedings paper’ are considered. This implies that references of the type ‘Editorial material’, ‘Book (review)’, ‘Correction’, ‘Meeting abstract’, ‘Conference proceeding’, ‘In memoriam’, ‘News item’, ‘Biographical item’, etc., are not included.

Appreciation of Scientific Publications
Scientific quality is assessed by bibliometric analysis. Analyses have been carried out annually as part of a national initiative of the Netherlands Federation of University Medical Centres (NFU), which includes all eight of the Dutch University Medical Centres. These analyses were carried out by the Centre for Science and Technology Studies (CWTS). The most striking feature of these analyses is the substantial rise in scientific output of the UMCG and GUIDE, with a near doubling over the past decade, and a steady rise in scientific quality to significantly above the world average (CPP/FCSm = 1.26 for the period 1997-2008). The concurrent increases in research funding and competitive research funding imply that these trends will continue for at least the next five years. Analyses by subject area show that GUIDE publishes most of its research in the areas of Oncology, and Cardiology and Cardiovascular Systems, together comprising roughly 13% of the total output of the UMCG. The area of General Medicine shows the highest contribution to quality (CPP/FCSm = 3.39).

7 Disclaimer: covers ISI subject areas down to 1% of the total UMCG output; data for subject areas in which less is published, e.g. high quality niche areas, were not made available by CWTS.
Section 1.5: Quantity of Scientific Output

Publication strategy
The publication strategy has been outlined in Section 4.

Overview of the results
Table 1.4 clearly shows an increase in the number of publications during the review period. Between 2003 and 2008, the gross increase was approximately 40%. This increase was paralleled by a similar increase in the number of PhD theses. The number of joint publications (i.e. publications with authors from at least 2 research programmes) was stable over time (approximately 10%), demonstrating the synergy between the GUIDE research institutes. In addition, the number of joint publications between the programmes of GUIDE-GRIP and those of the GUIDE-UMCG was stable (approximately 30%).

Table 1.5 shows that there was a steady increase in the number of PhD students, in particular non-employed PhD students. The ratio of PhD students to tenured staff members remained stable (c.f. Section 6), implying a constant fund-raising capacity per tenured staff member.

Number of publications

Table 1.4a  GUIDE – sum of all programmes
Main categories of research output

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refereed articles</td>
<td>644</td>
<td>697</td>
<td>774</td>
<td>882</td>
<td>924</td>
<td>954</td>
</tr>
<tr>
<td>PhD theses</td>
<td>49</td>
<td>59</td>
<td>62</td>
<td>99</td>
<td>101</td>
<td>86</td>
</tr>
<tr>
<td>Patents</td>
<td>16</td>
<td>14</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Total publications</td>
<td>709</td>
<td>770</td>
<td>844</td>
<td>991</td>
<td>1035</td>
<td>1054</td>
</tr>
</tbody>
</table>

Books and book chapters

326

Table 1.4b  GUIDE – corrected for joint publications at the programme level
Main categories of research output

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refereed articles</td>
<td>608</td>
<td>647</td>
<td>735</td>
<td>821</td>
<td>835</td>
<td>869</td>
</tr>
<tr>
<td>PhD theses</td>
<td>47</td>
<td>51</td>
<td>57</td>
<td>93</td>
<td>91</td>
<td>77</td>
</tr>
<tr>
<td>Patents</td>
<td>16</td>
<td>14</td>
<td>8</td>
<td>10</td>
<td>10</td>
<td>14</td>
</tr>
<tr>
<td>Total publications</td>
<td>671</td>
<td>712</td>
<td>800</td>
<td>924</td>
<td>936</td>
<td>960</td>
</tr>
</tbody>
</table>

Books and book chapters

303

Table 1.5  Number of PhD students

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PhD students per year</td>
<td>279</td>
<td>313</td>
<td>342</td>
<td>355</td>
<td>369</td>
<td>400</td>
</tr>
<tr>
<td>employed</td>
<td>250</td>
<td>281</td>
<td>285</td>
<td>274</td>
<td>268</td>
<td>272</td>
</tr>
<tr>
<td>non-employed</td>
<td>29</td>
<td>32</td>
<td>57</td>
<td>81</td>
<td>101</td>
<td>128</td>
</tr>
<tr>
<td>% non-employed</td>
<td>10.39%</td>
<td>10.22%</td>
<td>16.77%</td>
<td>22.82%</td>
<td>27.37%</td>
<td>32.00%</td>
</tr>
</tbody>
</table>
Section 1.6: Earning Capacity

Fund-raising strategy and support

Several initiatives have been taken to increase funding. The NWO operates a prestigious career development programme called Vernieuwingsimpuls. This is comprised of VENI for young researchers, VIDI for more experienced researchers and VICI for senior researchers. Special support activities are implemented to increase the success rate for this programme. They include i) Ruggesteun, which focuses mainly on presentation and interview skills and ii) UMCG support, which focuses on the scientific content of the application and is given by laureates.

Funding via European Community framework programmes is becoming increasingly important. European funding is largely concentrated in the Framework Programmes. An active policy is pursued to increase the participation in these programmes. This policy includes:

- establishing contacts with national agencies such as Senter or local RUG-affiliated agencies such as the Transfer and Liaison Group (TLG);
- informing GUIDE staff members about relevant work programme topics by e-mail, newsletters and investigator meetings;
- establishing and strengthening strategic collaborations;
- supporting European grant applications.

Participation in large-scale initiatives (e.g. Top Institute Pharma (TI Pharma), Top Institute Food & Nutrition (TIFN), Parelnoer and the Centre for Translational and Molecular Medicine (CTMM)) is promoted and supported. This is partly achieved by organising investigator meetings and fostering local consortia that were presented to these initiatives under the umbrella of GUIDE. In particular, the participation of GUIDE in TI Pharma, CTMM and Parelnoer is very substantial.

The quality of applications for national funding programmes (NWO equipment programmes) is improved by subjecting all proposals to an internal review and advice protocol implemented by the Graduate Schools, including GUIDE.

Support by GUIDE is restricted to principal investigators.

Results

The earning capacity of GUIDE is given in Table 1.6. It demonstrates a constant share of acquired grants per research staff input over the entire evaluation period. Specific results of the funding strategy and support are discussed in the chapters on the various research programmes.

<table>
<thead>
<tr>
<th>Table 1.6 Fund raising capacity at the level of GUIDE</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>Total funding</td>
</tr>
<tr>
<td>% (FTE)</td>
</tr>
<tr>
<td>Allocated funding</td>
</tr>
<tr>
<td>% (FTE)</td>
</tr>
<tr>
<td>Acquired funding</td>
</tr>
<tr>
<td>% (FTE)</td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are funded directly by the University of Groningen and/or the UMCG (allocated funding). To extend their research capacity, they acquire grants via internal and external competition (acquired funding) for non-tenured staff, employed PhD students, non-employed PhD students, and in some cases, a limited number of staff positions. The fund raising capacity is expressed in research FTE.

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8 Senter is an agency of the Ministry of Economic Affairs which implements government policy in the fields of technology, energy, environment, exports and international cooperation. Its objective is to make an enduring contribution to the position of the business sector and knowledge institutions in the Netherlands. It also assists with establishing EU contracts. URL: http://www.senter.nl/

9 The Transfer and Liaison Group (TLG) is part of the university bureau and aims at supporting the acquiring of contract research within the RUG. It is also involved in the establishment of EU contracts. URL: http://www.rug.nl/bureau/expertisecentral/tlg/
Section 1.7: Academic Reputation

The scientific reputation of GUIDE is reflected primarily in the:
- number and quality of peer-reviewed articles in reputable journals in the relevant fields of research,
- the number and size of grants obtained in open competition and anonymous peer review evaluation,
- patents,
- editorships in academic journals,
- memberships in scientific academies and on scientific boards,
- invitations to address major conferences, and
- awards and prizes earned by individual researchers.

Literature output is described in Sections 4 and 5. The scientific quality of the output is additionally measured through bibliometric analysis. This analysis was carried out by the Centre for Science and Technology Studies\(^\text{10}\) (CWTS). The most striking feature of this analysis is the substantial rise in scientific output, with a near doubling over the past decade, and a steady rise in scientific quality to significantly above world level. The area of General Medicine shows the highest contribution to quality\(^\text{11}\) (CPP/FCSm = 3.39).

Fund-raising capacity is described in Section 6. Valorisation and economic aspects are described in Section 8. Research environment and embedding are described in Section 3. A detailed description of indicators of esteem at the level of principle investigator is included in the sections on the individual programmes.

GUIDE has performed very well on all these aspects. A large proportion of the scientific output of GUIDE is in top journals (34% of the output is in the top 10% of the relevant ISI field and 71% of the output is in the top 30%) and these figures for all research programmes combined, are stable over the evaluation period. Participation in major competitive grant programmes reflects the size and share of the UMCG (and GUIDE), and most PIs of GUIDE participate or have participated in national and international boards, editorial boards, scientific associations and peer-review committees.

\(^{10}\) URL: http://www.socialsciences.leiden.edu/cwts/

\(^{11}\) Disclaimer: covers ISI-subject areas down to 1% of the total UMCG output; data for subject areas in which less is published, e.g. high quality niche-areas were not made available by CWTS.
Section 1.8: Societal Relevance

Societal Quality
Demographic developments in our society point to an increasingly ageing population accompanied by a concomitant increase in the incidence of chronic diseases. Thus, we are all living longer, but in most cases those extra years are not spent in good health, resulting in an increased demand for novel treatments (drugs) and health care.

The mission of GUIDE will be to perform research focused on chronic diseases and drug exploration. Therefore the mission of GUIDE fits perfectly in this societal demand. Recently, the UMCG adopted Healthy Ageing as its main theme, covering patient care, research, education and training. This strategy will contribute to the increase of the quality of life and prolonged participation in society for older people.

All ageing-related research is brought together in the UMCG Institute for Healthy Ageing. This institute will be the framework in which all UMCG activities related to healthy ageing are embedded. This will include the cohort study LifeLines, the UMCG Centre for Geriatric Medicine (UCO) and the European Research Institute on the Biology of Ageing (ERIBA) in formation. GUIDE fully complies with this mission.

Societal Impact
The societal impact of GUIDE research is evident because of its focus on chronic diseases and drug exploration: in our ageing society, chronic diseases and the need for novel drugs will increase steeply. Furthermore, the recently adopted focus on Healthy Aging will strengthen the societal impact. GUIDE participates, via the UMCG and its focus on Healthy Ageing, in the regional cluster Healthy Ageing Network Northern Netherlands (HANNN). This is a cluster of research institutes, regional authorities, insurance companies, industry and policy makers that allow GUIDE to participate in policy making and initiatives on health-related societal issues, not only at a regional level but also on the national and European level.

Furthermore, GUIDE researchers act as members of advisory councils of e.g. patient organisations, consultants for policy-making bodies and governmental advisory councils, advisory councils of charitable foundations and as members of the Royal Dutch Academy of Arts and Sciences, etc. Detailed information about these activities is given in Section 7 of the individual research programmes.

Valorisation
Valorisation is promoted by GUIDE at three levels:

1. Whenever appropriate, scientific results are incorporated in patent applications. An overview of obtained patents is included in Section 5.

2. Entrepreneurship is actively encouraged by the UMCG and GUIDE. The transfer from patents to spin-off companies is actively endorsed and supported by the Business Generator Foundation Groningen (SBGG); this is a UMCG and university-founded organisation that actively supports (also financially), patent applications and the establishment of spin-off companies. The management of GUIDE is interlocutor of the board of the SBGG, thus fine tuning the needs of GUIDE researchers.

3. Education. GUIDE supports entrepreneurship amongst its members by providing dedicated courses to young investigators (PhD students and postdocs), e.g. the course ‘Science to the Market’. Furthermore, GUIDE, in cooperation with the SBGG, organises the Summer School ‘Science and Entrepreneurship in Groningen’. The goal of these courses and activities is to enable scientists to view public or private enterprises as natural partners and a next step in their careers.
Section 1.9: Next Generation

Institutional embedding – Evolution from Research School to Graduate School

GUIDE evolved from a research school into a graduate school in September 2005. This entailed the formal incorporation of a two-year selective research Masters programme (Topmaster Medical and Pharmaceutical Drug Innovation). Successful Masters students from this programme enter the PhD programme at the graduate school GUIDE. Within the Masters programme, education is provided by the principal investigators of the graduate school, and the education (training of Masters students) takes place in the laboratories of the graduate school (‘learning by doing’). Since principal investigators of both GUIDE-GRIP and GUIDE-UMCG are involved in this programme, inter-disciplinarity in this programme is assured. Within the graduate school, the research management and research responsibilities remain the same. This differs from the situation in other graduate schools outside the UMCG.

Objectives

The most important goal of the Graduate School is to train and educate excellent researchers, and to facilitate and promote excellent research. In addition, more attention is given to the quality of supervision in the graduate school in order to improve the success rate of the PhD tracks.

A solid training programme has been developed for PhD students that enables the education of multidisciplinary researchers with a keen eye for the complete spectrum of medical and biomedical research in a unique research and teaching environment: from bed to bench to drugs. This will result in high quality PhD theses, and will prepare PhD students in the best possible way for their future careers.

GUIDE supports several categories of PhD students. Every PhD student in one of the GUIDE research institutes must be registered at the Graduate School and take part in its education programme. Each category of student (employed and non-employed PhD students, MD/PhD, AGIKO and ‘other researchers’) has its own conditions regarding the number of credits, depending on the number of years available for the research project. An overview is given in Table 1.7.

Completing the education programme with a sufficient number of credits leads to the GUIDE certificate.

Table 1.7 Overview categories of PhD students

<table>
<thead>
<tr>
<th>PhD Categories</th>
<th>Research Training (yr)</th>
<th>CP Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhD student</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>AIO (Research assistant)</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Bursaries</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Bursaries</td>
<td>2-3</td>
<td>9</td>
</tr>
<tr>
<td>AGIKO/AIO</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Pharmacists-in-training</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>MD/PhD</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Others (medical specialists in training, externals)</td>
<td>variable</td>
<td>to be determined</td>
</tr>
</tbody>
</table>

Structure and content of the programme

The Graduate School believes strongly that modern medical-scientific research should be interdisciplinary. Research benefits most when researchers are trained in a teaching environment with the knowledge and skills of various disciplines. Therefore, the research school has developed a solid training programme (Table 1.8) with a number of dedicated and connected courses, in combination with a large set of attractive general courses (presentation, negotiation, entrepreneurship, scientific writing, grant proposals, patent applications, etc.).

The strength of the Training and Education programme is that the PhD student can compile a programme of relevant courses from those offered by GUIDE or from external courses after approval by the PhD Training and Education Committee. This enables the PhD student to put together a tailor-made Training and Education programme that best supports his/her PhD project.

During this period the courses were highly quality-oriented, which means that the courses GUIDE considered as both of high importance for the PhD-students and of high quality, were classified with more credits than the ECTS required. ECTS means: 1 EC = approx 28 hrs. As of 1 January 2009, the GUIDE numeration of the education programme has been converted to European Credits (EC) in accordance with European Standards. The requirement for completing the training programme and obtaining the GUIDE certificate is 30 EC, based on 4 years of research (see Table 1.7).
Table 1.8: Contents of the PhD training and education programme

<table>
<thead>
<tr>
<th>Courses</th>
<th>CP</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Courses</td>
<td></td>
</tr>
<tr>
<td>Introduction to GUIDE</td>
<td>1</td>
</tr>
<tr>
<td>Project Management for Scientific Research</td>
<td>2</td>
</tr>
<tr>
<td>Publishing in English</td>
<td>2</td>
</tr>
<tr>
<td>Presentation Skills</td>
<td>2</td>
</tr>
<tr>
<td>Scientific Integrity</td>
<td>1</td>
</tr>
<tr>
<td>Medical Statistics</td>
<td>2</td>
</tr>
<tr>
<td>Laboratory Animal Science</td>
<td>3</td>
</tr>
<tr>
<td>Science to the market</td>
<td>6</td>
</tr>
<tr>
<td>Methodological and Practical Courses</td>
<td></td>
</tr>
<tr>
<td>GLP/GCP Good Laboratory Practice, Good Clinical Practice</td>
<td>3</td>
</tr>
<tr>
<td>Good Manufacturing Practice</td>
<td>1</td>
</tr>
<tr>
<td>Application of Modern Techniques in Life Sciences</td>
<td>3</td>
</tr>
<tr>
<td>Cellular Imaging</td>
<td>3</td>
</tr>
<tr>
<td>Working with Radioactive Substances</td>
<td>2</td>
</tr>
<tr>
<td>Working with Isotopes</td>
<td>3</td>
</tr>
<tr>
<td>Microarray Expression Studies</td>
<td>2</td>
</tr>
<tr>
<td>Microbiological Safety</td>
<td>1</td>
</tr>
<tr>
<td>Techniques of Molecular Biology</td>
<td>4</td>
</tr>
<tr>
<td>Bioinformatics</td>
<td>1</td>
</tr>
<tr>
<td>Epidemiology and Applied Statistics</td>
<td>3</td>
</tr>
<tr>
<td>Biomedical and Pharmaceutical Research Courses</td>
<td></td>
</tr>
<tr>
<td>Advanced Immunology</td>
<td>4</td>
</tr>
<tr>
<td>Microbiology and Infectious Diseases</td>
<td>1</td>
</tr>
<tr>
<td>Advanced Drug Delivery and Drug Targeting</td>
<td>3</td>
</tr>
<tr>
<td>Membranes, Signal Transduction and Transport</td>
<td>3</td>
</tr>
<tr>
<td>Design, Conduction and Evaluation of a Clinical Trial</td>
<td>3</td>
</tr>
<tr>
<td>Pharmacoepidemiology and Drug Policy</td>
<td>3</td>
</tr>
</tbody>
</table>

Active participation in research groups
- Attending at least 6 guest lectures in the International Seminar Programme
- Active participation in at least 3 workshops with an external guest speaker in one of GUIDE research groups
- Active participation in at least 20 seminars a year within one of GUIDE research institutes
- Manuscript review – reviewing at least 2 manuscripts per PhD student per research period
- Presentation (oral/poster) at (inter)national meeting

GUIDE Early Summer Meeting
- 1

Supervision

Within the Graduate School GUIDE, the quality of supervision of PhD students has a high priority. We expect the best researchers of GUIDE to supervise and support our PhD students. Every PhD student fills out a Training and Supervision Plan (TSP) together with his/her supervisor. The following data must be registered: name(s) of supervisor(s), a description of the way supervision will take place, meeting frequency, research plan, time schedule, training programme and courses, evaluation and assessment. Reports of the meetings are registered in the PhD student’s portfolio.

During the PhD research period, the PhD student must keep track of the research and educational activities. After termination of the research period and before the defence of the thesis, the completed log must be delivered to the GUIDE office. The log, signed by the doctoral candidate, the supervisor, the scientific director and the education coordinator, will be enclosed with the GUIDE certificate.

Only the most skilful researchers are allowed to supervise PhD students. This category of the best researchers also supplements the team of teachers for the PhD courses. The team consists of both skilful teachers and the best researchers with a great deal of experience in the world of science.

The Project Management course provides an extensive PhD student monitoring system to prevent delay and premature termination of the PhD tracks. Small groups of PhD students (10 PhD students) meet once a year under the supervision of two trusted mentors to discuss the progress of their PhD project. These meetings serve as an early warning system for delay and problems in the PhD project. The mentors can play a role as mediators in solving problems or can refer the PhD student to the PhD confidential advisor. All PhD students have the possibility to contact the PhD confidential advisor directly and at any time, in case of problems with their project or supervision.

Success rate

The number of successfully completed PhD projects per year has increased from 47 in 2003, to 104 in 2008. PhD students who have also successfully completed the education programme will receive the GUIDE certificate. A number of measures for improvement have been taken over the past years. These include:

Quality:
- Only scientists within the UMCG who qualify as principal investigator (PI) are eligible for funding, facilities, support and access to PhD students, Masters and Topmaster students and MD/PhD students.
Internationalisation:
GUIDE is adopting an active policy of recruiting potential PhD and Masters students. This will allow better selection of the best candidates and therefore improve the level of PhD and Masters students. This policy includes the use of networks of scientists, strategic alliances with high-ranking universities abroad, attendance at Masters fairs, dissemination of flyers at national meetings, etc. Consequently, the percentage of PhD and Masters students from abroad has steadily increased to about 40% in 2008.

International research experience:
PhD students are offered the possibility of spending 2-6 months of their PhD project in the laboratory of a collaborating partner abroad. This gives them the opportunity to extend their international network and to explore possibilities for postdoctoral fellowships.

Education:
The PhD education programme is under the supervision of the PhD Training and Education Committee. This committee consists of both principal investigators and PhD students, and monitors the quality of courses, validates the quality of external courses and discusses evaluations and feedback from course participants. As a result, there has been further improvement in the Training and Education programme in the past year.

Explanation of the Tables 1.9a - c:
1. The subsection ‘Success rate’ refers to 104 defences in 2008. This is the total number of persons involved in PhD research. Most of them are MDs, MD researchers, specialists and specialists in training. Although the Graduate School registers these categories, these individuals do not actively participate in the Graduate School training programme.
2. We also tracked PhD students with a 4-year contract who are expected to take part in the education programme of the Graduate School. These 4-year contracts concern PhD candidates with an employee status and PhD candidates with a fellowship contract.
3. A special category is MD/PhD: medical students who start a PhD research project during their medical study. The first MD/PhD students began in 2001 (see also Junior Scientific Masters class). We have included this category in the rates.
4. Since 2005, the Graduate School has also had 2-year fellowship contracts. These contracts are the result of collaboration programmes with universities abroad, where PhD candidates start their PhD research project at their home university. After the first two years, the research is continued at the Groningen graduate school for the second two years, and concluded with a RUG thesis. This category has not been included in the rates. During the period 2005-2008, 35 of these 2-year fellowships were granted.
Table 1.9A  Standard (employed) PhD candidates

Note 1: Standard (employed) PhD candidate with employee status, and conducting research with primary aim/obligation of graduation; (research assistants). Data of PhD students started after 2005 are not provided since these PhD students are not graduated yet.

<table>
<thead>
<tr>
<th>Starting year</th>
<th>Total number</th>
<th>Graduated after 4 years</th>
<th>Graduated after 5 years</th>
<th>Graduated after 6 years</th>
<th>Graduated after 7 years</th>
<th>Not yet finished</th>
<th>Discontinued</th>
</tr>
</thead>
<tbody>
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<td>2000</td>
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<td>8</td>
<td>14</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(7%)</td>
<td>(27.5%)</td>
<td>(48%)</td>
<td>(7%)</td>
<td>(7%)</td>
<td>(3.4%)</td>
</tr>
<tr>
<td>2001</td>
<td>34</td>
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<td>4</td>
<td>15</td>
<td>6</td>
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<td>2</td>
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<td></td>
<td>(8.8%)</td>
<td>(11.7%)</td>
<td>(44%)</td>
<td>(17.6%)</td>
<td>(8.8%)</td>
<td>(5.8%)</td>
</tr>
<tr>
<td>2002</td>
<td>24</td>
<td>10</td>
<td>7</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(41.6%)</td>
<td>(29%)</td>
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<td>(12.5%)</td>
<td>(12.5%)</td>
<td>(4%)</td>
</tr>
<tr>
<td>2003</td>
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<td>11</td>
<td>1</td>
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<td></td>
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<td>(31%)</td>
<td>(3%)</td>
<td>(14%)</td>
<td>(10%)</td>
<td></td>
</tr>
<tr>
<td>2004</td>
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<td>9</td>
<td>8</td>
<td>9</td>
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<td></td>
</tr>
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<td></td>
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<td>(30%)</td>
<td>(27%)</td>
<td>(30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>37</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>27</td>
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<td></td>
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<td></td>
<td>(8.1%)</td>
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<td>(27%)</td>
<td>(73%)</td>
<td>(5.5%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>183</td>
<td>10</td>
<td>39</td>
<td>49</td>
<td>24</td>
<td>5</td>
<td>47</td>
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<td></td>
<td>(5.5%)</td>
<td>(21.3%)</td>
<td>(26.8%)</td>
<td>(13.1%)</td>
<td>(2.7%)</td>
<td>(25.6%)</td>
</tr>
</tbody>
</table>

Table 1.9B  Non-employed PhD candidates

Note 1: Non-employed PhD candidates without employee status, receiving external funding or university scholarship, conducting research under the authority of the institute with primary aim of graduation; (PhD scholarship students). Data of PhD students started after 2005 are not provided since these PhD students are not graduated yet.

<table>
<thead>
<tr>
<th>Starting year</th>
<th>Total number</th>
<th>Graduated after 4 years</th>
<th>Graduated after 5 years</th>
<th>Graduated after 6 years</th>
<th>Graduated after 7 years</th>
<th>Not yet finished</th>
<th>Discontinued</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
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<td>(100%)</td>
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<td>(100%)</td>
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<td></td>
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<td>2002</td>
<td>22</td>
<td>12</td>
<td>6</td>
<td>3</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(54%)</td>
<td>(27%)</td>
<td>(13%)</td>
<td>(4.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>4</td>
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<td>2</td>
<td>2</td>
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</tr>
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<td></td>
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<td>(50%)</td>
<td>(50%)</td>
<td>(50%)</td>
<td>(50%)</td>
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</tr>
<tr>
<td>2004</td>
<td>5</td>
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<td>2</td>
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<tr>
<td></td>
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<td>(40%)</td>
<td>(20%)</td>
<td>(40%)</td>
<td>(40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005</td>
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<td>3</td>
<td>3</td>
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<td>16</td>
<td>4</td>
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<td>(15%)</td>
<td>(15%)</td>
<td>(80%)</td>
<td>(20%)</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
<td>20</td>
<td>7</td>
<td>3</td>
<td>21</td>
<td>4</td>
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<td></td>
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<td>(38.4%)</td>
<td>(13.4%)</td>
<td>(13%)</td>
<td>(40.3%)</td>
<td>(20%)</td>
<td></td>
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</tbody>
</table>

Table 1.9C  MD/PhD candidates

<table>
<thead>
<tr>
<th>Starting year</th>
<th>Total number</th>
<th>Graduated after 4 years</th>
<th>Graduated after 5 years</th>
<th>Graduated after 6 years</th>
<th>Graduated after 7 years</th>
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<td>(50%)</td>
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<td>2002</td>
<td>4</td>
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<td>4</td>
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<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>5</td>
<td>4</td>
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<td>4</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(80%)</td>
<td>(80%)</td>
<td>(80%)</td>
<td>(80%)</td>
<td>(80%)</td>
<td>(80%)</td>
</tr>
<tr>
<td>2004</td>
<td>8</td>
<td>7</td>
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<td>1</td>
<td>1</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(87.5%)</td>
<td>(12.5%)</td>
<td>(12.5%)</td>
<td>(12.5%)</td>
<td>(12.5%)</td>
<td>(12.5%)</td>
</tr>
<tr>
<td>2005</td>
<td>12</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
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<tr>
<td></td>
<td></td>
<td>(50%)</td>
<td>(50%)</td>
<td>(50%)</td>
<td>(50%)</td>
<td>(50%)</td>
<td>(50%)</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>21</td>
<td>2</td>
<td>2</td>
<td>7</td>
<td>1</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>(67.7%)</td>
<td>(6.5%)</td>
<td>(6.5%)</td>
<td>(22.5%)</td>
<td>(3.2%)</td>
<td>(3.2%)</td>
</tr>
</tbody>
</table>
Educational resources
The Education and Training programme is financed by contributions from the UMCG, based on the number of registered PhD students. The amount per PhD student covers — to a certain extent — the financial support necessary for each PhD student to i) take the courses offered by GUIDE, ii) take selected external courses and iii) contribute to travel expenses (€ 600/year). Furthermore, part of the budget is used for related PhD student activities, such as guest speakers in the International Seminar Programme, and the organisation of conferences and master classes. The financial requirements for short research stays abroad are separate from this budget and are paid for from the optional budget of the Graduate School GUIDE.

Career destinations of PhD Graduates
After their PhD thesis defence, graduates can proceed in many different ways.

- GUIDE/UMCG has an active policy of retaining the top 10% of graduates. These graduates can enter several career development tracks (Rubicon, VENI, pre-tenure track). Mandatory for this category is a research stay of at least 1 year at a reputable laboratory abroad.

- The majority of PhD students from abroad return to their home country and are well equipped to start a career there. It is expected that part of this group will become leading scientists in their home countries, thus reinforcing the international network of the Graduate School.

- Many PhD students (e.g. MD/PhD students) are MDs who continue their medical specialty training after graduation. The most talented of these MD/PhD students can enter several career development tracks, e.g. AGIKO, Klinische Fellow, VENI or Mandema Stipends, to continue their research activities.

- The majority of graduates will continue their career elsewhere, either in academia (postdoctoral fellows) or with pharmaceutical companies or science-related companies, including consultancy agencies.

- Some of the graduates will leave science entirely and continue their career in a completely different field.

Other aspects
Topmaster programme
In addition to the PhD education programme, the Graduate School GUIDE is responsible for the Topmaster programme 'Medical Pharmaceutical Drug Innovation' (MPDI). This programme started in 2003, and was accredited by the NVAO in 2007. Enrolment in this highly selective MPDI programme requires high standards (the top 5-10% of students; letters of motivation, applicant’s CV, interviews, etc.). Fifty-percent of the students are recruited from abroad. The Topmaster programme trains Masters students to enter the PhD programme. It is a very intensive and small-scale programme, with only 10-15 students per year. Students graduate from this Topmasters programme by designing and defending their own PhD project in a VENI-like procedure. After approval by the Board of Examiners, these students are admitted to the Graduate School as PhD students and can begin their own PhD project.

Junior Scientific Masters class/MD-PhD programme
The Junior Scientific Master class (JSM) encourages medical students to enter clinical scientific research. This programme – set up in 1998 – starts with an honours Bachelor in the Bachelors programme and continues in the 1st year of the Masters programme, when students are given the opportunity to write a project proposal for a MD/PhD position. This MD/PhD programme gives students the opportunity to do research and write their thesis during their medical study.

Employment after PhD degree
Every PhD student is invited to indicate their future activities after the PhD defence. However, this is not an obligatory step in the completion of the PhD project. The category ‘after PhD degree’ has 189 entries in the period 2003-2008.

The table shows the annual percentage of reported future activities. The diagram shows the categories of future positions. Note that only the first position held after obtaining the PhD is registered. GUIDE has no insight into the activities of former PhD students after more than one year.
Table 1.10  Percentage of indicated future activities

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>47</td>
<td>78</td>
<td>64</td>
<td>47</td>
<td>40</td>
<td>43</td>
</tr>
</tbody>
</table>

Employment situation after obtaining PhD degree

- Searching: 59%
- Research: 25%
- Medical/Specialist: 14%
- Other: 7%
- Business: 84%
Section 1.10: Viability, SWOT and Future Strategy

Viability

Resource management
Resource management focuses on excellence. There are programmes in place that will be extended to attract excellent staff (Rosalind Franklin programme, tenure track and pre-tenure track programmes, MD/PhD programme). The UMCG is increasingly able to attract talented researchers from outside the northern Netherlands. An active internationalisation policy is being implemented to scout for and recruit talented Masters and PhD students. The Topmaster programme is a good example of this policy. Applications for this programme are increasing steadily, and provide excellent students who continue on as PhD students within GUIDE.

Available infrastructure/research facilities
In the previous evaluation, the available infrastructure was rated as top level. During the present evaluation period, important new additions have been made (see SWOT analysis: Strengths). These facilities will allow us to perform cutting-edge research.

Innovative capacity
The innovative capacity depends on the quality of the research staff, the students and the available infrastructure to address complex scientific questions. These aspects have been described in detail throughout this chapter, demonstrating our innovative capacity.

Financial resources
The fund-raising capacity of the scientific staff is solid, and the financial position of UMCG is healthy. Therefore, the UMCG budget for GUIDE is stable and sufficient to perform all activities and implement all strategies. Furthermore, the funding that GUIDE receives from the UMCG depends on the number of registered PhD students. Consequently, future growth of the number of PhD students can be accommodated.

Mobility and attractiveness
The increased focus on visibility will lead to GUIDE being increasingly attractive to talented Masters and PhD students and as a collaboration partner (see SWOT: Opportunities). The possibilities for increasing our visibility are only now being explored and implemented via a dedicated officer.

Expertise within the institute
In recent years, many talented young staff scientists have been appointed as professors, associate professors or assistant professors (for details, see description of the research programmes). Furthermore, the tenure track and pre-tenure track programmes and the Rosalind Franklin programme enable junior, non-tenured talented scientists to progress to tenured positions. This will rejuvenate the existing senior staff and anticipate the efflux of retiring staff in the coming years.

SWOT Analysis

Strengths
- Strong clinical position. The UMCG has a catchment area of 3 million people. Together with the stability of the population in the northern part of the Netherlands (founder population) this will facilitate large-scale longitudinal studies (e.g. LifeLines) and the study of complex, multifactorial diseases.
- Multidisciplinarity. In the research programmes, biomedical scientists, clinicians and pharmaceutical scientists work in teams. Furthermore, the structure of the research institutes, which bring together specialists from various disciplines around a common theme, yields both focus and mass.
- Newly attracted talented staff. GUIDE is increasingly able to attract talented researchers from outside Groningen. These researchers often attract promising junior scientists, grants, expertise and networks. A special programme for recruiting talented female researchers (the Rosalind Franklin Fellowship programme), has proven to be a very valuable instrument in this regard and has been judged ‘Best Practice’ by the Minister of Education, Science and Cultural Affairs.
- Extensive programmes for talent development. In addition to attracting talent from outside Groningen, several programmes have been developed to scout, train and coach local talent, e.g. the tenure track programme, support for career development applications, MD/PhD programme and the GUIDE Topmaster Medical and Pharmaceutical Drug Innovation programme. Graduates from the Topmaster programme can enter the PhD programme.
• Education, training and research are integrated. PhD students perform research within the GUIDE research programmes supervised by PIs. In addition, they follow a training and education programme that supports their research, their research skills and their training as scientists.
• State-of-the-art infrastructure. In the previous evaluation report covering the period 1998-2002, the infrastructure of the UMCG was evaluated as top level. New additions to these already state-of-the-art facilities have been made: a new animal facility, a centre for Bio-Optical imaging, an advanced microscopy centre, a mouse clinic (transgenic and knockout mice, metabolic studies etc.) and a GMP facility. These facilities will allow the study of innovative research questions.
• Unique to the Netherlands is the presence of clinical wards, clinical laboratories, preclinical laboratories and pharmaceutical research groups, all in one complex (“under a single roof”). All these categories are represented within the research programmes of GUIDE.
• Medical faculty and academic hospital governed by a single board. The shared mission and interests of the medical faculty and the academic hospital have generated unprecedented strength that is best illustrated by the common focus on healthy ageing.

Weaknesses
• Insufficient focus. Considerable efforts have been made to increase focus, e.g. the status of principal investigator not only depends on the quality of output but also on the ability to contribute to existing research programmes. However, this results in a problem for newly recruited research staff, who often perform research outside the existing research lines. In part, this weakness is due to the organisation of research into rather rigid programmes (vide infra: Opportunities).
• Fundamental research. The position of fundamental research has improved greatly compared to the previous evaluation, especially in the areas of genetics and molecular biology. However, there is still a need for more fundamental research in the areas of immunology and transplantation to complement the clinical performance in these areas.
• Geographic isolation. The geographic position of Groningen limits the attractiveness to outside staff (and to a lesser extent to excellent students and PhD students). Although UMCG/GUIDE is increasingly able to attract talented researchers from outside Groningen, this remains a point of attention. In addition, Groningen is still under-represented in the decision-making bodies in the western part of the Netherlands.
• The UMCG and the University of Groningen have a limited international brand awareness. This also leads to underestimation in international rankings and results in a lack of visibility.

Opportunities
• To increase the focus of research, the organisation of research into large and rigid programmes will be abandoned and changed into multiple, but more flexible and smaller research entities that are strongly focused around a specific research topic (“meaner and leaner”).
• To promote excellence, the policy of rewarding only staff scientists who perform well (principal investigators) should be extended and intensified by increasing the reward for individual PIs and increasing the threshold to becoming a PI. The reorganisation of research into smaller clusters will facilitate this.
• A much stronger internationalisation policy to scout and recruit talented students and PhD students and staff from abroad will be implemented. This will be realised by establishing strategic alliances with selected institutes and universities abroad, including shared PhD projects, marketing activities and web-based marketing activities and intensifying the use of our alumni network, both at home and abroad.
• The focus of the UMCG on Healthy Ageing is very timely, taking into account the ageing population. This can be further exploited, thereby strengthening our societal relevance. Furthermore, this focus is shared by the entire northern region of the Netherlands, brought together in the Healthy Ageing Network Northern Netherlands (HANNN), a cluster of research institutes, regional authorities, insurance companies, industry and policy makers. This will make more financial resources available for research and strengthen our position in acquiring competitive grants.
• Valorisation can still be improved according to the recent initiatives described in Section 8. A prominent role for the SBGG is envisioned in this process.
• The concept of Graduate Schools (freedom of choice for excellent PhD students, as in the Topmaster programme of our Graduate School) has been adopted by the Dutch Government and is implemented via a competitive NWO programme.
Threats

- Financial restrictions are still a threat. Spending on research and development (and education) in the Netherlands is lagging behind other countries, both inside and outside the EU. The Lisbon goals of the EU have not been met, and the current financial crisis will only exacerbate this situation.
- Emerging economies like China and India are increasingly able to accommodate their own excellent students by providing state-of-the-art research facilities. Therefore, talented students from these and other countries are less likely to go to Europe/USA for a scientific career. In the long term, a brain drain may occur, with talented Dutch students earning their PhD in emerging economies, where facilities and financial resources are better.

Future Strategy

Based on the SWOT analysis and in order to implement our strategy, the following measures will be taken:

- The organisation of research will be changed from large and rigid programmes into more numerous, but flexible and smaller research entities that are strongly focused on a specific research topic.
- The policy of rewarding only staff scientists who perform well (principal investigators) will be extended and intensified by increasing the rewards for individual PIs and increasing the threshold to becoming a PI.
- Along the same lines, the instruments to promote excellence (Topmaster programme, JSM, MD/PhD, Rosalind Franklin programme) will be continued and extended.
- A much stronger internationalisation policy to scout for and recruit talented students and staff from abroad will be implemented. This will be realised by establishing strategic alliances with selected institutes and universities abroad, including shared PhD projects, marketing activities and web-based marketing activities and intensifying the use of our alumni network both at home and abroad. A dedicated officer has recently been appointed.
- An active policy will be implemented to embed part of the research portfolio of the GUIDE research programmes into the Healthy Ageing initiatives.
- Recently, the UMCG decided to merge the various Graduate Schools and institutes (GUIDE, BCN, SHARE, Kolff Institute) into a single Graduate School of Medical Sciences. This merger will be implemented in the near future. The advantages of this merger will be greater uniformity of rules and regulations, a stronger Training and Education programme and increased clarity and visibility for the outside world.
CHAPTER 2

Groningen Institute for Kidney Diseases
Section 2.1: Objectives and Research Area

Programme Leaders
Prof. P.E. de Jong and Prof. D de Zeeuw

Objectives
- To identify the pathophysiological mechanisms of progressive loss of renal function
- To identify the link between renal and cardiovascular complications of common risk factors
- To develop strategies for the prevention of renal and related cardiovascular function loss and to resolve individual therapy resistance, based on insight into these mechanisms

Research Area
These pathways and the potential therapeutic interventions are studied under three sets of circumstances, thereby integrating experimental, clinical, and epidemiological approaches.

1. Renal function in normal subjects. Little is known about the incidence and magnitude of renal function loss in the general population (i.e. in subjects not previously diagnosed as having renal disease), and the mechanisms underlying the susceptibility to renal damage in healthy subjects, including common pathways with cardiovascular disease.

2. Renal diseases of various origin. It has been well documented that a patient who experienced a certain type of renal disease will progress to end stage renal failure, independent of the type of the initial insult.

3. Renal transplantation. Because the mechanisms underlying chronic renal transplant dysfunction overlap the mechanisms underlying renal function loss in diseases of native kidneys, the mechanisms as studied in diseases of native kidneys are also evaluated in renal transplantation.

In this report we will describe the results and the future perspectives of this kidney programme, divided into the following sub-programmes:

1. Early loss of renal function in otherwise healthy people
   a. Mechanisms of renal function loss and its complications
   b. Kidney-Heart and Kidney-Vessel interactions
   c. Detection strategies and therapeutic interventions

2. Progressive loss of renal function in established kidney diseases
   a. Mechanisms of renal function loss and its complications
   b. Kidney-Heart and Kidney-Vessel interactions
   c. Therapeutic interventions

3. Chronic Renal Transplant Dysfunction
   a. Mechanisms of renal function loss and its complications
   b. Kidney-Heart and Kidney-Vessel interactions
   c. Therapeutic interventions

Strategy and policy
During the first evaluation period (1992-97) the Groningen Institute for Kidney Diseases (GIKD) focused only on research into the progression of chronic kidney disease (CKD) in primary renal disease (presently sub 2), but during the second evaluation period (1997-2002) we extended our work to similar studies in subjects with renal function loss in earlier phases and in subjects who donated a kidney (presently sub 1).

During the third period currently under evaluation, further extensions were realised. In the areas of healthy individuals and established CKD, we included studies on heart-kidney interactions, studying the effect of traditional and novel risk factors on renal and cardiovascular outcome, as well as how kidney function influences cardiac function and vice versa. Another extension of our programme involved the studies on progressive renal function loss in renal transplantation (presently sub 3). These studies are also based upon a large longitudinal follow up of our transplant programme.
Section 2.2: Composition of the research unit

Description of the research unit

Compared to the previous SEP, the tenured staff of the institute expanded from 8 staff members (2.5 FTE) to its current size of 13 staff members (4.4 FTE), see Table 2.1. In proportion to this staff expansion, the number of fellows working in GIKD grew from 22 in 2003 to 38 in 2008 (see Table 2.1; for details, see appendix Section 2.2).

Table 2.1 Overview of research staff at the level of programme GIKD

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>Tenured staff</td>
<td>2.53</td>
<td>2.60</td>
<td>2.60</td>
<td>2.90</td>
<td>4.40</td>
<td>4.40</td>
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<tr>
<td>(8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full professors</td>
<td>1.60</td>
<td>1.60</td>
<td>1.60</td>
<td>1.60</td>
<td>2.00</td>
<td>2.00</td>
</tr>
<tr>
<td>(5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associate professors</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
<td>0.70</td>
<td>1.40</td>
<td>1.70</td>
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<tr>
<td>(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assistant professors</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.30</td>
<td>1.00</td>
<td>0.70</td>
</tr>
<tr>
<td>(0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other senior staff</td>
<td>0.23</td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>(1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-tenured staff</td>
<td>0.00</td>
<td>0.90</td>
<td>1.58</td>
<td>0.90</td>
<td>2.03</td>
<td>1.35</td>
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<tr>
<td>(0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhD students</td>
<td>12.78</td>
<td>15.93</td>
<td>13.30</td>
<td>11.73</td>
<td>12.08</td>
<td>13.13</td>
</tr>
<tr>
<td>(22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>12.78</td>
<td>15.93</td>
<td>13.30</td>
<td>11.73</td>
<td>12.08</td>
<td>13.13</td>
</tr>
<tr>
<td>(20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non employed</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>(2/9.09%)</td>
<td>(4/14.29%)</td>
<td>(5/17.24%)</td>
<td>(6/26.09%)</td>
<td>(11/32.35%)</td>
<td>(15/40.54%)</td>
<td></td>
</tr>
<tr>
<td>Total research staff</td>
<td>15.30</td>
<td>19.43</td>
<td>17.48</td>
<td>15.53</td>
<td>18.50</td>
<td>18.88</td>
</tr>
<tr>
<td>(30)</td>
<td></td>
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</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers also have obligations for patient care. For the sake of simplicity, a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD students with an employment contract. For non-employed PhD students (student status), expression as FTE is not appropriate.

Strategy and policy

The expansion of GIKD has mainly taken place in two areas: experimental research and clinical cohort follow up and trials. The experimental expansion was recommended during the previous evaluation to strengthen a relative weakness in our programme. The expansion in the clinical cohort and trial area was a further enhancement of a strong area of GIKD.

Clinical staff expansion:
First, based upon our studies of interactions between the kidney and the heart, we focused more on the mechanisms by which the metabolic syndrome induces renal (and cardiac) abnormalities. To that end, Stephan Bakker of Internal Medicine became involved in the programme with his expertise in the study of metabolic factors and their association with progressive renal function loss. Second, based upon the first results of the ongoing PREVEND study, and as it became clear that there were opportunities to continue this programme, Ron Gansevoort became involved in GIKD to expand the studies on early screening for chronic kidney disease. His expertise in both renal risk management and renal (and cardiovascular) protective therapy strengthened our staff in the areas of our research objectives.

Experimental staff expansion:
In recognition of the good performance of Gerjan Navis and in line with the recommendation of the previous evaluation that more attention should be given to experimental research, we appointed Jaap van den Born (formerly of the Cell Biology group at VU University Amsterdam), with a five year start-up grant. For some time, GIKD has operated experimental labs at the Pharmacology Department (head: Rob Henning) and at the Pathology Department (head:
Harry van Goor). In January 2008, we started our experimental Nephrology Lab under the supervision of Jaap van den Born. As an experimental pathobiologist and immunologist, he is fully dedicated to fundamental science. His primary interest is renal tissue remodelling and tubular regeneration. He has a strong background in proteoglycans, inflammation and innate immunity. One of his major interests is in chronic renal transplant dysfunction. We anticipate that this new lab will greatly enhance our basic and translational renal scientific output. Because this lab is located on the same floor as the Experimental Pharmacology lab, more intensive collaboration can be expected. The Experimental Pharmacology lab extended its expertise in studies on vascular pharmacology to include the kidney.

PhD expansion:
The growth in the number of PhD students (see Table 2.1) is related to several factors. First, as described above, the number of tenured staff increased in accordance with the advice of the previous evaluation. Second, we were successful in attracting funding for research projects (see Section 6). The most prominent funding acquisitions were grants from the

1. Dutch Kidney Foundation for the continuation of the PREVEND study,
2. European Union for studies on
   a. diabetic nephropathy (PREDICTIONS, FP6),
   b. the genetic basis of cardiovascular complications in CKD (GENECURE, FP6, coordinated by our nephrology department),
   c. improved biomarker techniques (Nanosense, FP6)
   d. using systems biology for novel CKD diagnosis and treatment (SysKID, FP7),
3. TI-Pharma consortium for studies on the use of biomarkers to shorten the time required for registering new drugs in nephrology (ESSCHER),
4. TI Food and Nutrition for studies on the effect of dietary protein, peptides and amino acids on blood pressure and CKD,
5. CTMM consortium for biomarkers on diabetic kidney disease,
6. Health Insurance and GP’s for the Groningen Initiative to analyse Type 2 diabetes treatment (GIANT), creating a database of more than 20,000 Type 2 diabetics, their risk factors treatment and renal and cardiovascular outcome
7. Biochemistry industry for studies on biomarkers for progressive CKD and the pharmaceutical industry for the studies on drug interventions to prevent progressive CKD, such as studies on vitamin D metabolites and vasopressin antagonists.

Third, we were very successful in attracting students from the junior Scientific Masterclass and the MD-PhD programmes of the medical faculty. Staff of GIKD are quite active in training junior investigators during the first part of their curriculum.

Table 2.2 Overview of the research funding at the level of programme GIKD

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE (FTE)</td>
<td>(46.24%)</td>
<td>(63.96%)</td>
<td>(67.95%)</td>
<td>(65.06%)</td>
<td>(60.81%)</td>
<td>(44.64%)</td>
</tr>
<tr>
<td>Total funding</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(100%)</td>
<td>15.30</td>
<td>19.43</td>
<td>17.48</td>
<td>15.53</td>
<td>18.50</td>
<td>18.88</td>
</tr>
</tbody>
</table>

Expenditure (k€)

Personnel costs (k€) 642.6 857.3 876.2 792.5 1,054.4 1,088.7
Other costs personnel (k€) 247.4 330.1 337.4 305.1 406.0 419.2
Costs non-employed PhD students (k€) 31.9 49.1 70.9 88.1 115.2 194.7
Other costs - non-employed PhD students (k€) 17.0 25.5 36.1 44.6 57.4 87.1
Total expenditure k€ 938.9 1,262.0 1,320.6 1,230.3 1,633.0 1,789.7

Explanation: The expenses for research include both personnel and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the donation to the unemployment pay (wachtgelden)
provision (i.e. the obligation to provide personnel reduced pay in case of unemployment for a restricted period of time; not applicable to direct funding), the costs for temporary workers or agency staff and other costs such as allowances for child care and commuting. Although non-employed PhD students do not represent research FTE, the costs of these PhD students have been included. Other costs include exploitation costs (consumables) and investment debits, and are based on a long-term average of 27.7%.

1 Direct funding by the university;
2 Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programmes ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3 Funding for specific research projects obtained from external organisations, such as industry, governmental ministries, European Commission (Framework programmes) and charity organizations.
Section 2.3: Environment and Embedding

Position and reputation

Formal collaborations

Together with the group of Prof. G. Remuzzi (Mario Negri Institute in Bergamo, Italy) and the group of Prof. M. El Nahas (Sheffield, UK), we established the European Kidney Initiative. This takes an integrated approach in public health education to address CKD. Consequently, in 2002 an agreement was signed for scientific and educational cooperation between the University of Groningen and the Mario Negri institute. In recent years this has resulted in various Groningen PhD students visiting Bergamo (Goos Laverman, Liffert Vogt, Martin de Borst, Stefan Vegter), and Giuseppe Monteferrante from Bergamo visiting Groningen. In the context of this exchange of research fellows, our aim is to send PhD students who we are preparing for scientific careers. In this context it should be mentioned that Goos Laverman recently acquired a position in our group, and that Martin de Borst was awarded a Mandema clinical research fellowship. As a consequence of the cooperation with Sheffield, two PhD students from Sheffield participated in PREVEND research projects (Aminu Bello and Bisher Kawar).

In addition, a trial collaboration network has been set up with the George Institute (Sydney, Australia), and the first training fellow has been sent on exchange (Hiddo Lambers Heerspink).

Participation in networks

Due to the present availability of large databases at our institute (PREVEND, the Groningen chronic renal transplant dysfunction (CRTD) cohort and the Clinical Trials Database, GIANTT), we have launched international initiatives to establish the following networks.

- **PREDICTIONS** An FP6-funded programme to identify pathophysiological-relevant genes and biomarkers correlated with the onset, progression and response to therapy of diabetic nephropathy.
- **TI Food Nutrition** A network to unravel the mechanisms by which dietary proteins may influence blood pressure and kidney function.
- **Global BP Gen** This is a network of research centres having GWAS data of large cohorts with an emphasis on blood pressure regulation. With data on (parts of) the PREVEND cohort and the Lifelines cohort soon to be available, we will initiate studies on the genes responsible for early and late CKD progression.
- **Parelsnoer** The nephrology departments of the 8 University Medical Centres in the Netherlands will include clinical and biomedical data for a longitudinal follow up of their CKD patients in a database with the aim of creating a cohort of CKD patients for future translational studies as well as for multi-centre clinical trials. This network will be coordinated by Prof. Navis.
- **KDIGO Collaborative group for the CKD diagnosis and staging system** After our PREVEND study showed that the present CKD classification system is not optimal for diagnosing patients with the greatest risk for ESRD and progressive CVD, we started an initiative to combine data from many population cohorts in a standardised way. This has resulted in a collaboration between about 50 patient cohorts, including a total of more than 1.5 million subjects with long-term follow up. These cohorts all have data available on CV risk parameters, eGFR and albuminuria at baseline, and longitudinal information on CV events and renal events. Pooling these data will enable us to better define whether it is low eGFR or high albuminuria (and in what combination) that determines the risk of CKD.
- **Nanosense** Many novel biomarkers entering clinical practice are currently assessed by separation-based assays. Typically these are low-throughput and expensive. As part of the European Sixth Framework Programme (FP6), we began a collaboration to shift from slow and expensive sensitive separation-based immunoassays to fast and affordable nanoparticle-based homogenous assays with similar or even better sensitivity. This will not only reduce health care costs, but also improve the quality of health care by making important biomarkers more easily and widely available.
- **sysKID** (Systems Biology towards Novel Chronic Kidney Disease Diagnosis and Treatment) As part of project in the recent European Seventh Framework Programme (FP7) we began collaboration with 24 European partners in a network to unravel the molecular and cellular mechanisms of chronic kidney disease development, combining this information with clinical risk factors, and on this basis to delineate chronic kidney disease biomarkers. These markers will allow us to conduct preclinical studies of novel therapy approaches for halting disease progression, and will provide us with the materials for the development and clinical evaluation of tools for early stage diagnosis as well as prognosis and treatment monitoring.
- **(Groningen, Steno Center Denmark, University of Chicago, University of Melbourne, George Institute, Mario Negri Bergamo).** We have created a network to collaborate on the formation of a large clinical trial database of type 2 diabetic patients. The database comprises of RENAAL, IDNT, IRMA2, SUNmicro, SUNmacro, ADVANCE, PREVEND-IT. This network and database will allow studies on the impact of biomarkers on renal/
cardiovascular risk as well as therapy assessment. Unravelling individual susceptibility to renal risk and determining individual variability in response will be the primary targets.

- **Clinical trial networks** GIKD participates in many different multinational clinical trials that study the effect of several different existing and novel medications on renal (and cardiovascular) outcome. Examples are:
  - SHARP trial (NCT00125593) on the effect of statins on renal outcome
  - TREAT trial (NCT00093015) on the effect of EPO on cardiovascular and renal outcome
  - SUN-micro trial (NCT00130208) and SUN-macro trial (NCT00130312) on the effect of sulodexide on renal outcome
  - PLANET trial (NCT00296400) on the effect of statins on renal outcome
  - ALTITUDE trial (NCT00549757) on the effect of renin-inhibition on cardiovascular/renal outcome
  - VITAL trial (NCT00421733) on the effect of Vitamin D analogues on renal outcome
  - TEMPO trial on the effect of vasopressin antagonists on cyst growth and renal function in polycystic kidney disease
  - the GIANTT diabetes cohort on the effect of daily practice on cardiovascular and renal outcome.

- **Turkey network** We initiated collaboration with Ankara University and Hacettepe University. A collaborative research project including a PhD student and a post-doc was funded by the Turkish Scientific and Technological Research Council (TUBITAK).

**Guest researchers**
During this evaluation period, 35 guest speakers participated in GIKD symposia. GIKD frequently holds internal symposia on the occasion of the thesis defence of PhD students. During such symposia, 2-3 guest speakers from elsewhere in the Netherlands or from abroad are invited. Moreover, internal symposia are held once every month during which a guest researcher either from the Netherlands or from abroad is invited to give a lecture on a topic being studied by one of the present PhD students (for details, see appendix Section 2.3).

**Strategy and policy**
Collaboration within Groningen, but particularly outside Groningen, is clearly the current and future strategy and policy for the GIKD. For experimental work we have been working, and will continue to work, on enhancing the collaboration between the nephrology, pathology, cardiology and pharmacology experimental laboratories in Groningen. In addition, collaboration with the Mario Negri in Bergamo, and Turkey will be encouraged.

In clinical work, collaborations involving our general population and CKD cohorts will focus both on clinical outcome and on biobanking. International collaboration will take place with KDIGO and the partners that have large general population cohorts. In addition, Groningen will enhance its participation in a worldwide clinical trial network with Utrecht, Australia and USA.
Section 2.4: Quality and Scientific Relevance

Quality of the output
The quality of the output is, of course, even more important than the quantity. An important indicator for the quality of the output is the percentage of papers that are published in higher ranking journals. Table 2.3 shows the percent of papers that were published in the top 10% and top 30%. All top publications have been marked in appendix Section 2.5.

We also evaluated the citation frequency of the GIKD by counting the number of citations of the publications in this evaluation report. Considering that it generally takes 2-3 years before the number of citations of a manuscript increases, we are happy that by mid 2009, 10 papers published by the GIKD staff in the period of 2003-06 had been cited more than 100 times, another 10 papers had been cited 50-100 times and another 38 papers had been cited 25-50 times. Altogether, therefore, 58 papers – or 1 manuscript per staff member per year – achieved good citations during a period of about 4 years. This should be considered in relation to the average number of publications per staff member: 8-9 per year.

Table 2.3 Number of papers published in the top 10% and 30% journals of relevant disciplines

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<tbody>
<tr>
<td>(n of articles)</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Belongs to the best 10%</td>
<td>43%</td>
<td>49%</td>
<td>44%</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Belongs to the best 30%</td>
<td>24%</td>
<td>28%</td>
<td>30%</td>
<td>27%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Most important results
In this section we will emphasise some of the results that transcend the borders of the individual programmes.

Albuminuria measurement methods to optimise screening efficacy
Measurement of albuminuria in urine is still biased by many different factors. GIKD has been focusing on several aspects to enhance the reliability of the measurement as well as to improve the quality of the predictive power, and to bring the measurement closer to clinical practice. Important findings are the fact that non-immunoreactive albumin in the urine may play an important role in predicting outcome (Brinkman, Clin Chem 2007). Considering that in epidemiological studies 24-hr urine collection is not feasible, we were pleased to show that a first morning Albumin–to-Creatinine Ratio is as reliable to predict future events as an accurately measured 24-hr Urinary Albumin Excretion (Lambers Heerspink, Am J Epidem 2008). An interesting development is the point-of-care measurement of albuminuria (Lambers Heerspink, Kidney Int 2008). This latter approach will allow GPs and ultimately patients to monitor albuminuria more closely for more effective risk and treatment assessment.

Novel therapy approaches
Intervention in the renin-angiotensin system has been a very important topic for renal/cardiovascular protection, in particular the effects of such interventions on albuminuria. We found that the degree of albuminuria reduction is both renoprotective and cardioprotective. The cardioprotection is found both in very early stages, when only microalbuminuria is present as a risk factor (Asselbergs, Circulation 2004), and at later stages, like diabetic nephropathy (de Zeeuw, Circulation 2004). Interestingly, we found the renoprotective effect of RAAS intervention to be variable per individual; this was clearly related to the albuminuria reduction, irrespective of the blood pressure effect of the drugs (Eijkelkamp, JASN 2007). Even in normotensive type 2 diabetics, renal and cardiovascular protection was shown to be related to albuminuria reduction of RAAS intervention (Zandbergen, Annals Int Med 2003).

Despite the success of RAAS intervention on renal/cardiovascular outcome, the residual risk is still very high; interestingly, this risk is related to the residual albuminuria. New therapy approaches to reduce albuminuria are therefore very important. GIKD has been and is still involved in such efforts, both in the experimental lab and in clinical trials. Examples include 1) the new class of renin inhibitors, which drew the attention of the GIKD many years ago and in which we are now investing for the future (Parving et al, NDT 2009); 2) the interesting effect of Vitamin D analogues...
on albuminuria (Lambers Heerspink, Am J Nephrol 09), which will trigger new programmes on this drug class on hard outcomes as well as experimental work on mechanisms by which vitamin D is related to progressive function loss.

Pharmaco-economics
Nowadays, intervention strategies must not only be effective, but also cost-effective. GIKD has been working on the pharmaco-economics on both the treatment of albuminuria in the general population and in diabetes (Atthobari, J Clin Ther 2006, Palmer and de Zeeuw, Diabetes Care 2004). The most important outcome is that early intervention strategies targeted at albuminuria are not only renal (and cardiovascular) protective, but also appear to be more cost-effective than late intervention.

Key publications
In the section below we describe the 4-6 most important publications in recent years for each programme and sub-programme. Full text articles of these key publications are provided in appendix Section 2.4

1. Early Loss of renal function in otherwise healthy people
   a. Mechanisms of renal function loss
      We showed in our PREVEND population cohort that it is not obesity per se (high BMI), but abdominal fat in particular (high waist/hip ratio) that determines renal risk (Pinto-Sietsma, Am J Kidney Dis 2003). It was also shown that sodium intake affects albuminuria, especially in overweight subjects (Verhave, J Int Med 2004). Additionally, we studied the impact of BMI on renal hemodynamics: a higher BMI, even in the “normal” range, is associated with a more unfavourable renal hemodynamic pattern (Bosma, Kidney Int 2004). We next studied the interaction between obesity and sodium intake on renal hemodynamics: high (but not low) sodium intake elicits a hyperfiltration pattern in subjects with obesity, but not in those with normal BMI. It should thus be studied whether low sodium intake or diuretics prevent the renal risks of weight excess (Krikken, Kidney Int 2007). Finally, we tested the hypothesis that the impact of abdominal fat on renal hemodynamics is mediated by inflammation: an elevated CRP (as found in abdominal adiposity) may result in a glomerular hyperfiltration related renal function loss (Stuveling, Kidney Int 2003). We extended these studies to the impact of obesity on donation of a kidney: donor nephrectomy unmasks an age and overweight induced loss of reserve capacity in donors (Rook, Am J Transpl 2008)

   b. Kidney-Heart and Kidney-Vessel interactions
      In an experimental setting we showed that the individual level of renal endothelial function predicts the severity of the renal damage that results from a myocardial infarction, suggesting an individual’s renal susceptibility for the detrimental effects of a CV event (Ochodnicky, JASN 2006). Also, renal disease was shown to affect vascular beds outside the kidney, which was prevented by ACEi. It was additionally shown that both ACEi and vasopeptidase inhibition prevent the renal damage in an experimental model of cardio-renal interaction (Windt, JASN 2006).

      The link between CV risk factors and kidney dysfunction is being extensively studied in PREVEND: age, plasma glucose, BMI and SBP are cross-sectionally associated with higher albuminuria. Interestingly, these relations are steeper in men than women (Verhave, JASN 2003). In addition, CRP was found to modify this relationship between blood pressure and albuminuria (Stuveling, Hypertension 2004). Moreover, in a longitudinal follow up, elevated albuminuria (which could well be a demonstration of an impaired endothelial function) was associated with an increased risk of developing impaired GFR, even after adjustment for the well-known CV risk factors (Verhave, Kidney Int 2004). While it is generally accepted that hypertension and diabetes precede the development of renal damage, we showed that the reverse may also be true. Subjects with microalbuminuria have a greater risk of developing de novo hypertension (Brantsma, JASN 2006) and de novo diabetes mellitus (Brantsma, Diabetes Care 2005).

   c. Detection strategies and therapeutic interventions
      In our studies on the impact of albuminuria to predict progressive CKD, we first showed that macroglobulinuria predicts future renal risk better than a low GFR and also better than erythrocyturia (Halbesma, JASN 2006). We then showed that it is not only macroglobulinuria, but also microalbuminuria that predict future progressive renal function decline (van der Velde, JASN 2009). We argued that screening for albuminuria identifies patients at increased renal and cardiovascular risk. Indeed, most of the Wilson criteria to implement systematic albuminuria screening seem to be fulfilled (de Jong, JASN 2006).
We also studied the impact of ACE inhibition on preventing future CV events. Reducing albuminuria during ACEi was associated with better CV survival (Asselbergs, Circulation 2004). It was found that the costs of systematic screening for albuminuria, with concomitant ACEi treatment of those with microalbuminuria, were below the limit of €20,000/LYG (Atthobari, Therapeutics 2006). In addition we showed that it is more effective to prescribe antihypertensive drugs to the hypertensive subjects with microalbuminuria, than to those without albuminuria, questioning the need to treat all hypertensive subjects without microalbuminuria (Boersma, Br J Clin Pharm 2008).

2. Progressive loss of renal function in Established Kidney Diseases
   a. Mechanisms of renal function loss
      In our longstanding work on the studies of the RAAS in the kidney, we were motivated by the recent finding that ACE2 counterbalanced ACE. We therefore studied ACE2 expression in renal biopsies, and demonstrated ACE2 neo-expression in primary and secondary kidney diseases and in transplanted kidneys in glomerular and peritubular capillary endothelium, while ACEi treatment did not alter ACE2 expression (Lely, J Pathol 2004).

      We also studied KIM-1, which is not detectable in normal kidneys. KIM-1 appeared to be up-regulated in human kidney diseases and was associated with renal inflammation and fibrosis (van Timmeren, J Pathol 2007). In addition, KIM-1 was also upregulated in proteinuria-induced renal damage (proteinuria overload model). It was limited to areas with inflammation and fibrosis and with tubular damage (van Timmeren, Am J Physiol 2006). We next tested whether dysregulation of the RAAS can also induce KIM-1 expression. Indeed, in the Ren2 rat KIM1 is associated with development of RAAS-mediated renal damage. Antifibrotic treatment through RAAS blockade or p38 MAPkinase inhibition reduces KIM-1 (de Borst, Am J Physiol 2007). Most recently, we showed that urinary KIM-1 is elevated in non-diabetic kidney disease with proteinuria and that RAAS blockade and salt depletion reduces KIM-1 parallel with proteinuria (Waanders Am J Kidney Dis 2009).

   b. Kidney-Heart and Kidney-Vessel interactions
      We showed that albuminuria (an indicator of CKD) is not only associated with a poorer CV prognosis, but also that reducing albuminuria is associated with a better CV prognosis. This indicates that renal risk markers better reflect CV prognosis than the CV risk markers themselves (de Zeeuw, Circulation 2004). Considering the increasing interest in renal function amongst cardiologists, we also studied the reliability of eGFR measurements in subjects with heart failure: when interpreting true GFR based upon the GFR estimates, caution should be exercised, especially since they appear not to appropriately reflect the spectrum of progressive renal function decline. In early GFR loss, they underestimate true GFR, but in more advanced disease they overestimate true GFR (Smilde, Circulation 2006).

      We also studied how hemodynamically mediated renal dysfunction influences CV prognosis: the renal function deterioration (transient or otherwise) observed after coronary bypass surgery predicts long-term CV prognosis (Loef, JASN 2005). This shows that renal responsiveness to a hemodynamic insult (bypass surgery) is a reflection of a generalised vascular malfunction. In another study we showed the impact of heart-failure-related venous congestion on renal function. Although renal blood flow itself is the main factor determining GFR in patients with cardiac dysfunction, venous congestion, characterised by an increased right atrial pressure, is also adjusted for renal blood flow, related to GFR. Therefore, treatment to preserve GFR should not only focus on improving renal perfusion, but also on decreasing venous congestion (Damman, Eur J Heart Fail 2007).

      In this research programme we also studied the cause of the anaemia in heart failure. We found that anaemia is not only related to impaired renal perfusion and blunted EPO production, but also to fluid retention (Westenbrink, Eur Heart J 2007)

   c. Therapeutic interventions
      While various studies in small group of patients, amongst which some of our own institute that have been described in the previous evaluation, had shown the impact of ACE inhibition on albuminuria, in the large RENAAL trial we convincingly demonstrated that lowering albuminuria with RAAS intervening agents slows down progressive renal function loss (de Zeeuw, Kidney Int 2004). We also showed that treatment-induced changes in albuminuria are not concordant with changes in blood pressure and that the prevention of progressive renal function loss is related more to
albuminuria reduction than the blood pressure reduction with these RAAS blockers (Eijkelkamp, JASN 2007). We intensified the RAAS intervention approaches by adding aldosterone blockade to ACE inhibition. We showed in adriamycin nephrosis that the combination of both agents effectively reduces not only proteinuria, but also markers of tubular injury and proteinuria-induced renal damage (Kramer, Kidney Int 2007). It should still be studied whether it is just the diuretic action of aldosterone blockade that explains these beneficial effects, or if a specific antifibrotic effect of spironolactone is also involved.

In our search for new therapeutic strategies to prevent renal inflammation and renal fibrosis, we also studied the effects of local inhibition of p38 MAP kinase in proximal tubular cells. To that end, a renal specific conjugate of a p38 inhibitor and the carrier lysozyme was developed. The conjugate reduced intrarenal p38 phosphorylation and alpha smooth muscle actin protein expression in a unilateral renal ischemia reperfusion model. This strategy could therefore be useful in the treatment of renal fibrosis (Prakash, J Pharm Exp Ther 2006).

3. Chronic Renal Transplant Dysfunction
   a. Mechanisms of renal function loss

As emphasised in Section 1 above, we extended our studies on progressive renal function loss to include subjects who received a renal transplant, since loss of transplant function is currently one of the most important causes of the need for dialysis or return to dialysis. Considering the major impact of metabolic syndrome and its components on progressive CKD, we also studied the role of metabolic syndrome on chronic renal transplant dysfunction (CRTD). The association of metabolic syndrome components and transplant function in the long term did not change after adjustment for established risk factors for CRTD. However, only systolic blood pressure and hypertriglyceridemia were independently associated with impaired renal allograft function (de Vries, Am J Transpl 2004).

In addition, we found evidence that accumulation of advanced glycation end products plays a role in the pathogenesis of CRTD (Hartog, NDT 2007). As a follow up to our studies on KIM-1 (see above), we also studied the urinary excretion of KIM-1 in relation to loss of renal allograft function. Indeed, KIM-1 appeared to be an independent predictor of long-term graft loss (van Timmeren, Transplantation 2007). In this programme we also evaluated the origin of the cells involved in interstitial and vascular remodelling after transplantation. We showed that, within the interstitial and vascular compartments of the transplanted kidney, the myofibroblasts, vascular smooth muscle cells and endothelial cells involved in chronic remodelling are derived from different sources, either donor or recipient. The data suggest different pathogenetic mechanisms within the renal compartments (Rienstra, Am J Transplant 2009).

b. Kidney-Heart and Kidney-Vessel Interactions

We investigated whether albuminuria is associated with endothelial dysfunction in CRTD and whether these markers affect the link between albuminuria and mortality. Albuminuria was indeed associated with sVCAM-1, and transplant patients with albuminuria and high sVCAM-1 or sICAM-1 concentrations have an increased risk of death compared to albuminuric subjects with normal sVCAM-1 and sICAM-1 levels and patients without albuminuria (van Ree, Transplantation 2008). The link between the heart and the kidney in renal transplantation was also studied. We compared the impact of an elevated BNP level as risk factor for mortality in renal transplant patients and in the general population. It was found that BNP was more strongly associated with mortality in transplant patients than in the general population, which suggests that increased mortality in the transplanted patients may be related more to heart failure than to accelerated atherosclerosis (Oterdoom, Transplantation 2009).

c. Therapeutic interventions

We aimed to use gene therapy on the renal graft. To that end we first studied the use of a modified adenovirus that has an RGD motif inserted in the HI loop of the fibre knob. This appeared to be a highly efficient vector system, as enhanced gene expression was achieved selectively in renal interstitial fibroblasts in the transplanted kidney as compared to unmodified adenovirus (Sandovici, Kidney Int 2006). We then tested the potential of Interleukin-13 delivered by the modified adenovirus to protect the kidney from ischemia-reperfusion injury. Kidney function and renal histology were significantly better after IL-13 gene delivery (Sandovici, Gene Med 2007). After this,
we tested the effect of gene therapy with IL-13 in renal transplantation. This approach significantly attenuated structural features of acute kidney transplant rejection (Sandovici, Kidney Int 2008).

In another series of experiments on the impact of aldosterone blockade (see above), we studied whether spironolactone may protect against chronic allograft nephropathy. In the Dark Agouti to Wistar Furth rat model we showed that spironolactone ameliorates the development of proteinuria, focal segmental glomerulosclerosis and transplant arteriopathy (Waanders, Am J Pathol 2009).
Section 2.5: Quantity of Scientific Output

Overview of the results
Table 2.4 shows that the output has risen over the years. However, this is directly related to the increase in staff at the institute. In fact, the number of publications per staff member has remained fairly stable at 8-9 papers per year. All publications are listed in appendix Section 2.5.

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
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<td>81</td>
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<td>112</td>
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<tr>
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Publication strategy
As mentioned before, we believe that the quantity of publications should not necessarily be increased. Instead, we are aiming to publish in higher ranking journals, although the percentage of publications in the top 30% of journals is already reasonable. There are only a few high ranking nephrology journals, so we are pleased that during the past 5 years we have published more in General Medicine journals, such as Circulation, Annals of Int Med and JAMA. We aim to further increase that visibility in such General Medicine journals as The Lancet, BMJ and NEJM.

Number of PhD students
Table 2.5 shows that the number of PhD students has increased over the years. Of course this is not unexpected, since the number of staff has also increased (see Section 2). However, the ratio of PhD students per staff member has remained fairly stable (about 3 PhD students per staff member).

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<thead>
<tr>
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<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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<tbody>
<tr>
<td>Number of PhD students per year</td>
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<td>28</td>
<td>29</td>
<td>23</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>Employed</td>
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<td>24</td>
<td>24</td>
<td>17</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Non-employed</td>
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<td>4</td>
<td>5</td>
<td>6</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>% non-employed</td>
<td>9.09%</td>
<td>14.29%</td>
<td>17.24%</td>
<td>26.09%</td>
<td>32.35%</td>
<td>39.47%</td>
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Section 2.6: Earning Capacity

Fund raising strategy and support
As emphasised in Section 2.1, we are focussing more and more on participation in networks. This strategy has been quite successful and has resulted in a good earning capacity for the group (see Table 2.6). This is based partly on our own initiatives to create networks, and partly on our participation in pre-existing networks. See Section 2.3.

Table 2.6 Fund raising capacity at the level of programme GIKD

<table>
<thead>
<tr>
<th>Year</th>
<th>Total funding</th>
<th>Allocated funding</th>
<th>Acquired funding</th>
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<tr>
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<td>100.0%</td>
<td>14.60%</td>
<td>85.40%</td>
</tr>
<tr>
<td>2004</td>
<td>100%</td>
<td>11.59%</td>
<td>88.41%</td>
</tr>
<tr>
<td>2005</td>
<td>100.0%</td>
<td>11.97%</td>
<td>88.03%</td>
</tr>
<tr>
<td>2006</td>
<td>100%</td>
<td>13.96%</td>
<td>86.04%</td>
</tr>
<tr>
<td>2007</td>
<td>100%</td>
<td>17.43%</td>
<td>82.57%</td>
</tr>
<tr>
<td>2008</td>
<td>100%</td>
<td>15.11%</td>
<td>84.89%</td>
</tr>
</tbody>
</table>

*(FTE)*

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are funded directly by the University of Groningen and/or the UMCG (allocated funding). To extend their research capacity, they acquire grants via internal and external competition (acquired funding) for non-tenured staff, employed PhD students, non-employed PhD students and in some cases a limited number of staff positions. The fund raising capacity is expressed in research FTE.

Results
During the 6 years of this evaluation period, the staff members of GIKD succeeded in acquiring the financial support listed below. The fund raising capacity of Bruce Wolfenbuttel for the LifeLines programme should be mentioned separately. Although this long-term cohort follow up only recently started, members of GIKD are involved in including renal studies in the LifeLines project. Other grants that should be mentioned are the following:

6 grants of more than €1.0 million
1. PREVEND 4th period 2006-09 Dutch Kidney Foundation
2. PREVEND 5th period 2009-12 Dutch Kidney Foundation
3. PREDICTIONS European Union FP 6
4. GENECURE European Union FP 6
5. ESSCHER TI Pharma
6. GIANTT Health Care Insurance

5 grants of €0.5-1.0 million
1. Parelsnoer Ministry of Health and Min of Economics
2. Prevention of diabetic nephropathy Pharmaceutical Industry
3. Prevention of CKD progression Pharmaceutical Industry
4. Prevention of CRTD Pharmaceutical Industry
5. PROPRESS TI Food Nutrition

3 grants of €250,000 – 500,000
1. AGEs in CRTD Dutch Kidney Foundation
2. The pro-renin receptor TCN
3. Cyclosporin and mitochondrial function Dutch Kidney Foundation

10 grants of €100,00 – 250,000
1. Dual RAS blockade Pharmaceutical industry
2. Atherosclerotic risk factors in CKD Dutch Kidney Foundation
3. TGFbeta in diabetic nephropathy Dutch Kidney Foundation
4. Gene therapy TCN
5. Gene therapy Dutch Heart Foundation
6. EGFR in renal disease Dutch Kidney Foundation
7. CETP as risk factor Dutch Heart Foundation
8. Altered HDL in type 2 DM Diabetes Federation
9. Vitamin D in renal fibrosis Dutch Kidney Foundation
10. Biomarkers in CKD Nanosense
Section 2.7: Academic Reputation

Investigators of GIKD have an excellent academic reputation. Due to their activities in international networks, they are frequently invited as speaker at international meetings. Some function in Editorial Boards of the most important Nephrology Journals. Moreover, Dick de Zeeuw and Paul de Jong organised some meetings on the role of albuminuria in risk prediction. Prestigious awards have also been received (see below). For a detailed overview, see appendix Section 2.7.

Awards Dick de Zeeuw
2006  Lennart Hansson Memorial Lecture Award
2007  American National Kidney Foundation International Distinguished Medal
2008  Special lecture award Japanese Society of Nephrology.

Award Paul E de Jong
2010  American National Kidney Foundation International Distinguished Medal

Award Jaap van den Born
2006  Jonas Bergstrom Award of the International Society of Nephrology
Section 2.8: Societal Relevance

Societal Quality

For many years research in nephrology was mainly directed at optimising renal replacement therapies. Of course, nephrology was the first specialty with the option for life sustaining treatments after organ failure. Due to the great success of dialysis and especially the success of transplantation programmes, less attention was paid to the prevention of progressive renal function loss in both diabetic and non-diabetic kidney disease. Thanks to the availability of RAAS blocking agents during the 1990s, we learned to prevent loss of renal function in patients with established kidney disease (stage 3 and 4 CKD, especially when associated with albuminuria). Researchers from GIKD were the first to describe that agents that lower albuminuria not only result in renoprotection, but also in cardioprotection. We also documented that such interventions are cost-effective. This latter data helps to convince healthcare providers to broadly implement such strategies. Moreover, in experimental studies as well as in clinical studies in various CKD cohorts, we demonstrated that this albuminuria lowering effect of RAAS blocking agents is only fully manifest when the patient also adheres to a low-salt diet. These findings now are generally accepted and have been included in CKD guidelines.

Our studies on early CKD also received much attention. Various articles have been accompanied by editorials that emphasised their impact. Traditionally, it was argued that the presence of microalbuminuria in situations where GFR is relatively preserved (stages 1 and 2) may be an early manifestation of vascular damage and a predictor of future CVD. We were the first to show that microalbuminuria is also an early predictor of progressive renal function loss, and thus of future ESRD. This link between the heart and the kidney has placed nephrology in a complete different perspective than 20 years ago; it is now driving much research in vascular medicine. Furthermore, the need for early detection now has priority due to the finding that more than half of the subjects that are ultimately presented to ESRD programmes develop ESRD not because of primary renal disease, but because of other, frequently undiagnosed vascular and or metabolic diseases. This trend is clearly shown in our recent data on the options for screening for early CKD! It can be expected, although thus far proven only in type 2 diabetes, that early interventions (in stage 1 and 2 CKD) will not only help to prevent future CV events, but also to prevent progression to established CKD.

The emphasis on renal pathophysiology in subjects without renal disease is not only relevant to high-risk subjects in the general population, but will also become increasingly important for the living kidney donation programme. Due to the pressure of donor shortage, the donation criteria have become more liberal over the years in terms of donor age, donor obesity and blood pressure. The risk profile of the donor population is thus shifting – and better insight into the determinants of renal risk after donation is therefore pivotal. A successful living donation programme has a large impact, both for individual patients and for society, in terms of reduction of costs of healthy care. Donor safety is a prerequisite for a successful living donation programme. The recognised risk factors for renal function loss (albuminuria, uncontrolled hypertension, diabetes) are exclusion criteria for donation by default, and accordingly, specific exploration of the determinants of susceptibility of the healthy kidney to damage after donation is required. The other way round, better insight into the determinants of appropriate adaptive capacity of the kidney may help to provide clues to the regenerative capacity of the kidney in CKD. So far, the studies of donors showed that increased age and higher body mass index were associated with less renal adaptive capacity in the short term, but with similar long-term adaptive capacity. Consequently, the healthy kidney has the capacity to circumvent the adverse effects of age and weight excess over the long term! Detailed renal hemodynamic assessment before and after donation is central to this programme, and has shown that the concept of renal hemodynamic reserve capacity may be useful in the development of renal risk profiling in these healthy subjects.

Obesity is an increasingly recognised risk factor for renal damage, not only in CKD, but also in the general population. We found that high sodium intake potentiates the impact of BMI on albuminuria in the general population. In subsequent renal hemodynamic studies in healthy volunteers, we were able to show that the combination of high sodium and weight excess (even if mild) induces hyperfiltration, whereas neither of the two risk factors did so alone. This was associated with exaggerated volume expansion, so again the renal and cardiovascular risk profile go hand-in-hand. This could be detected by the combined measurement of GFR and extracellular volume that we recently developed, and that will also be an important tool for future studies on combined renal and cardiovascular pathophysiology.

The combined impact of weight excess and sodium intake points towards nutritional factors and lifestyle in general as determinants of renal risk that will become more important in our increasingly sedentary society. Traditionally, nephrologists are familiar with unbiased nutritional monitoring in pre-dialysis or dialysis patients, where strict dietary measures are required. In several projects, we have now applied this expertise to a nutritional monitoring approach for subjects who are at a much lower risk. The added value of the nephrology approach for nutrition research has been recognised by the TIFN programme, which addresses the role of dietary protein in blood pressure in the general population. We are now a full partner in this programme, which has other partners with a specific nutritional background. This provides access to specific expertise that was not easily available before, and provides a novel impetus to our research on metabolic risk factors.
Societal Impact

Our studies on strategies to detect CKD have drawn much attention in society. That is not only related to the fact that we frequently publish reports in Dutch medical journals, but also to the fact that new data on screening for CKD and on the impact of obesity for CKD have been discussed in general newspapers. In addition we started initiatives to convince the Ministry of Health of the importance of screening for albuminuria (other than only for hypertension and diabetes) for the prevention of future CV events.

In 2007, together with the Dutch Kidney Foundation we started the Niercheck campaign. All adult inhabitants were given the opportunity to ask for three proteinuria dipstick tests to evaluate (at home) the presence of proteinuria. The tests were requested by more than 1 million subjects (12% of the population). Together with a large media campaign and the involvement of the Dutch general practitioners, this campaign resulted in increased awareness of the impact of albuminuria for both renal and CV prognosis.

We also took the lead in providing guidelines to the general practitioners on how to screen and track subjects with CKD. These guidelines, which were written both by nephrologists and general practitioners, are currently at the final review stage. These guidelines have used much data from the PREVEND study to improve general health care. Simply stated, the guidelines refer to the ABCDE for healthy ageing: you should be aware of your (or your patient’s) Albuminuria, Blood pressure, Cholesterol, Diabetes and Estimated GFR. In other words, information on the traditional risk factors alone is not sufficient unless it includes the parameters of CKD: albuminuria and eGFR.

Our group also emphasised the need for an update of the KDOQI guidelines for the staging and stratification of CKD. Although the system was implemented in 2002, at that time it was not based on the prognoses of the various stages. During the past five years, many studies have been published showing that it is not the level of eGFR itself, but the level of albuminuria, which is probably more important for both renal and cardiovascular prognosis. Data from the PREVEND study substantially contributed to that awareness. In the autumn of 2009, a KDIGO meeting will be held in London during which researchers from about 50 cohort studies will share their data on CV and renal prognosis for the various CKD stages. All cohorts will deliver their data according to a strict format provided by a KDIGO working group (in which GIKD has the lead); this is a replica of the PREVEND format. We expect this meeting to result in an adaptation of the classification system which takes better account of the impact of albuminuria. In line with the above-mentioned studies on accurately measured eGFR before donation, we took the initiative to formulate Dutch guidelines for the donor evaluation prior to kidney donation.

Besides setting up general population studies to assess the importance of renal disease in Groningen, we are also setting up projects like GIANTT, which involves benchmarking more than 20,000 type 2 diabetic patients in the province of Groningen. The recent finding that fewer than half of GPs measure albumin in the urine of diabetes patients, and that they rarely use guideline therapy in cases where microalbuminuria are detected and measured, are important for future measures that will have great societal impact.

In addition, the participation of GIKD in large international clinical trials not only impacts on the treatment of patients in Groningen, but also worldwide. Building databases for clinical trials on type 2 diabetes and using this data to optimise therapy strategies also contributes to this impact.

Finally, the programme that GIKD has started on optimising the design of clinical trials has the aim of accelerating the availability of new drugs for patients. This may ultimately have an impact on general health.

Valorisation

We are pleased to have fruitful collaboration with the Department of Pharmacoeconomics and Pharmacoeconomics (LTW de Jong-van den Berg and M Postma) of our university. Together we not only perform studies on the relationship between drug use and CKD, but also evaluate the cost effectiveness of RAAS treatment for CKD, and the cost effectiveness of screening for albuminuria in association with the treatment of macro-albuminuria or even microalbuminuria. While it was previously shown in diabetic nephropathy that RAAS-inhibiting treatment is cost effective to prevent ESRD, our studies in subjects with microalbuminuria recently showed that screening the general population for albuminuria is also cost effective. This favoursable cost-effectiveness ratio is not primarily because treatment of positive subjects results in the prevention of ESRD (a follow up <5 years), but because it initially prevents CV events, and will also prevent ESRD only in the long run. We showed that this cost effectiveness is even better when we screen and subsequently treat subjects with microalbuminuria, instead of limiting our focus to subjects with macroalbuminuria. We also showed that the benefits for antihypertensive drugs to prevent CV events in hypertensive subjects are predominantly restricted to subjects with hypertension associated with microalbuminuria. If there is no microalbuminuria, the benefits of drug treatment are limited. These data could have a major impact on the costs of general health care.
Section 2.9: Next Generation

With regard to the education offered through GUIDE, please refer to the main part of the GUIDE evaluation.

We are actively training young researchers in the Junior Scientific Masterclass, and are encouraging good students to participate in the MD/PhD programme of our faculty as well as in the Mandema clinical research fellowships. Moreover, for more than 10 years, two member of our staff (Gerjan Navis and Rob Henning) have been the main organisers of the ISCOMS (International Students Congress of Medical Sciences). This congress not only attracts many Groningen and foreign students to Groningen for presentations of their research projects, but it also gives international students the opportunity to take a two-week class in research at one of the research institutes. Every year, several students participate in this two-week research class in kidney diseases. In this way we become acquainted with the quality of international students and their potential to do a PhD project later on. Many students who participated in such a class later returned to the unit as non-employed PhD students.

During the past five years, we have succeeded in attracting many students to the MD/PhD programme, as well as recruiting various foreign students as non-employed PhD students. We are also pleased with Martin de Borst and Titia Lely; they are the first post-docs to receive a Mandema grant to continue their research during the clinical training programme (they are exempt from clinical duties for 20% of their time). After finishing their theses in 2007, they started their clinical fellowships as internist and gynecologist, respectively. Their research projects focus on vitamin D (Martin de Borst) and pre-eclampsia (Titia Lely). Martin de Borst also received the Kolff stipend of the Dutch Kidney Foundation to encourage his development as researcher. In addition, due to Hiddo Lambers Heerspink’s successful PhD project, we admitted him to the prestigious pre-tenure track programme of our medical faculty. His research will focus on local and international renal clinical trials, thereby ensuring that GiKD will remain an important player in the renal trial field.

Finally, we are recruiting young post-docs, both from other cities in the Netherlands and from abroad. After having had experience in foreign institutions, we can offer them a research career (see “viability” in Section 2.10)
Section 2.10: Viability, SWOT and Future Strategy

Viability

Developments in staff positions
We believe that our prospects for the future are good. Considering the age distribution of the staff, we realise that one of the directors will retire during the next 5-year period. Six of the other staff members are between 50 and 60, while the other six are around 40 years of age. Moreover, the number of young assistant professors on the staff has increased in recent years, and we have another group of six young post-docs and assistant professors who will likely apply for full membership in GIKD. In the clinical nephrology group, this includes Marc Seelen, who previously worked in the lab of Prof Daha in Leiden on complement; Casper Franssen, who is studying the CV complications in haemodialysis patients; Goos Laverman, who, after his stay in Bergamo is now coordinating the Dutch CKD Parelsnoer initiative; and Martin de Borst, who, also after a period in Bergamo, has been awarded a Mandama grant. In clinical pharmacology, Hiddo Lambers Heerspink joined the group after his epidemiological and clinical trial studies at the George Institute in Sydney. Finally, Jan Luuk Hillebrands joined the pathology group of Harry van Goor. They in the future can all participate substantially and strengthen the research of GIKD.

See also our efforts in research training in “Next Generation, Section 9”.

Formation of databases and participation in networks
Based on participation in large clinical trials, the formation of large databases with good biobanking facilities will guarantee future research options for many years to come. The PREVEND cohort has an ongoing 12-year follow up, and the Lifelines cohort presently is being formed. The latter is gathering renal data in the same way as PREVEND, also with the intention of a long-term follow up. As a result, we expect many research opportunities for the future. This holds true not only for databases involving the general population, but we are also leading the formation of patient cohorts, as in GIANTT (type 2 diabetes) and Parelsnoer (progressive CKD). We are also aiming to establish a regional Parelsnoer, where we will try to involve the large hospitals in the Northern region of the Netherlands (20% of the country’s population) as part of the CKD Parelsnoer initiative.

Thanks to these initiatives we have been invited to join larger networks, such as PREDICTIONS, GENECURE, and SysKID, to apply for EU grants, as well as to join Genetic Consortia (Global BPGen).

SWOT

Strengths
- A well focussed programme combining studies in progressive CKD in the general population, subjects with primary kidney diseases and patients with a kidney transplant
- A training programme that is attractive for young researchers
- A considerable and fairly stable long-term research output per staff member
- A good earning capacity, with good potential to participate in networks
- A good number of PhD students per staff member
- A programme with clear deliverables for improving patient care
- A research focus that has relevant societal impact using early detection and intervention strategies

Weaknesses
- Too few publications per staff member that earn a high number of citations
- An earning capacity that depends on a relative small part of the staff
- Insufficient integration of the various research groups

Opportunities
- By broadening our field of interest from nephrological to general internal, diabetic and cardiovascular medicine, there is also an opportunity to submit papers to higher ranking journals
- By guiding young staff, and by promoting foreign exchange of young staff, we can build future leaders in nephrology
- Even better anchoring in and capitalising on existing networks
- Optimising research opportunities (clinical trials) by forming regional collaborations with nephrologists and GPs
- Extending the PREVEND and GIANTT programmes into LifeLines
Threats
- Relative weakness of the overall nephrology research in the Netherlands
- Worsening climate for the Pharma Industry in the Netherlands
- Limitation of the research budget of the Dutch Kidney Foundation
- Insufficient support from the University for lab technicians, except by external funding

Future strategy
Although we believe in general that we made much progress during the past period, we will continue to emphasise the recruitment of young research staff and capitalising on the established networks.
CHAPTER 3

Cardiovascular Centre
Section 3.1: Objectives and Research Area

Programme Leaders
Prof. W.H. van Gilst
Prof. D.J. van Veldhuisen

Objectives
Heart failure has a poor prognosis. After diagnosis, short-term and long-term life expectancy (5 years) is lower than for most cancers. The pathophysiology is complex, and many different mechanisms are involved and studied in the programme.

Therefore, the mission of the Cardiovascular Centre is to develop new treatment strategies that will improve the prognosis of patients with heart failure. The ultimate goal is to prevent or formulate a cure for this lethal disease.

This goal will be achieved by using advanced experimental studies including both the exploration of pathophysiological mechanisms and the identification of molecular and cellular targets for treatment. Furthermore, state-of-the-art clinical studies are used to prove the validity of hypotheses generated by the experimental studies.

The current intermediate goals of the research programme are to:

• Design and evaluate strategies to prevent the onset and/or progression of heart failure. In addition, to design and evaluate treatment strategies to improve clinical outcome in heart failure.
• Identify and characterise key mechanisms responsible for the progression of heart failure. These include factors at the genetic, cellular and organ levels.
• Develop and use sophisticated animal, human and in vitro models to study the cellular mechanisms of heart failure.
• Conduct large population studies to identify environmental and genetic factors that lead to a higher susceptibility for heart failure.
• Evaluate the role of atrial fibrillation, which clearly complicates the course of heart failure (and which may also cause heart failure), and to subsequently develop adequate treatment and prevention methods for atrial fibrillation in order to improve the prognosis of heart failure.
• Prevent and treat myocardial damage due to ischemia and/or reperfusion following acute myocardial infarction, in order to reduce left ventricular dysfunction and the development of heart failure.
• Pharmacologically modulate pulmonary arterial hypertension in order to prevent right ventricular adaptation.

Research Area
The heart failure research programme at the Cardiovascular Centre is divided into four sub-programmes:

1. Clinical programme on heart failure and early LV dysfunction post MI (P1)
2. Experimental programme on heart failure (P2)
3. Programme on atrial fibrillation, with a focus on atrial fibrillation in heart failure (P3)
4. Programme on congenital heart disease and pulmonary hypertension, with a focus on right ventricular failure (P4)

In many ways, the four sub-programmes share topics relevant to the central research question on heart failure. The strategy of sharing similar topics throughout the four sub-programmes reinforces the coherence of the overall research area. Important topics include:

• Heart failure and concomitant disease (P1, P2). For example, changes in cardiac function will be negatively influenced by existing renal failure and anaemia. In a similar way loss of vascular function will accelerate the loss of cardiac function. Change of cellular composition and function, not only concerning the cardiac myocyte, but also the cells of the extracellular matrix, cells of the conduction system and vascular endothelial cells are influenced by concomitant diseases in heart failure. Studies into the role of diabetes in the development of heart failure have also recently begun.
• Neurohumoral activation (P1-P4). During the development of heart failure, a complex pattern of various neurohumoral systems are activated, such as the renin-angiotensin system, the natriuretic peptide system and the sympathetic system. The CVC has a strong track record with regard to studies involving strategies for modulating neurohumoral activation in order to improve the prognosis of heart failure.
• Genetic constitution (P1-P3). Are there genetic factors that may predispose for the development of heart failure? Our aim is to identify genetic and/or environmental factors that determine the response or lack of response to therapy. By modulating these factors, we strive to improve therapy efficacy, including treatment
of atrial arrhythmias that may cause or complicate heart failure. Several CVC staff members are participating in international consortia evaluating the involvement of genes in several phenotypes related to heart failure.

- Cellular hypertrophy and cardiac remodelling (P1, P2). Post-infarction hypertrophy and left ventricular remodelling are a major cause of systolic and diastolic wall motion abnormalities leading to chronic heart failure. Cellular models of stretch-induced hypertrophy and, in vivo, post myocardial infarction or aortic-banding-induced hypertrophy are both used in sub-programme 2. Genomic and proteomic approaches are aimed at revealing the molecular heart-specific basis for early maladaptive hypertrophy.

- Right ventricular dysfunction (P4). Right ventricular failure, due to chronic abnormal loading conditions, is a major problem in the follow up of patients with congenital heart disease. Insight into the adaptation of the heart and vasculature to these abnormal loading conditions will help to improve treatment strategies, and ultimately, to prevent early heart failure in the rapidly growing population of patients with congenital or corrected congenital heart diseases. P4 specifically focuses on right ventricular hypertrophy and failure in response to pressure or volume overload as can be observed in pulmonary hypertension and congenital heart disease.

**Strategy and policy**

The heart failure research programme within the CVC has been very successful, and has led to the identification of new medical needs beyond the understanding of the pathophysiology of heart failure.

The scientific output of the CVC has continued to improve, both in terms of quality and quantity, and according to national surveys ranks among the leaders in national and international cardiovascular research. The decision to develop a dedicated centre for experimental heart failure research (Experimental Cardiology, sub-programme 2) has further facilitated optimal collaboration, both with other departments at the UMCG and at a national level. Especially the collaboration with the newly created ‘mouse clinic’ will enable the development of transgenic mice based on clinical gene finding. Strengthening the basic experimental lab and integration with major European networks are major targets for the coming years.

Furthermore, strengthening the collaboration with the Paediatric Cardiology Department within the UMCG was successful and resulted in the formation of sub-programme 4. International collaboration, with both experimental and clinical groups within this programme, has continued to increase. All efforts are being directed at strengthening the performance of the CVC in accordance with its mission.

Participation of CVC staff members in heart failure networks across Europe and beyond was part of the strategy of staying up-to-date with frontline drug development and will therefore be strengthened. Staff members are participating on several institutional boards of the European Society of Cardiology. Recently, the editorial office of the European Journal of Heart Failure moved to Groningen, and many CVC staff members are playing important roles on the editorial board of this journal.
Section 3.2: Composition of the Research Unit

Composition of the research unit
Table 3.1 describes the development of the CVC research staff. The most prominent change has been the increase in the number of full professors, which has doubled from four to eight chairs. This increase has resulted from the success of the four sub-programmes. Several topics within these programmes required supervision by a full professor to assist the various PhD students active in these research lines. These new chairs are concerned with the role of renal function in heart failure, genetics, and right ventricular dysfunction (for details see appendix Section 3.2).

Furthermore, the relatively low number of postdocs participating in the CVC research programme needs attention. This has been partially due to the fact that the number of international PhD students has been increasing. These students usually return to their home countries after successful completion of their thesis. Another reason for this low number of postdocs is that medical PhD students continue training as medical specialists after their thesis defence. Some of these postdoctoral trainees are still active in the research programme, but are not registered in the GUIDE administration as postdocs. Nevertheless, in line with the intention of designing active career planning for high potentials, the CVC is currently expanding the number of postdoctoral positions.

Table 3.1 Overview of research staff at the level of programme CVC

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>Tenured staff</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full professors</td>
<td>5.05</td>
<td>5.05</td>
<td>5.05</td>
<td>5.45</td>
<td>5.85</td>
<td>4.88</td>
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<tr>
<td>(15)</td>
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<td>(15)</td>
<td>(16)</td>
<td>(18)</td>
<td>(15)</td>
<td></td>
</tr>
<tr>
<td>Associate professors</td>
<td>1.15</td>
<td>1.15</td>
<td>1.15</td>
<td>1.95</td>
<td>2.35</td>
<td>2.48</td>
</tr>
<tr>
<td>(4)</td>
<td>(4)</td>
<td>(4)</td>
<td>(6)</td>
<td>(8)</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>Assistant professors</td>
<td>1.50</td>
<td>1.90</td>
<td>1.90</td>
<td>1.50</td>
<td>0.80</td>
<td>0.80</td>
</tr>
<tr>
<td>(4)</td>
<td>(5)</td>
<td>(5)</td>
<td>(4)</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Other senior staff</td>
<td>1.40</td>
<td>1.40</td>
<td>1.40</td>
<td>1.40</td>
<td>1.30</td>
<td>1.00</td>
</tr>
<tr>
<td>(4)</td>
<td>(5)</td>
<td>(4)</td>
<td>(4)</td>
<td>(3)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>PhD students</td>
<td>14.70</td>
<td>19.43</td>
<td>18.38</td>
<td>18.55</td>
<td>15.23</td>
<td>14.00</td>
</tr>
<tr>
<td>(26)</td>
<td>(29)</td>
<td>(30)</td>
<td>(31)</td>
<td>(26)</td>
<td>(24)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>14.70</td>
<td>19.43</td>
<td>18.38</td>
<td>18.55</td>
<td>15.23</td>
<td>14.00</td>
</tr>
<tr>
<td>(26)</td>
<td>(29)</td>
<td>(30)</td>
<td>(31)</td>
<td>(26)</td>
<td>(24)</td>
<td></td>
</tr>
<tr>
<td>Non-employed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total research staff</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19.75</td>
<td>24.48</td>
<td>23.43</td>
<td>24.00</td>
<td>21.08</td>
<td>18.88</td>
<td></td>
</tr>
<tr>
<td>(41)</td>
<td>(47)</td>
<td>(49)</td>
<td>(52)</td>
<td>(53)</td>
<td>(49)</td>
<td></td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers also have obligations for patient care. For the sake of simplicity, a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD students with an employment contract. For non-employed PhD students (student status), expression as FTE is not appropriate.
Research Funding

Research funding has increased steadily in recent years. This has been achieved by an increase in research contracts. The majority of these grants were unrestricted. The realisation of a new experimental cardiology group has required an especially large investment, but it is already paying off.

Table 3.2 Overview of research funding at the level of programme CVC

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Funding: (k€)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct funding (1) (FTE (%))</td>
<td>9.73 (49.24%)</td>
<td>11.65 (47.60%)</td>
<td>10.78 (46.00%)</td>
<td>11.53 (48.02%)</td>
<td>11.93 (56.58%)</td>
<td>9.55 (50.60%)</td>
</tr>
<tr>
<td>Research grants (2) (FTE (%))</td>
<td>1.40 (7.09%)</td>
<td>1.75 (7.15%)</td>
<td>1.58 (6.72%)</td>
<td>1.05 (4.38%)</td>
<td>0.00 (0.00%)</td>
<td>0.00 (0.00%)</td>
</tr>
<tr>
<td>Contract research (3) (FTE (%))</td>
<td>8.63 (43.67%)</td>
<td>11.08 (45.25%)</td>
<td>11.08 (47.28%)</td>
<td>11.43 (47.60%)</td>
<td>9.15 (43.42%)</td>
<td>9.33 (49.40%)</td>
</tr>
<tr>
<td>Total funding</td>
<td>19.75 (100%)</td>
<td>24.48 (100%)</td>
<td>23.43 (100%)</td>
<td>24.00 (100%)</td>
<td>21.08 (100%)</td>
<td>18.88 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expenditure: (k€)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel costs (k€)</td>
<td>870.0</td>
<td>1,093.4</td>
<td>1,145.4</td>
<td>1,205.8</td>
<td>1,174.8</td>
<td>1,082.3</td>
</tr>
<tr>
<td>Other costs personnel (k€)</td>
<td>335.0</td>
<td>421.0</td>
<td>441.0</td>
<td>464.3</td>
<td>452.4</td>
<td>416.7</td>
</tr>
<tr>
<td>Costs non-employed PhD students (k€)</td>
<td>39.9</td>
<td>49.1</td>
<td>58.4</td>
<td>79.7</td>
<td>72.5</td>
<td>171.0</td>
</tr>
<tr>
<td>Other costs non-employed PhD students (k€)</td>
<td>21.3</td>
<td>25.5</td>
<td>29.8</td>
<td>40.4</td>
<td>36.1</td>
<td>76.5</td>
</tr>
<tr>
<td>Total expenditure</td>
<td>k€1,266.1</td>
<td>k€1,589.0</td>
<td>k€1,674.6</td>
<td>k€1,790.3</td>
<td>k€1,735.9</td>
<td>k€1,746.5</td>
</tr>
</tbody>
</table>

Explanation: The expenses for research include both personnel and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the donation to the provision “wachtgelden” (i.e. the obligation to provide personnel with a reduced pay in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff and other costs like allowances for child care, and commuter traffic. Although non-employed PhD students do not represent research FTE, the costs of these PhD students have been included. Other costs include operational costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

1 Direct funding by the university;
2 Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programmes ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3 Funding for specific research projects obtained from external organisations, such as industry, governmental ministries, European Commission (Framework programmes) and charity organizations.

Strategy and policy

During the previous peer review, it was observed that the CVC had a limited staff, which was perhaps too small to meet the ambitions of the institute. With the addition of new structural chairs, the critical mass of the institute has increased and has been attracting more young researchers. It is expected that even more chairs supporting the research goals of the CVC will be established in the near future.

There has been a clear trend of diminished availability of money for unrestricted grants in collaboration with the pharmaceutical industry. Therefore, the CVC is focusing more and more on identifying and investing in young researchers with high potential. At an early phase, individual programmes are designed to link up with the programmes available through government or governmental institutes to support young talent. Creating more postdoctoral positions will support the strategy of creating career programmes for young researchers with high potential. Approximately 50% of our PhD students have spent at least one year doing research outside the Netherlands. At present, the strategy of investing in young talent has been rewarded with eight personal grants from the Dutch Heart Foundation and three major grants from the NWO.
Section 3.3: Research Environment and Embedding

Relationships with academia – national
The Cardiovascular Centre is part of the Graduate School GUIDE. The research team is formed by members of various departments, including the Thorax Centre, Paediatric Cardiology, Pathology, and Internal Medicine. At the national level, there is a great deal of collaboration with almost all eight medical schools in the Netherlands. This extensive network largely due to the fact that several CVC staff members are coordinators of national clinical trials. In addition, CVC researchers are active in projects at the Interuniversity Cardiology Institute of the Netherlands (ICIN), which is a KNAW institute and a consortium of all eight University Medical Centres in the Netherlands. Prof. Van Veldhuisen, Prof. Van Gelder and Prof. Zijlstra are members of the scientific board of the ICIN. Prof. van Gilst is co-director of the ICIN. Several staff members have positions on scientific committees of the Dutch Heart Foundation. For details, see appendix Section 3.3.

In GUIDE and the ICIN, collaborative projects with various groups are ongoing and have a structural character, as evidenced by joint publications and joint PhD research projects.

Relationships with academia – international
The leadership of the CVC is closely involved with the international heart failure research community. Members of the CVC hold positions on the board of the Heart Failure Society of the European Society of Cardiology, positions on national and European guideline committees, editorial positions with important cardiovascular journals and positions as principal investigators or steering committee members in important international clinical trials. In addition, the editorial office of the Journal of Heart Failure will be located at our institution from 2010 to 2015. For details, see appendix Section 3.3.

Relationships with industry
The mission of the CVC – to develop effective treatment strategies for heart failure – has induced collaboration at many levels with pharmaceutical and biotech companies. Several companies have provided research funds through structural and long-standing collaborations (e.g. Medtronic, Bristol-Myers Squibb, Astra Zeneca, MSD, Merck, Sanofi Aventis, Pfizer). In the past, the group has collaborated with other centres and sponsors in many clinical studies to evaluate the effectiveness and safety of new compounds and new non-pharmacological treatment strategies in the treatment of heart failure and atrial fibrillation. These studies were either designed by the group itself or were part of larger multinational programmes. Several staff members have served as principal investigators or national coordinators for these studies. Consequently, they have been members of many international steering committees. For details, see appendix Section 3.3.

Relationships with non-profit organisations
These relationships have been limited mostly to board positions at cardiovascular foundations such as the Vascular Biology Working Group and the Netherlands Foundation of Cardiovascular Excellence. In addition, staff members have been involved in local initiatives like ERIBA and Lifelines. For details, see appendix Section 3.3.

Strategy and policy
The CVC leadership believes strongly in collaborative research. PhD students are actively advised to seek collaboration with colleagues from other groups (at both the national and international levels). With this strategy, an active network has been developed over the years, and CVC members have obtained powerful positions with influential international bodies. Young staff members are encouraged to take positions on relevant committees. In this way, an active role for the CVC in the heart failure field has been secured for at least the next five years.
Section 3.4: Quality and Scientific Relevance

Most important results and key publications

1. Clinical programme on heart failure
For the last 15 years, heart failure has been the main research topic at the Department of Cardiology. Heart failure is a growing health problem, because it is the only cardiovascular disorder that is still increasing in incidence and prevalence. In Groningen, clinical research into heart failure has gradually shifted from an emphasis on pharmacologic interventions to studies on pathophysiology, epidemiology and genetics/genomics. Clinical heart failure research currently focuses on a broad spectrum of subjects. These range from studies which evaluate the effect of nurse-led interventions in heart failure to more sophisticated and in-depth studies, which focus on, for example, genetic predisposition and molecular changes in heart failure.

Important achievements of the clinical programme during the last three years include:

- The completion of a large national study on the effects of a nurse-led intervention in heart failure (COACH).
- Expansion of the strong research line on cardiorenal interaction in heart failure. A new chair was created to lead this group, and important publications have resulted from these investments.
- In accordance with the highly translational character of the research within the CVC, clinical studies on the effect of erythropoietin have been initiated.
- In line with the central theme of the UMCG, the CVC has started to look at the aging aspects of heart failure. Our work has focused on telomere length in heart failure, and important new observations on this topic have been reported by researchers from the CVC.

Publications:


2. Experimental programme on heart failure
The most important change in recent years has been the creation of a new lab for dedicated cardiovascular research. This lab has state-of-the-art equipment for molecular and physiologic work. Furthermore, a new cell culture facility with a cell stretch apparatus has been acquired to specifically study the process of hypertrophy. Since the experimental research had been using more and more transgenic mouse models, equipment for functional measurements in mice (including a dedicated echo facility) was obtained. For preclinical studies on pathophysiology and therapy for heart failure, the mouse and rat models of myocardial-infarction-induced left ventricular dysfunction and aortic banding were used. In these models, heart failure was studied from a molecular level to measurements of in vivo cardiac function. Studies in cell cultures and measurements of vascular function in isolated blood vessels completed the broad spectrum of available tools. During the last 20 years, the CVC has established a good track record in studies related to the renin-angiotensin system. Presently this work is focusing on the regulation of renin production and release. Furthermore, the role of the (pro)renin receptor in the heart is being studied.
Since 2003, an important line of research has been the studies on the cardioprotective effects of erythropoietin in heart failure. Many publications from CVC researchers have led the international field. At present, new studies have been initiated on genes identified by our group which play an important role in the development of hypertrophy.

**Publications:**

3. Programme on atrial fibrillation, with a focus on atrial fibrillation in heart failure

The research topic in this line is atrial fibrillation with or without heart failure. Since only 30% of patients maintain sinus rhythm for four years after electrical cardioversion, this programme studies (a) how to improve rhythm control therapy (i.e. serial electrical cardioversions), (b) whether rate control (i.e. acceptance of atrial fibrillation) is an alternative for rhythm control, and (c) the reciprocal relationship between heart failure and atrial fibrillation.

First, with regard to the improvement of rhythm control, the importance of electrical remodelling for atrial fibrillation has been shown in several patient studies. Important molecular, protein and ultrastructural changes in tissue of patients with atrial fibrillation were also observed, which may relate to the fact that ‘atrial fibrillation begets atrial fibrillation’. This may provide new opportunities for pharmacological interventions to prevent or adequately suppress atrial fibrillation. Second, it has been studied whether prevention of remodelling improves the outcome of rhythm control. Third, it has been studied whether episodic amiodarone prophylaxis is associated with a lower morbidity and higher quality of life compared to chronic amiodarone, while atrial fibrillation is still suppressed.

Rate control is not inferior to rhythm control. The RACE study showed that rate control is not inferior to rhythm control in terms of morbidity and mortality. New studies focused on (a) new treatment strategies for improving suppression of atrial fibrillation, especially in the setting of heart failure including new, non-pharmacological tools, (b) adequate rate control to prevent or slow the progression of heart failure or, c) prevention of atrial fibrillation in patients at risk for atrial fibrillation – patients with heart failure and/or hypertension, d) further identification of proteins and pathways involved in the genesis of the substrate for atrial fibrillation generating new pharmacological treatment strategies.

**Publications:**

4. Programme on congenital heart disease and pulmonary hypertension, with a focus on right ventricular failure

Clinical projects have included epidemiological and genetic research in pulmonary hypertension (paediatric and adult), assessment of new diagnostic tools and treatment modalities for patients with pulmonary hypertension or right ventricular failure in congenital heart disease, and studies on cardiovascular consequences of pregnancy in women with congenital heart diseases. The latter has generated new findings in the largest database available on this topic.

Experimental research projects focused on the molecular mechanisms of the myocardial and pulmonary vascular adaptation to abnormal loading conditions and its relationship to function. We used rat and mouse models of pressure
and volume overload. Different advanced techniques were used to study the adaptive mechanisms at functional, morphological and molecular levels, including small animal echocardiography, MRI and invasive pressure-volume loops.

**Publications:**


**High-quality publications**

The top 10% and 30% of relevant publications are summarised in Table 3.3 and have been noted in appendix Section 3.5.

<table>
<thead>
<tr>
<th>CVC</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td>(n of articles)</td>
</tr>
<tr>
<td>Belongs to the best 10%</td>
<td>45%</td>
<td>41%</td>
<td>29%</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>of a relevant subject area</td>
<td>(37)</td>
<td>(47)</td>
<td>(35)</td>
<td>(20)</td>
<td>(20)</td>
</tr>
<tr>
<td>Belongs to the best 30%</td>
<td>72%</td>
<td>70%</td>
<td>69%</td>
<td>61%</td>
<td>55%</td>
</tr>
<tr>
<td>of a relevant subject area</td>
<td>(59)</td>
<td>(80)</td>
<td>(84)</td>
<td>(60)</td>
<td>(62)</td>
</tr>
</tbody>
</table>

**Explanation:** A ranking for publications present in the on-line database ‘ISI Web of Knowledge’, sub-database ‘Web of Science’ can be calculated and is presented here. Papers are categorised based on the journal in which they appear. Approximately 175 subject areas have been designated (ISI-fields). The percentages are calculated based on the number of journal titles in the subject area. Papers published in subject areas relevant to the research programme are included in this analysis. According to the methodology of bibliometric analysis, only papers of the reference types ‘Article’, ‘Note’, ‘Letter’, ‘Review’, and ‘Proceedings paper’ are considered. This implies that references of the type ‘Editorial material’, ‘Book (review)’, ‘Correction’, ‘Meeting abstract’, ‘Conference proceeding’, ‘In memoriam’, ‘News item’ ‘Biographical item’, etc., are not included.

**Strategy and Policy**

Although the output has increased over recent years, the percentage of high quality papers has declined slightly. This requires special attention from the leadership of the CVC. Part of the explanation may be the larger influx of international PhD students. Some of these students have problems adapting to the Dutch system, and this reduces their period of effective production. In order to complete their thesis, their work is often submitted at a premature stage to lower impact journals. More careful selection could be a solution for this problem.

The leaders of the various sub-programmes have above-average publishing quality ratings, as shown by the often used international individual quality indicator, the H-index. These are the scores for the respective programme leaders:

- D.J. van Veldhuisen 45
- W.H. van Gilst 45
- H. Hillege 33
- I.C. van Gelder 33
- F. Zijlstra 32
- H. Snieder 29
- T. Ebels 20
- R.M.F. Berger 11

It is the task of these programme leaders to transfer this publishing quality to their co-workers when reporting the results of the various research projects.
Section 3.5: Quantity of Scientific Output

Overview of the results

Table 3.4 shows the scientific output of the CVC. Output has increased, but as was discussed in the previous section, the quality of publication has not kept pace with this trend. A partial explanation might be that several new areas of research were started during this period. All publications are listed in appendix Section 3.5.

Table 3.4 Main categories of research output at the level of programme CVC

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refereed articles</td>
<td>78</td>
<td>106</td>
<td>134</td>
<td>153</td>
<td>142</td>
<td>163</td>
</tr>
<tr>
<td>PhD theses</td>
<td>8</td>
<td>5</td>
<td>16</td>
<td>8</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>Patents</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total publications</td>
<td>88</td>
<td>112</td>
<td>153</td>
<td>161</td>
<td>159</td>
<td>176</td>
</tr>
<tr>
<td>Books and book chapters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

Number of PhD students

Table 3.5 Number of PhD students

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PhD students per year</td>
<td>26</td>
<td>32</td>
<td>34</td>
<td>36</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>employed</td>
<td>23</td>
<td>29</td>
<td>30</td>
<td>31</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>non-employed</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>% non-employed</td>
<td>11.54</td>
<td>9.38</td>
<td>11.76</td>
<td>13.89</td>
<td>25.71</td>
<td>29.41</td>
</tr>
</tbody>
</table>

Contribution to books or book chapters

Several staff members have contributed to books in the field of cardiology and cardiovascular disease. Due to the fact that the research area in which the CVC is active is rapidly changing over time, more energy has been devoted to publication in high impact journals than in textbooks with a relatively short half life.

Patent applications

In recent years, the UMCG has given more attention to the protection of intellectual property (IP) generated by its researchers. Support for patent applications has also been organised. This has certainly created more awareness within the CVC that the sub-programmes are generating patentable IP. Since 2000, thirteen patents have been generated, including the seven patent application filed in this reporting period. This number will certainly increase in the near future.
Section 3.6: Earning Capacity

**Fund raising strategy and support**
There was a clear trend of diminished availability of funding for unrestricted grants in collaboration with the pharmaceutical industry. Therefore, the CVC focused more and more on identifying and investing in young researchers with high potential. This was accomplished by designing individual programmes at an early stage to link up with the programmes available through government or governmental institutes to support young talent. Approximately 50% of our PhD students have spent at least one year of research abroad. At present, the strategy of investing in young talent has been rewarded with eight personal grants from the Dutch Heart Foundation and three major grants from the NWO.

**Results**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total funding FTE (%)</th>
<th>Allocated funding FTE (%)</th>
<th>Acquired funding FTE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>100% (22.25)</td>
<td>20.90% (4.65)</td>
<td>79.10% (17.60)</td>
</tr>
<tr>
<td>2004</td>
<td>100% (27.48)</td>
<td>16.92% (4.65)</td>
<td>83.08% (22.83)</td>
</tr>
<tr>
<td>2005</td>
<td>100% (26.93)</td>
<td>17.27% (4.65)</td>
<td>82.73% (22.28)</td>
</tr>
<tr>
<td>2006</td>
<td>100% (28.75)</td>
<td>17.57% (5.05)</td>
<td>82.43% (23.70)</td>
</tr>
<tr>
<td>2007</td>
<td>100% (25.33)</td>
<td>21.52% (5.45)</td>
<td>78.48% (19.88)</td>
</tr>
<tr>
<td>2008</td>
<td>100% (27.88)</td>
<td>16.05% (4.48)</td>
<td>83.95% (23.40)</td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are funded directly by the University of Groningen and/or the UMCG (allocated funding). To extend their research capacity, they acquire grants via internal and external competition (acquired funding) for non-tenured staff, employed PhD students, non-employed PhD students and in some cases a limited number of staff positions. The fund raising capacity is expressed in research FTE.
Section 3.7: Academic Reputation

Academic reputation - Awards and prizes
The CVC has been successful in recent years in obtaining personal grants from the Dutch Heart Foundation. These grants have included clinical investigatorships, support grants for students prior to and during their training in cardiology, and a junior staff position. In addition, five one-year travel stipends for postdocs were obtained from the ICIN. A VENI stipend from the NWO was also acquired (see appendix Section 3.7).

Academic reputation – Editorships in academic journals
CVC staff members hold positions as chief editors (2) and editors (12) of many journals in cardiovascular research (see appendix Section 3.7).

Academic reputation – Memberships of Academies and on Scientific Boards
Staff members of the CVC have been active on national boards of the Dutch Heart Foundation and the ICIN. Participation of CVC staff members in heart failure networks across Europe and beyond has also been part of the strategy to stay up-to-date with frontline drug development and will therefore be strengthened. Staff members have contributed to several institutional boards of the European Society of Cardiology. Recently, the editorial office of the European Journal of Heart Failure was moved to Groningen, and many CVC staff members are playing important roles on the editorial board of this journal (see appendix Section 3.7).

Academic reputation – Invitations to address major conferences
The members of the programme have received 70-80 invitations per year to lecture. These lectures have been contributions to major international and national cardiovascular conferences and to international and national educational programmes (see appendix Section 3.7).
Section 3.8: Societal Relevance

Societal Quality and Societal Impact
The rate of heart failure is increasing in our society. Heart failure is a disease that is continually rising in incidence and prevalence, and thus greatly affects the population as a whole. Therefore, the group goal has been to develop novel therapeutic strategies for the early prevention and treatment of heart failure. Such strategies are useful in helping identify causes of disease occurrence and the population at risk.

In today’s society, people’s lives are dominated by poor lifestyle choices, making the need for research into and the development of treatments of cardiovascular diseases even more important. Educating society about various preventative methods will not only increase awareness of heart failure, but also prevent and reduce disability and death caused by heart failure. It is essential to develop new strategies to improve individual health and minimise the economic and social burdens caused by heart failure. Results from the present programme may have helped to develop diagnostic techniques, medical treatment and surgical advances that save and improve lives every year. Furthermore, recent technological advances in non-pharmacological treatment options for heart failure have given us the opportunity to find new solutions that not only improve prognosis, but also the quality of life.

To effectively manage the importance of therapy, members of the programme have frequently been speakers at national research organisations, institutes, non-profit health organisations and patient groups. These presentations have aimed to identify new developments in treatment and prevention, the optimal use of existing therapies and/or optimising heart failure management in clinical practice. Through this programme, the group members have been able to educate society about the risk factors (i.e. high-fat diets, lack of physical activity or smoking) of heart failure and recent findings about the disease. The programme has also been able to inform patients about various therapies available and the importance of adherence to therapy for those individuals affected with a heart-related disease.

In keeping with current trends, group members have also been involved in post-academic teaching in cardiology, internal medicine and primary care. With their knowledge, they have contributed to several scientific boards of institutes, non-profit organisations and pharmaceutical companies. The group has found it essential to be actively involved in a variety of organisations and institutes so they could stay informed about the scientific needs of those organisations. This has enabled the members to relay new information to society and to maintain constant interaction between hospitals, industry, organisations and patient groups, which has brought ample opportunity for new research projects. By studying effective educational programmes and other programmes to optimise care, the programme has sought to maximise the impact of the efforts to inform society (doctors and patients as well as the general population).

Valorisation
In 2008, a large national programme on heart failure was started. This programme, TRIUMPH, was funded by government, universities and industry. The total budget was approximately €16 million, and the programme will run for five years. The aim of the programme is to find, evaluate and valorise new biomarkers and genes for the early detection and risk classification of patients with heart failure. Prof. Hillege heads the clinical part of the study.

Furthermore, plans are currently being developed to further characterise the findings as described in the patents filed by the CVC.
Section 3.9: Next Generation

With regard to the education offered through GUIDE, please refer to the main part of the GUIDE evaluation.

The quality and output of research and teaching activities have been continuously evaluated. Targets have been determined for the year to come and arrangements made for the training that follows.

Recently, a procedure was developed to monitor the progress of PhD students. Every year (of their four-year appointment), PhD students have an interview with their supervisor and the scientific coordinator. The research progress is evaluated as well as the progress of the PhD training programme. Special attention is given to potential problems that might have arisen for the PhD student. The aim is quality assurance, to prevent the PhD training period from becoming excessively long, and to protect the PhD student from future trouble with unemployment.

The coordinators of the Cardiovascular Centre meet every week. Every two months, the project leaders of the different lines meet to discuss progress and to coordinate new initiatives with existing commitments. Applications for the NWO, the Netherlands Heart Foundation and other public funds are also coordinated by this group. The CVC is focusing more and more on identifying and investing in young researchers with high potential. At an early phase, individual programmes are designed to link up with the programmes available through government or governmental institutes to support young talent. Approximately 50% of our PhD students have spent at least one year of research abroad. At present, the strategy of investing in young talent has been rewarded with eight personal grants from the Dutch Heart Foundation and three major grants from the NWO.
Section 3.10: Viability, SWOT and Future Strategy

Viability
The CVC has increased its number of staff positions, especially for full professors. Consequently, the scientific output of the CVC has continued to improve, both in terms of quality and quantity, and according to national surveys, now ranks among the top groups in national and international cardiovascular research. A dedicated centre for experimental cardiology with state-of-the-art facilities has been realised. All efforts have been directed at strengthening the performance of the CVC in accordance with its mission.

The collaboration with the Dept. of Paediatric Cardiology within the UMCG has been re-established and is focusing on right ventricular failure due to congenital heart disease or pulmonary arterial hypertension. International collaboration, both with experimental groups and clinical groups, has continued to increase.

SWOT

Strengths
The leadership of the programme has established a well recognised position in the field of heart failure research. This is shown by the memberships on many scientific boards of working groups on heart failure of national and European Societies of Cardiology. Furthermore, the leaders of the programme are also principal investigators or members of the steering committees for many multinational clinical studies on heart failure. This position in clinical heart failure is coupled with a well-run laboratory in Groningen with excellent state-of-the-art heart failure models. These conditions create an optimal environment for translational medicine. The size of the group and the inter-individual relationships further optimise this link between basic and clinical research. In the topics studied over the past six years, the group has always been able to attain a well-recognised leading position. Examples are: 1) the role of RAS modulation in early post infarction remodelling, 2) the role of ischemia in heart failure and the cardioprotective role of erythropoietin in heart failure, 3) the role of kidney function in heart failure and 4) the rate or rhythm control in atrial fibrillation.

Weaknesses
The limited size of the programme and the strategy to create and maintain an environment for translational medicine reduces the possibility to have a large number of research goals, certainly at the basic level. Therefore, the success of the institute largely depends on the choice of topics and the ability and expertise of the members to study these topics.

The complex organisation of the UMCG, with the co-existence of divisions, departments and institutes, sometimes creates conflicts of interest.

Opportunities
The well-established position of the staff members of the programme in the field of heart failure makes the institute an attractive partner for pharmaceutical industries and other research organisations working on a different aspect of cardiac failure.

The large investments of the UMCG in aging research and the creation of the ERIBA institute will certainly promote heart failure research. In addition, the large population study, LifeLines, will create the opportunity to further study the natural course of heart failure, and the role of genetic factors and the environment on this natural course.

The appointment of new expert staff members has increased the national and international status of the institute. This has already led to an increased influx of graduate and postgraduate students who want to do their training at the institute.

Threats
Maintaining an environment of translational medicine requires a steady influx of physician-researchers. The rapid change in the profile of students entering medical school and the change in training for cardiology will sharply reduce the number of talented candidates for a position at the institute. Furthermore, rapid changes in health care and the curriculum of medical training will divert a substantial amount of energy of the members of the programme away from research.

A significant portion of the research funding for the programme depends on the investment of industry in the search for treatment of heart failure. Despite the urgent clinical need, the present attitude of the government towards the pharmaceutical industry reduces the willingness to invest in high-risk projects. For large pharmaceutical companies, there is a trend towards diverting investments away from the cardiovascular field.

Future Strategy
Based partially on the recommendations of the previous peer review, the CVC has upcaled the research programme of the centre. The decision to develop a dedicated centre for experimental heart failure research (Experimental Cardiology, sub-programme 2) has further facilitated optimal collaboration with both other departments within the UMCG
and those on a national level. The collaboration with the newly created mouse clinic will specifically enable the development of transgenic mice based on clinical gene findings. Strengthening the basic experimental lab and the integration with major European networks are major targets for the coming years.

Furthermore, strengthening the collaboration with Paediatric Cardiology within the UMCG has been successful and has resulted in the formation of sub-programme 4. International collaboration, with both experimental and clinical groups within this programme, is still increasing. All efforts are directed at strengthening the performance of the CVC according to its mission.

Great care has been taken not to jeopardise the coherence of the different parts of the overall programme. It is now time to further strengthen the new initiatives. This will also further improve the quality of publication, which needs attention from the leadership of the institute.

At present, a new generation of future leadership has been identified. It very important that these candidates are well coached and embedded, certainly at the basic level, in the programme.
CHAPTER 4

Groningen Research Institute for Asthma and COPD
Section 4.1: Objective and Research Area

Programme leaders
Prof. W. Timens
Prof. H.M. Boezen (from 15-2-2008)
Prof. D.S. Postma (until 15-2-2008)

Objectives
The mission of Groningen Research Institute of Asthma and COPD (GRIAC) is the multidisciplinary study of all aspects of obstructive airway and pulmonary diseases through interaction between clinicians and fundamental researchers. Research takes place at the interface of fundamental and applied patient-related research. A central goal of the research is to translate fundamental findings into the clinical situation, and vice versa. The main theme is unravelling the underlying mechanisms of the development and progression of airway obstruction, allergy, and airway hyperresponsiveness, and their mutual interactions. These phenomena constitute, in interaction with environmental factors, risk factors for the development of asthma and COPD and are crucial characteristics in their clinical pictures.

Research Area
The focus of research is on asthma and COPD, which involves the sub-programmes:
1. Epidemiology
2. Genomics
3. Pathophysiology and pathogenesis of allergen, smoking and other lifestyle factors, and environment-induced diseases
4. Assessment, modulation and intervention in disease severity, progression and remission.

1) Epidemiological studies on endogenous, environmental and lifestyle risk factors, both in general and patient-based populations, from prenatal onwards to old age.

2) Studies on genes, gene expression and function, molecular mechanisms and gene-gene and gene-environment interactions in disease development, progression, remission, and severity, as well as disease intervention (pharmaco-genomics).

3) In vivo studies in humans and animal models using mice and unrestrained guinea pigs. Investigations include lung function techniques and studies of blood, tissues and/or cells derived from airways or lungs. Furthermore, in vitro studies assess cellular activation and interaction as well as signalling pathways in cells and tissue explants (e.g. lymphocyte subsets, epithelial cells, fibroblasts, intact airway, and smooth muscle preparations). Interactions of different cell types are studied in cells obtained by sputum induction as well as airway and lung tissue obtained by bronchoscopy, by surgical biopsy or autopsy.

4) Disease outcome assessment is being studied with techniques such as exhaled breath analyses and small airway function. In addition, validated questionnaires on Quality of Life, drug side effects, hyperresponsiveness and symptoms are developed for diagnostic purposes as well as outcome assessment. Interventions can be at the level of cell cultures, animal models and clinical studies with targeted therapy.
**Strategy and policy:**
Several adjustments have been made to the programme, partly in response to weaknesses that were noted in the last self-evaluation 6 years ago and partly embracing developments from new areas of research that have opened new horizons in the research field of this group.

The comments in the previous self-evaluation and PRC were: 1) cohesion is important in our multidisciplinary research group and 2) expand the expertise in our research field with particular attention to Molecular Biology.

Note to 1) Multidisciplinary discussions and meetings have continued and new members have been encouraged to take part in these meetings. It is interesting to note that cohesion in the research programme between the various disciplines within GRIAC is even more substantial than during the preceding period.

Note to 2) We have increased the expertise in different fields of asthma and COPD research within GRIAC. Specifically, molecular biology, molecular pharmacology and epidemiology have now been firmly established in GRIAC. Further details about newly appointed staff are given in Section 4.10.

The main strategies to reach our goals are discussed below:

**Genomics**
The availability of genetic techniques and the collaboration with the Department of Genetics (Head: Prof. C. Wijmenga) have greatly extended the genetic sub-programmes, allowing genome-wide association studies, high throughput genetic SNP detection, fine-mapping in relevant chromosomal regions and candidate gene studies. Deep sequencing techniques and analysis strategies are currently being developed. The availability of and collaboration with the bio-informatics group of Prof. Ritsert Jansen is important for adequate data-mining, which is essential for genomics and proteomics research. Since gene-environment interactions are important for understanding complex diseases like asthma and COPD, these have been explored in several sub-programmes, in collaboration with multiple groups in the Netherlands and abroad. This has resulted in gene-environment interaction studies on atopy and asthma, and on COPD onset and progression. The GRIAC group collaborates internationally and takes the lead in some EC-funded FP6 (asthma: GABRIEL) and FP7 (COPD: COPACETIC) projects on genetics of asthma and COPD, and in exploration of specific gene-environment interactions in these projects.

**Molecular biology techniques**
Molecular biology techniques are being used more effectively and widely, and are being introduced when not present (either in our own labs or as part of local facilities; for example, the recently developed custom micro-array development and accompanying data-mining). In vivo and in vitro silencing of genes are now established techniques that are operational at the University Medical Centre and Pharmacy. This has enabled the use of RNAi and pharmacological modulation of membrane and nuclear receptors and signalling proteins. Fundamental to this line of research is the exploration of intracellular pathways relevant for disease development.

**Proteomics**
Proteomic research has added important possibilities to develop disease susceptibility markers and disease progression and intervention tools.

**Clinical studies**
To enable clinical studies that require greater power, continuing and promoting collaboration with general hospitals in the region has expanded the recruitment population. To enhance the quality of the collaboration, local physicians in these hospitals are more involved in the research group and also propose their own studies for discussion in research meetings.

**Healthy ageing**
"Healthy Aging" has been adopted as the main theme for research and clinical profile of the UMCG. An important long-term project within this theme is "LifeLines" a planned 30-year survey on risk factors (obtained by questionnaire, objective physiological data and biological and genomic markers) for disease development, COPD being one of the leading themes. This fits very well with the research agenda of GRIAC, including co-morbidity and systemic manifestations of COPD. We are and will be actively participating in the development of this programme within the UMCG. In addition, we are participating actively in the development of ERIBA, the programme on aging in the UMCG that is important to both fundamental and clinical research developments.
Section 4.2: Composition of the Research Unit

Description of the research unit
The GRIAC staff consists of a multidisciplinary group of researchers who jointly perform transdisciplinary research. The GRIAC staff is relatively young; we do not foresee major changes due to retirement in the coming years. However, within 5-10 years a number of staff members will retire, and the programme leaders of GRIAC will be actively involved in recruiting new young researchers; continuation and reinforcement of all disciplines involved in research on asthma and COPD is considered to be very important. Omitting one area of expertise is a disadvantage for the other disciplines. Prof Postma has appointed two young researchers (clinical and fundamental) as part of her KNAW (Royal Academy of Sciences) grant to strengthen future GRIAC research. Furthermore, the importance of retaining promising young investigators is acknowledged by the University and University Medical Centre organisation, and support has been promised. One aspect of this support is the Tenure Track programme of the UMCG, which allows excellent young scientists to be offered a career perspective. Currently, 4 young GRIAC members are taking part in this programme (see Table 4.1; for details see appendix Section 4.2). The size of the research staff, including the number of PhD students, has been stable throughout the evaluation period. The level of funding has also been stable in recent years (see Table 4.2), despite the enormous drawback of a 3-year absence of funding from the Dutch Asthma Foundation, the main provider of grants in the field of asthma and COPD, which was due to organisational problems at the Foundation. Grants from NWO, ZonMW, “doelmatigheid”, Spinoza prize, De Cock Foundation, Combating Asthma Foundation (Stichting Astma Bestrijding), TI Pharma (a collaboration between government, universities and industry) as well as many unrestricted/educational research grants from industry have been acquired.

Strategy and policy
The programme leaders support research on asthma and COPD and try to open new avenues for research within GRIAC. Their goal is to enhance multidisciplinary collaboration and cross-pollination between the disciplines involved in research on asthma and COPD. Furthermore, they aim to develop enthusiasm about interdisciplinary research among newly appointed members and young investigators, and to optimise the level of knowledge of young investigators and post-docs on all various topics within GRIAC, with the ultimate goal of developing a new pool of researchers for the future. The structure within GRIAC is described below.

Each employee regularly has an appraisal interview with his/her supervisor, e.g. following the first year of employment, at the transition from a temporary to a permanent position, or for a promotion to a higher salary scale. Each employee has an annual performance interview with his/her direct supervisor. The quality and output of research and teaching activities are evaluated. Targets are determined for the year to come and agreements are made about training.

In addition, the progress of the PhD projects is monitored externally, for example through the obligatory course for the PhD students on project management of GUIDE that evaluates the research progress and scientific output of the students. The PhD training programme is monitored internally by the direct supervisors and the GUIDE staff. The same training is given to students of the Ubbio Emmius PhD programme who train and perform research; some of these PhD students are from (scientifically) relatively underdeveloped countries inside or outside Europe. Furthermore, research projects have been set up for international students (China, Indonesia, Bulgaria, Greece), students from the European Erasmus Programme. Special attention is given to possible personal problems of the PhD student. The aim is quality assurance, to prevent the PhD periods from becoming excessively long, and to protect the PhD students for future problems with unemployment. In recent years, efforts have been made to start tenure tracks with members of GRIAC:

- Dr. G.H. Koppelman was appointed Assistant Professor and entered the tenure track with a focus on the genetics of asthma. Dr. H.I. Heyink has been training for one year in Toronto to perform research on the role of epithelial cells in pathogenesis of asthma and COPD.
- Dr. M van den Berge was given a 5–year grant by the KNAW professorship fund and will train in Boston, USA, for one year in gene expression profiling.
- Dr. R. Gosens has been training for 2 years at the University of Manitoba, Winnipeg, Canada on a Marie Curie Outgoing International Fellowship from the European Community (2005-2008). In November 2009 he will be appointed as tenure track Assistant Professor in Translational Pharmacology.

In 2003, Dr. M.N. Hylkema was appointed Assistant Professor with a focus on chronic animal models of asthma. Dr. N.H.T. ten Hacken was appointed Associate Professor in 2005 with a main research focus on the pathophysiology of asthma and COPD and on finding new treatment strategies. Dr. A.E.J. Dubois was appointed Professor of Paediatric Allergy in 2005. His main research interest is anaphylaxis and food allergy. Dr. H. Meurs was appointed Professor of Immunopharmacology in 2004. Dr. A.E.J. Dubois was appointed Professor of Paediatric Allergy in 2005 and Professor of Molecular Pharmacology in 2006, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Immunopharmacology in 2004, focussing on signal transduction mechanisms.

In 2003, Dr. M.N. Hylkema was appointed Assistant Professor with a focus on chronic animal models of asthma. Dr. N.H.T. ten Hacken was appointed Associate Professor in 2005 with a main research focus on the pathophysiology of asthma and COPD and on finding new treatment strategies. Dr. A.E.J. Dubois was appointed Professor of Paediatric Allergy in 2005. His main research interest is anaphylaxis and food allergy. Dr. H. Meurs was appointed Professor of Immunopharmacology in 2004. Dr. M. Schmidt was appointed as Rosalind Franklin Fellow in 2005 and Professor of Molecular Pharmacology in 2006, focussing on signal transduction mechanisms. Dr. H.M. Boezen was appointed Professor of Epidemiology in 2008 with a focus on genetic epidemiology of chronic airway diseases.
An overview of the research staff is shown in Table 4.1; for details, see appendix Section 4.2.

Table 4.1  Overview of the research staff at the level of programme GRIAC

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
</tr>
<tr>
<td></td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
</tbody>
</table>

**Tenured staff**

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td>5.57</td>
<td>6.50</td>
<td>8.08</td>
<td>7.80</td>
<td>6.40</td>
<td>6.75</td>
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<tr>
<td>(n)</td>
<td>(17)</td>
<td>(19)</td>
<td>(24)</td>
<td>(23)</td>
<td>(18)</td>
<td>(20)</td>
</tr>
<tr>
<td>Full professors *</td>
<td>.05</td>
<td>2.90</td>
<td>3.18</td>
<td>3.60</td>
<td>3.10</td>
<td>3.30</td>
</tr>
<tr>
<td></td>
<td>(72)</td>
<td>(8+1)</td>
<td>(9+1)</td>
<td>(9+2)</td>
<td>(7+2)</td>
<td>(8+2)</td>
</tr>
<tr>
<td>Associate professors</td>
<td>1.90</td>
<td>1.50</td>
<td>1.70</td>
<td>1.00</td>
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<td>0.45</td>
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<td></td>
<td>(5)</td>
<td>(4)</td>
<td>(5)</td>
<td>(3)</td>
<td>(3)</td>
<td>(2)</td>
</tr>
<tr>
<td>Assistant professors</td>
<td>0.80</td>
<td>1.10</td>
<td>1.20</td>
<td>1.20</td>
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<td>1.20</td>
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<tr>
<td></td>
<td>(2)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
<td>(3)</td>
</tr>
<tr>
<td>Other senior staff</td>
<td>1.00</td>
<td>1.00</td>
<td>2.00</td>
<td>2.00</td>
<td>1.10</td>
<td>1.80</td>
</tr>
<tr>
<td></td>
<td>(3)</td>
<td>(3)</td>
<td>(6)</td>
<td>(6)</td>
<td>(3)</td>
<td>(5)</td>
</tr>
<tr>
<td>Non-tenured staff</td>
<td>4.95</td>
<td>6.75</td>
<td>4.50</td>
<td>5.18</td>
<td>7.20</td>
<td>7.43</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(8)</td>
<td>(5)</td>
<td>(7)</td>
<td>(8)</td>
<td>(9)</td>
</tr>
</tbody>
</table>

**PhD students**

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td>18.55</td>
<td>17.68</td>
<td>17.15</td>
<td>15.05</td>
<td>9.28</td>
<td>10.33</td>
</tr>
<tr>
<td>Employed</td>
<td>18.55</td>
<td>17.68</td>
<td>17.15</td>
<td>15.05</td>
<td>9.28</td>
<td>10.33</td>
</tr>
<tr>
<td></td>
<td>(31)</td>
<td>(28)</td>
<td>(26)</td>
<td>(24)</td>
<td>(17)</td>
<td>(18)</td>
</tr>
<tr>
<td>Non employed</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td></td>
<td>(1/3.13%)</td>
<td>(1/3.45%)</td>
<td>(2/7.14%)</td>
<td>(7/22.58%)</td>
<td>(8/32.00%)</td>
<td>(11/37.93%)</td>
</tr>
</tbody>
</table>

**Total research staff**

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td>23.85</td>
<td>26.23</td>
<td>25.18</td>
<td>22.73</td>
<td>18.78</td>
<td>19.90</td>
</tr>
<tr>
<td>(n)</td>
<td>(55)</td>
<td>(56)</td>
<td>(57)</td>
<td>(61)</td>
<td>(51)</td>
<td>(58)</td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers also have obligations for patient care. For the sake of simplicity a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD students with an employment contract. For non-employed PhD students (student status), expression as FTE is not appropriate.

* In between brackets after the + symbol the number of adjunct and extraordinary professors is given.
### Table 4.2 Overview of the research funding at the level of programme GRIAC

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTE (%)</td>
<td>FTE (%)</td>
<td>FTE (%)</td>
<td>FTE (%)</td>
<td>FTE (%)</td>
<td>FTE (%)</td>
</tr>
<tr>
<td><strong>Funding:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct funding (1)</td>
<td>11.20</td>
<td>12.50</td>
<td>11.48</td>
<td>11.65</td>
<td>9.73</td>
<td>9.75</td>
</tr>
<tr>
<td></td>
<td>(38.29%)</td>
<td>(40.42%)</td>
<td>(38.60%)</td>
<td>(41.57%)</td>
<td>(42.51%)</td>
<td>(39.80%)</td>
</tr>
<tr>
<td>Research grants (2)</td>
<td>3.38</td>
<td>3.53</td>
<td>2.80</td>
<td>2.33</td>
<td>1.25</td>
<td>1.98</td>
</tr>
<tr>
<td></td>
<td>(11.54%)</td>
<td>(11.40%)</td>
<td>(9.42%)</td>
<td>(8.30%)</td>
<td>(5.46%)</td>
<td>(8.06%)</td>
</tr>
<tr>
<td>Contract research (3)</td>
<td>14.68</td>
<td>14.90</td>
<td>15.45</td>
<td>14.05</td>
<td>11.90</td>
<td>12.78</td>
</tr>
<tr>
<td></td>
<td>(50.17%)</td>
<td>(48.18%)</td>
<td>(51.98%)</td>
<td>(50.13%)</td>
<td>(52.02%)</td>
<td>(52.14%)</td>
</tr>
<tr>
<td><strong>Total funding</strong></td>
<td>29.25</td>
<td>30.93</td>
<td>29.73</td>
<td>28.03</td>
<td>22.88</td>
<td>24.50</td>
</tr>
<tr>
<td></td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
</tr>
<tr>
<td><strong>Expenditure:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel costs (k€)</td>
<td>1,374.9</td>
<td>1,638.7</td>
<td>1,705.3</td>
<td>1,652.2</td>
<td>1,489.0</td>
<td>1,623.6</td>
</tr>
<tr>
<td>Other cost personnel (k€)</td>
<td>529.4</td>
<td>631.0</td>
<td>656.6</td>
<td>636.1</td>
<td>573.3</td>
<td>625.2</td>
</tr>
<tr>
<td>Costs non-employed PhD students (k€)</td>
<td>15.9</td>
<td>16.4</td>
<td>20.9</td>
<td>83.9</td>
<td>115.2</td>
<td>171.0</td>
</tr>
<tr>
<td>Other costs - non-employed PhD students (k€)</td>
<td>8.5</td>
<td>8.5</td>
<td>10.6</td>
<td>42.5</td>
<td>57.4</td>
<td>76.5</td>
</tr>
<tr>
<td><strong>Total expenditure</strong></td>
<td>k€ 1,928.7</td>
<td>k€ 2,294.5</td>
<td>k€ 2,393.4</td>
<td>k€ 2,414.7</td>
<td>k€ 2,234.9</td>
<td>k€ 2,496.2</td>
</tr>
</tbody>
</table>

Explanation: The expenses for research include personnel costs and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the donation to the provision “wachtgelden” (i.e. the obligation to provide personnel a reduced pay in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff and other costs like allowances for child care, and commuter traffic. Although non-employed PhD students do not represent research FTE, the costs of these PhD students have been included. Other costs include operational costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

1. Direct funding by the university;
2. Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programmes ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3. Funding for specific research projects obtained from external organisations, such as industry, governmental ministries, European Commission (Framework programmes) and charity organizations.
Section 4.3: Research environment and embedding

Position and reputation

The programme ‘Groningen Research Institute for Asthma and COPD’ (GRIAC) is a division of GUIDE. In GRIAC itself, ongoing collaborative projects with various groups have a structural character, as evidenced by joint publications and joint PhD research projects.

The participants in GRIAC are appointed from the Departments of General Practice, Epidemiology, Pulmonology and Tuberculosis, Paediatrics (Paediatric Pulmonology and Allergology), and Pathology and Medical Biology and the Division of Allergology of the Department of Internal Medicine, as well as the Department of Molecular Pharmacology (Faculty of Mathematics and Natural Sciences).

GRIAC members collaborate locally with several research groups at UMCG (for details, see appendix Section 4.3), including:

- The Department of Genetics (Head: Prof. C. Wijmenga) (Studies on genetics of asthma and COPD)
- The Department of Haematology (Studies on post-receptor lymphocyte pathways in Th-1/Th-2 balance; Prof. E. Vellenga)
- The Department of Oncology (Role of MDR expression in the development of COPD, Prof. E.G.E. de Vries, Oncology Centre)
- The Department of Analytical Biochemistry. (Prof. R. Bischoff, Proteomics)
- Epsylon project: NCG (Prof. R. Sanderman, psychological factors in chronic diseases: Cardiac failure and COPD).
- The Department of Medical Physiology (Prof. H.M.W.G. Boddeke, studies on chemokine receptors)
- Pharmaceutical technology and biopharmacy (Prof. H.W. Frijlink)
- Department Obstetrics and Gynaecology (Dr. T.I.F.H. Cremers, Prof. Dr. B.H.W. Westerink, studies on arginine and Epac specific inhibitors)
- Department of Molecular Neuroscience (Prof. Ulrich Eisel, healthy aging animal models)
- Faculty of Human Movement Sciences (Dr. MH de Greef, studies on physical activity in elderly and chronic diseases).

Staff members of GRIAC are participating in the LifeLines study (Prof. Postma, Dr. Vonk) and the Healthy Ageing initiatives like ERIBA (Prof. Postma, Prof. Boezen) that are ongoing at UMCG.

Within the Netherlands GRIAC collaborates closely with:

- The Department of Pulmonology in Leiden (Sterk (now at AMC, Amsterdam), Hiemstra, Rabe), where the joint GLUCOLD study – funded by a grants from NWO, Dutch Asthma Foundation, Glaxo Smith Kline and the joint universities – has focused on the pathophysiology, pathology and progression of COPD and has led to many publications and 5 theses (one finished thesis, two nearly finished and two in preparation). This is a good example of the added value of our joint research groups within GRIAC, where the Departments of Allergology, Epidemiology, General Practice, Pathology, and Pulmonology all contribute equally and interact mutually. GRIAC also collaborates on muscarinic receptors with the Department of Molecular Pharmacology.
- The Department of Pulmonology at the University Medical Centre Utrecht (Prof. L. Koenderman, Prof. J.W. Lammers) and at Maastricht (Prof. A. Schols and Prof. E. Wouters) who, together with Groningen (Prof. D.S. Postma, Dr. N.T.H. ten Hacken, Prof. W. Timens, Prof. A. van Oosterhout, Prof. H.M. Boezen) lead two Top-Institute Pharma projects on COPD. Both projects relate to fundamental and clinical studies on mechanisms of COPD development and the effects of cigarette smoke in susceptible individuals and on systemic inflammation. Altana/Nycomed, AstraZeneca, GlaxoSmithKline and Numico/Danone are industry partners in these projects.
- IRAS, University of Utrecht (Prof. Brunekreef, Prof. Heederik and Dr. J.M. Wouters)
- GRIAC takes part in the PIAMA study, a collaborative study on risk factors and intervention in these risk factors for development of atopy and asthma. A large birth cohort is being followed to the age of 8 years or older. Participants are the University of Amsterdam (Prof. Aalberse), Groningen (Dr. J. Gerritsen, Dr. G.H. Koppelman, Dr. M.Kerkhof, Prof. D.S. Postma), RIVM (Dr. H.A. Smit), Rotterdam (Prof. J. de Jongste, Utrecht (Prof. B. Brunekreef)).
- Allergenic, a national network for genetics on allergy and asthma. This encompasses three birth cohorts: PIAMA (Prof. B. Brunekreef, Utrecht, Dr. H.A. Smit, Bilthoven), Prof. J. de Jongste (Rotterdam), Dr. J. Gerritsen, Dr. M. Kerkhof, Dr. G.H. Koppelman, Prof. D.S. Postma (Groningen), PREVASK (Prof. O. Van Schayck, Maastricht) and KOALA (Dr. P.C. Thijs, Maastricht).
The staff members of GRIAC all collaborate with many international groups and with industry partners. Several are highlighted below (for details, see appendix Section 4.3).

**European collaborations:**
- European collaboration takes place within the GABRIEL project, which is an EU-funded FP6 multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community. GRIAC is the lead centre for specific work packages (Prof. D.S. Postma, Dr. G.H. Koppelman, Prof. A.J. van Oosterhout, Dr. M.N. Hylkema, Prof. H.M. Boezen). International collaborators are: Prof. W. Cookson (UK), Prof. E. Von Mutius (Germany), Prof. D. Strachan (UK), Prof. J. Henderson (UK), Prof. N. Probst (Switzerland), Dr. F. Kauffmann and Dr. F. Demenais (France), and Prof. M. Kabesch (Germany).
- European collaboration is funded by an FP7 grant on COPD (‘COPD Pathology: Addressing Critical gaps, Early Treatment & diagnosis and Innovative Concepts - COPACETIC‘. GRIAC UMCG is one of the lead centres together with the University of Utrecht (Prof. D.S. Postma, Prof. H.M. Boezen). International collaborators are: Prof. J. Vestbo (Denmark), Prof. E. Nizankowska (Poland) and Prof. H.U. Kauczor (Germany).
- A COPD centre of excellence collaboration has been established which is funded by a non-restricted grant from Glaxo-Smith-Kline. Five European centres are involved: Padua, Palermo, Palma, Maastricht and Groningen. These participants have met yearly for the last four years, and collaborative projects have evolved (Prof. Postma, Prof. Timens, Prof. A.J. van Oosterhout, Dr. I. Heijink). International collaborators are: Prof. M. Saetta (Italy), Prof. E. Wouters (Maastricht), Prof. A. Agusti (Spain), Prof. M. Gjomarkaj (Italy).

**International collaboration outside Europe**
International collaboration outside Europe is maintained with many investigators, (for details, see appendix Section 4.3), as illustrated in number of joint publications:
- The University of Hamilton, Canada (O’Byrne), University of Manitoba, Winnipeg, Canada (Halayko), Harvard University, USA (S.T. Weiss), University of Baltimore/ Wake Forest University, USA (Bleecker, Meyers, Penn), University of British Columbia (Hogg, Paré), Boston University (Spira), University of Nevada, USA (Gerthoffer), Monash University, Melbourne Australia (Hirst), University of Singapore (Tran), University Beijing (Han).

**Relations with companies and non-profit organisations**
Several industry partners have awarded grants to research-projects within GRIAC. Such projects must be compatible with the sub-programmes of GRIAC. Consequently, the studies usually involve drug studies (evaluating asthma and COPD management). Care is taken to always enhance the quality of the studies and where possible to add fundamental scientific questions to the research plans by discussing the study protocols at research meetings. This strengthens the patient oriented, fundamental scientific research within GRIAC.

Companies with which GRIAC collaborates include:
- ALK (De Monchy), Altana (Nycomed) (the Netherlands and Switzerland; Postma, Kerstjens, Van der Molen), AstraZeneca (the Netherlands and Sweden; Ten Hacken, Heijink, Hylkema, Kerstjens, Van der Molen, Postma, Timens, Van Oosterhout, Zaagsma, Meurs), Boehringer Ingelheim (the Netherlands and Germany; Ten Hacken, Kerstjens, Postma, Zaagsma, Meurs, Gosens), Chiesi (ten Hacken, Postma, van den Berge), Glaxo Smith Kline (the Netherlands and the UK; Duiverman, Gerritsen, Koppelman, Ten Hacken, Van den Berge Kerstjens, De Monchy, Postma, Timens, Van Oosterhout, Heijink), MSD (the Netherlands and the USA; Duiverman, Van der Molen, Postma, Timens, Novartis (in Switzerland and the UK; Postma, Van Oosterhout), Numico/Danone Research (Wageningen, Duiverman, Dubois, De Monchy, Postma, Ten Hacken), Organon/Schering-Plough (the Netherlands and the USA, Kerstjens, Postma, Zaagsma Meurs, Maarsingh, Van Oosterhout), Philips (the Netherlands, De Monchy), Philips/Respironics (Wijkstra), Resmed (Wijkstra), HAL Allergy (Haarlem, the Netherlands; van Oosterhout), Citeq (Groningen, the Netherlands; van Oosterhout), Neurosearch (Denmark, van Oosterhout), Decode Iceland (Postma, Koppelman, Boezen).
- Top Institute Pharma projects: TIP1-108 (Kerstjens, Ten Hacken, Postma, Timens, Boezen, Oosterhout, Bischoff) collaboration with Nycomed and GSK. In TIP1-201 (Kerstjens, Timens, Postma, Boezen, Oosterhout, Ten Hacken) with Nycomed, Glaxo Smith Kline, Astra-Zeneca, Danone).

All GRIAC members also collaborate closely with the Dutch Asthma Foundation, with J.K. de Cock Foundation, Stichting Astma Bestrijding, and the National Institute of Health (USA). Furthermore, GRIAC has participated in the development and world-wide implementation of guidelines for management of COPD. This also applies to the development of guidelines for asthma management in the Netherlands (adult and paediatric asthma), and the development of two guidelines for COPD (disease management and medical management).
Guest researchers

Every year at GRIAC, 10-15 guest researchers give lectures or workshops, participate in research or are appointed visiting professor on their own request.

These guest researchers (for details, see appendix Section 4.3) have included:

- Prof. B. Lambrecht, Univ. Ghent, Belgium
- Prof. Holgate, University of Southampton, School of Medicine Southampton UK
- Prof. D.S. Meyers, Prof. E. Bleecker, Wake Forrest University of Winston-Salem USA
- Prof. H. Ross Anderson, Dept. of Community Health Sciences, St. George’s Hospital, London
- Prof. S.J. Hirst, Monash University, Melbourne Australia
- Prof. T. Bai, Vancouver University, Canada
- Prof. L.M. Fabbri, Dept. Pulmonary Diseases University of Modena and Reggio Emilia Modena, Italy
- Prof. Peter LeSouef, University Western Australia, Perth, Australia
- Prof. Fernando Martinez, Arizona Respiratory Center, Arizona Health Sciences Center, and Dept. of Pediatrics, University of Arizona, Tuscon Arizona, USA
- Prof. A.J. Halayko, University of Manitoba, Canada
- Prof. James C. Hogg, Dept. of Pathology and Laboratory Medicine, University of British Columbia and iCapture Centre, St. Paul’s Hospital, Vancouver, Canada

Strategy and policy

In response to the last QANU Peer Review Committee, we fully agree with the remark in the conclusion of the QANU evaluation that cohesion is important to our multidisciplinary research group. Multidisciplinary discussions and meetings have been continued, and new members have been encouraged to take part in these meetings. Cohesion in the research programme of the different disciplines within GRIAC is now even more substantial than during the preceding period. At this time, findings from animal models are being translated to human settings and vice versa. Other projects relate findings in signal transduction to genetics in asthma and COPD, with appropriate gene-environment interaction as suggested by previous findings. Thus, a homogeneous research programme spanning all disciplines is now envisaged.

New research projects are actively embedded in main sub-programmes of GRIAC.

Whenever external grant applications are submitted, general discussions are held about whether the research is compatible with our sub-programmes. Furthermore, during a twice-yearly retreat of the GRIAC staff and post-docs, we set goals for implementing new research as part of the existing research questions.

Many national and international connections are maintained due to the extensive network of the GRIAC principal investigators. This network is actively supported by attending national and international conferences and visiting other institutes. GRIAC members have been invited to join several industry advisory boards and scientific organisations. Senior members encourage junior members and trainees to visit and participate in the above meetings and introduce them to their networks, thus supporting continuity and expansion of these networks over time. The continuous establishment and dynamic support of the scientific network of GRIAC, in combination with the recognised international scientific quality, allows for easy recognition of mutual interests and development of collaborative research projects and grant proposals.
Section 4.4: Quality and Scientific Relevance

Most important results

1. Epidemiology
   - Role of ADAM33 in lung function decline in patients with asthma and in the general population, and development of COPD.
   - Defining asthma remission based only on symptoms and medication use overlooks subjects with subclinical active disease and possibly associated airway remodelling.
   - Prematurity predicts airway obstruction, low CO diffusing capacity and lower exercise level, which might be due to impaired physical fitness.
   - Identification of GCLC as a novel susceptibility gene for low level of lung function in the general population, acting through interaction with smoking and low vitamin C intake.
   - Airway obstruction should be defined by FEV(1)/FVC and FEV(1) being below the LLN using appropriate reference equations.
   - High birth weight and day care attendance increase the risk of atopic dermatitis in the first year of life, while exclusive breastfeeding is a protective factor when dermatitis is found on inspection.

2. Genomics
   - Association of SNPs in ADAM33 and AHR and airway inflammation in COPD patients.
   - Lymphocytes of subjects bearing the CysGlyGln haplotype of the beta2-adrenoceptor at position 19 of the 5' leader cistron and positions 16 and 27 of the receptor, respectively, have increased susceptibility to beta-agonist-induced desensitisation and reduced beta-agonist-induced inhibition of Th2- cytokine production.
   - Association of SNPs in arginases 1 and 2 with asthma susceptibility, asthma severity (lung function, airway hyperresponsiveness) and responsiveness to beta2-agonists and glucocorticosteroids.
   - Linkage of chromosomes 3p and 5q with asthma susceptibility genes.
   - Association of IL1RL1, IL18R1, and IL18RAP gene cluster polymorphisms with asthma and atopy.
   - Mrp1/Mdr1a/1b knock-out mice have reduced inflammatory response to cigarette smoke, and expression levels of several cytokines and chemokines are lower in lungs of Mrp1/Mdr1a/1b knock-out mice independent of smoke exposure.

3. Pathophysiology and pathogenesis of allergen, smoking and other lifestyle factors, and environmental-induced diseases
   - Evidence for a central role of arginase in the pathophysiology of allergic asthma.
   - Muscarinic receptor stimulation promotes airway smooth muscle proliferation in response to growth factors, demonstrating a novel pathological action of acetylcholine airway remodelling in asthma.
   - Modulation of airway smooth muscle phenotype and function by receptor tyrosine kinases, G-protein-coupled receptors and integrins.
   - Modulation of inflammatory and contractile properties of airway smooth muscle cells by the cAMP effector Epac.
   - Development of several mouse models for asthma (ovalbumin and house dust mite) and COPD.
   - Up regulatory and down regulatory effects of cigarette smoke on inflammatory parameters in mice and humans.
   - Role for the B cell in pathogenesis of COPD.
   - Role of epithelial cells and fibroblasts in the pathogenesis of asthma and COPD.

4. Assessment, modulation and intervention in disease severity, progression and remission
   - Inhalation of the Rho kinase inhibitor Y-27632 protects against allergen-induced bronchoconstriction, airway hyperresponsiveness and inflammation in an animal model of allergic asthma.
   - Chronic ventilation enhances effects of rehabilitation in COPD GOLD IV stage.
   - Smoking affects the protecting role of steroids in asthma.
   - A specific cytokine agonist, anti-TNF, is ineffective on COPD in the short term.
   - Ongoing inflammation after smoking cessation in COPD.
   - Immunotherapy improves health-related quality of life in yellow jacket allergic patients.
   - Development of methodology for validation of blinding of challenge materials for double blind food challenges and quality of life instruments for patients with food allergy.
   - VitD3 as adjuvant for allergen immunotherapy; resulted in translational clinical trial (Vital study).
   - Development of Clinical COPD Questionnaire (CCQ).
Key publications
For full-text publications, see appendix Section 4.4.

1. Epidemiology

2. Genomics
- Reijmerink NE, Postma DS, Bruinenberg M, Nolte IM, Meyers DA, Bleecker ER, Koppelman GH. Association of IL1RL1, IL18R1, and IL18RAP gene cluster polymorphisms with asthma and atopy; J Allergy Clin Immunol. 2008; 122: 651-654.
- van der Deen M, Timens W, Timmer-Bosscha H, van der Strate BW, Scheper RJ, Postma DS, de Vries EG, Kerstjens HA. Reduced inflammatory response in cigarette smoke exposed Mrp1/Mdr1a/1b deficient mice. Respir Res. 2007 Jul 7;8:49.

3. Pathophysiology and pathogenesis of allergen, smoking and other lifestyle factors, and environment-induced diseases


4. Assessment, modulation and intervention in disease severity, progression and remission.


High quality publications
During the evaluation period, the output of GRIAC has increased considerably. Since the size of the research staff over the evaluation period remained stable, this implies an increased number of papers per staff member. In addition, the output of GRIAC maintained its share in top 10% and top 30% of publications (see Table 4.3.). All top publications have been marked in appendix Section 4.5.

Table 4.3 Number of papers published in the top 10% and 30% of relevant disciplines

<table>
<thead>
<tr>
<th>GRIAC</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td>(n of articles)</td>
<td>(n of articles)</td>
</tr>
<tr>
<td>Belongs to the best 10% of a relevant subject area</td>
<td>30%</td>
<td>41%</td>
<td>35%</td>
<td>33%</td>
<td>38%</td>
</tr>
<tr>
<td>of a relevant subject area</td>
<td>(13)</td>
<td>(23)</td>
<td>(23)</td>
<td>(25)</td>
<td>(24)</td>
</tr>
<tr>
<td>Belongs to the best 30% of a relevant subject area</td>
<td>82%</td>
<td>68%</td>
<td>53%</td>
<td>77%</td>
<td>65%</td>
</tr>
<tr>
<td>of a relevant subject area</td>
<td>(36)</td>
<td>(38)</td>
<td>(35)</td>
<td>(58)</td>
<td>(41)</td>
</tr>
</tbody>
</table>

Explanation: A ranking for publications present in the on-line database ‘ISI Web of Knowledge’, sub-database ‘Web of Science’ was calculated and is presented here. Papers are categorised based on the journal they appear in. Approx. 175 subject areas have been designated (ISI-fields). The percentages are calculated based on the number of the journal titles in the subject area.

Section 4.5: Quantity of Scientific Output

Overview of the results
During this programme period there has been an increase in publications, which has been stable for the last three years. During the entire period, GRIAC has been able to maintain the percentage of top 10% and top 30% publications (see Section 4.4). There has been a small increase in number of theses (see Table 4.4; all publications are listed in appendix Section 4.5).

Publication strategy
Publication strategies were discussed by the Board of GRIAC and during meetings with junior scientists to make them aware of the relevance (and limitations) of impact factors, citations and the most important journals in the GRIAC disciplines. This included promoting awareness of criteria and relevance, as well as rewards for achieving full membership in GUIDE.

Number of publications

Table 4.4 Main categories of research output at the level of programme GRIAC

<table>
<thead>
<tr>
<th>Category</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refereed articles</td>
<td>54</td>
<td>59</td>
<td>67</td>
<td>89</td>
<td>87</td>
<td>79</td>
</tr>
<tr>
<td>PhD theses</td>
<td>7</td>
<td>5</td>
<td>3</td>
<td>5</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Patents</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total publications</td>
<td>63</td>
<td>65</td>
<td>70</td>
<td>94</td>
<td>97</td>
<td>89</td>
</tr>
<tr>
<td>Books and Book chapters*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>74</td>
</tr>
</tbody>
</table>

*In the review period, 13 researchers contributed to books or book chapters. All together, they contributed to 74 books or book chapters (not corrected for joint publications).

Number of PhD students
The number of PhD students in GRIAC remained stable during the evaluation period, with an increasing share of non-employed PhD students (see Table 4.5).

Table 4.5 Number of PhD students (for details, see appendix Section 4.2)

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of PhD students per year</th>
<th>% non-employed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>employed</td>
<td>non-employed</td>
</tr>
<tr>
<td></td>
<td>28</td>
<td>11</td>
</tr>
<tr>
<td>2003</td>
<td>32</td>
<td>3.13%</td>
</tr>
</tbody>
</table>
Section 4.6: Earning Capacity

Fund raising strategy and support
The Dutch Asthma Foundation is still the largest funding body for GRIAC, and members of GRIAC have been very successful in obtaining new funding. In addition, we have actively and successfully sought other funding sources such as ZonMw, VENI awards on the functional relevance of a gene found for asthma, and on the role of the β-catenin/GSK-3 axis in asthma, and two Top Institute Pharma grants on heterogeneity of COPD in a national collaborative network (Groningen, Maastricht, Utrecht as university partners and Altana, AstraZeneca, GlaxoSmithKline and Numico/Danone as industry partners) that we initiated ourselves. Furthermore, we received a large EU grant as part of a European network for genetics of asthma to extend our animal work and genetics programme, an EU grant on genetics and COPD, and an EU-Marie Curie Outgoing International Fellowship. Prof. Martina Schmidt received a Rosalind Franklin Fellowship from RUG; in addition, research is funded by grants from the NWO and the Deutsche Forschungs Gemeinschaft.

Prof. Postma has been able to appoint two young (clinical and fundamental) researchers as part of her KNAW (Royal Academy of Sciences) grant for future strengthening of GRIAC research.

A new animal facility has been opened recently. This completely renewed facility will provide optimal support for our animal research studies.

To enhance collaboration and stimulate new areas of research, GRIAC holds a research retreat twice yearly. During the retreats, the members of the scientific advisory board and post-docs of GRIAC discuss new research developments and look into new collaborations within their research, based on international developments in the field. In general terms, one of the retreats is fully dedicated to the presentation and discussion of new grant proposals and ideas. This gives researchers the opportunity to hold extensive mutual discussions involving the broad expertise of our staff members, who are experts in specific fields of many relevant disciplines.

Results
After a period during which it was extremely difficult to obtain research grants due to grant restrictions at the Dutch Asthma Foundation – the largest funding body for GRIAC – we have actively and successfully sought other funding sources: ZonMw grant on genetics of asthma, Veni on functional relevance of a gene found for asthma, two Top Institute Pharma grants on heterogeneity of COPD in a national collaborative network (Groningen, Maastricht, Utrecht as university participants and Altana, AstraZeneca, GlaxoSmithKline and Numico as industry partners) that we initiated ourselves. Furthermore, we received a large EU grant as part of a European network for genetics of asthma to extend our animal work and genetics programme, and an EU grant on the genetics of COPD. In the renewed Dutch Asthma Fund programme, we have obtained a relatively large number of grants.

Most important projects
1. Epidemiology
   • Genetics of COPD and role of diet and smoking (Groningen University Institute for Drug Studies, 2004-2009)
   • Genetics of COPD and lung function decline in the general population (NAF project number 3.2.02.51)
   • PIAMA study Prevention and intervention of asthma and mite allergy (NAF project number 98.27/ZON/VROM)
   • EC Respiratory Health Survey II (European Community QLK4-CT-1999-01237).

2. Genomics
   • Role of genetic polymorphisms of the β2-adrenoceptor in allergic asthma (Groningen University Institute for Drug Studies, 1999-2004)
   • VENI project Koppelman: Research into the action of the Asthma gene PCDH1 (NOW 916.56.091)
   • COPACETIC: COPD Pathology, Addressing Critical Gaps, Early treatment and Diagnosis and Innovative Concepts (FP, European Community)
   • European Community, GABRIEL (LSH-2004-1.2.5-1) A multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community (European Community LSH-2004-1.2.5-1; 2006-2010).
   • Identification of susceptibility gene(s) in an experimental asthma locus in the mouse. (NAF 03.55; 2005-2009,

3. Pathophysiology and pathogenesis of allergen, smoking and other lifestyle factors, and environment-induced diseases
   • Risk factors for progression of asthma: inflammation and remodelling (REPAIR); (NAF 3.2.00.38; 2001-2005)
• Asthma en Smoking: short and longstanding effects in Asthma. (NAF project number 3.2.0.49; 2004-2009)
• Role of oestrogen and oestrogen receptors in the pathogenesis of asthma (NAF project number 3.4.05.041; 2006-2009).
• Interactive role of Arginase, polycation and NO synthase in allergen-induced hyperreactivity and remodelling (NAF project number 00.24; 2001-2006 and Organon, 2006-2008)
• Natural T regulatory T cells in asthma (NAF project number 03.54; 2005-2008).
• Role of B-cell in the pathogenesis of COPD (NAF project number 3.2.06.75; 2007-2009).
• Emphysema: TGF-beta and cigarette smoke induced signalling in fibroblasts as major factors contributing to inadequate tissue repair. (NAF 3.2.0.47; 2003-2006)
• Airway remodelling in asthma: functional interactions of neurotransmitters and growth factors (NAF project number 99.83; 2000-2004)
• Ca2+ sensitization and myogenic tone. A new view on airway hyperresponsiveness (NAF project number. 01.83; 2002-2006)
• Mechanisms of airway hyperresponsiveness and -remodelling in a new guinea pig model of COPD. (Research institute of Cognitive and Behavioural Neurosciences; Boehringer Ingelheim, 2006-2010)
• Caveolae and caveolins: Integrating signals for airway smooth muscle cell proliferation» (Marie Curie Outgoing International Fellowship (EU MOIF-CT-2005-008823; 2005-2008)

4. Assessment, modulation and intervention in disease severity, progression and remission.
• Top Institute Pharma I: Acute and chronic inflammation response induced by smoking in COPD (project nr 1-108; 2008-2012); Top Institute Pharma II: Transition of systemic inflammation in to multiorgan pathology (projectnr 1-202; 2008-2012).
• Protective effects of tiotropium bromide in the progression of airway remodelling. A comparative study. (Boehringer Ingelheim; 2005-2006).
• Top Institute Pharma I: Acute and chronic inflammation response induced by smoking in COPD (project number 1-108; 2008-2012); Top Institute Pharma II: Transition of systemic inflammation in to multiorgan pathology (project number 1-202; 2008-2012).
• Protective effects of tiotropium bromide in the progression of airway remodelling. A comparative study. (Boehringer Ingelheim; 2005-2005)
• Effect of extracellular matrix proteins on airway smooth muscle contractility and proliferation in chronic asthma (NAF project number 03.36; 2005-2009)
• A phase-2 trial of Anti-TNF-alpha Chimeric Monoclonal Antibody (Infliximab, Remicade TM) in patients with COPD. (Centocor; 2002-2004)
• A Prospective Feasibility Study to Evaluate the Safety and Performance of the Exhale® Drug-Eluting Stent System in Patients with Emphysema (Broncus Technologies Inc.; 2005-2006).
• Role of chronic artificial ventilation in rehabilitation in hypercapnic patients with COPD (NAF project number 3.4.04.71).
• Modification of disease outcome in COPD. Intermittent versus continuous treatment with inhaled corticosteroids, either or not combined with a long-acting ß2-agonist.
• GLUCOLD study (NAF/NWO/GlaxoSmithKline; 940-35-033; 199-2006).
• Effects of smoking cessation on inflammatory events in airways of patients with chronic bronchitis and mild or severe airflow limitation (NAF 97.74; 1998-2003)
• Quality of life in hymenoptera allergy (ALK) (project ended 2008)
• Multidisciplinary, multicenter study on food allergy EUROPREVALL (European Community 584386; 2005 – 2009).

Numerical overview
As indicated in the explanation of Table 4.6, the earning capacity is expressed in research FTE, as the UMCG administration data did not allow accurate calculation of actual acquired funding. This earning capacity appeared to be stable during the observed period. From our own analyses, the actual earning capacity is higher and has also increased during the last 6 years.
### Table 4.6  Fund raising capacity at the level of programme GRIAC

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>(FTE)</strong></td>
<td>(FTE)</td>
<td>(FTE)</td>
<td>(FTE)</td>
<td>(FTE)</td>
<td>(FTE)</td>
<td>(FTE)</td>
</tr>
<tr>
<td><strong>Total funding</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>(30.25</td>
<td>(31.93)</td>
<td>(30.98)</td>
<td>(33.03)</td>
<td>(29.63)</td>
<td>(33.50)</td>
</tr>
<tr>
<td><strong>Allocated funding</strong></td>
<td>19.01%</td>
<td>20.36%</td>
<td>22.84%</td>
<td>20.59%</td>
<td>20.25%</td>
<td>18.96%</td>
</tr>
<tr>
<td></td>
<td>(5.75)</td>
<td>(6.50)</td>
<td>(7.08)</td>
<td>(6.80)</td>
<td>(6.00)</td>
<td>(6.35)</td>
</tr>
<tr>
<td><strong>Acquired funding</strong></td>
<td>80.99%</td>
<td>79.64%</td>
<td>77.16%</td>
<td>79.41%</td>
<td>79.75%</td>
<td>81.04%</td>
</tr>
<tr>
<td></td>
<td>(24.50)</td>
<td>(25.43)</td>
<td>(23.90)</td>
<td>(26.23)</td>
<td>(23.63)</td>
<td>(27.15)</td>
</tr>
</tbody>
</table>

*Explanation:* Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are funded directly by the University of Groningen and/or the UMCG (allocated funding). To extend their research capacity, they acquire grants via internal and external competition (acquired funding) for non-tenured staff, employed PhD students, non-employed PhD students and in some cases a limited number of staff positions. The fund raising capacity is expressed in research FTE.
Section 4.7: Academic Reputation

Description and overview
GRIAC members have an excellent academic reputation, as demonstrated by important awards, prizes, visiting professorships, editorships or participation on editorial boards of academic journals, memberships in academies, and participation on scientific advisory councils. GRIAC members have organised and/or chaired conferences in the Netherlands and abroad, and members from all disciplines are regularly invited to address major conferences. GRIAC members serve as reviewers for many high-ranking journals and for national, international and European (EC) funding agencies (for all details, see appendix Section 4.7)

Awards and prizes
GRIAC members received 33 rewards, honorary memberships and/or prizes, including appointment as Fellow in the Royal College of Physicians (FRCP) and Academy Professor of Royal Dutch Academy of Arts and Sciences for Prof. D.S. Postma, and a Rosalind Franklin Fellowship and Organon Prize for Pharmacology for Prof. M. Schmidt

Editorships in academic journals
GRIAC members are editors for or members on the editorial boards of the following peer reviewed scientific journals:

- American Journal of Respiratory and Critical Care Medicine - Prof. D.S. Postma
- BMC Pulmonary Medicine - Prof. H.A.M. Kerstjens
- British Journal of Pharmacology - Prof. H.Meurs
- Clinical Respiratory Journal - Dr. G.H. Koppelman
- Current Opinion in Allergy and Clinical Immunology - Prof. A.E.J. Dubois
- European Journal of Pharmacology - Prof. H.Meurs
- Journal of Allergy - Prof. J.G.R. de Monchy, Prof. A.J.M. van Oosterhout
- Journal of Pathology - Prof. W. Timens
- Molecular Pharmacology - Prof. M.Schmidt
- Nederland Tijdschrift voor Allergie - Dr. S. van der Heide
- Respiratory Research - Prof. H. Meurs
- Tijdschrift voor Kindergeneeskunde - Dr. E.J.L.E.Vrijlandt

Memberships in academies and on scientific boards
GRIAC members hold 74 memberships in academies and/or on the scientific boards. These include the following: Belgian Royal Academy of Sciences; Medical Sciences Council (Raad voor Medische Wetenschappen), Royal Dutch Academy of Arts and Sciences, ZonMW-TOP, ZonMW-Clinical Research of the Netherlands Organization for Scientific Research (NWO), Scientific Advisory Board Dutch Asthma Foundation, Dutch Society for Allergy and Clinical Immunology, Netherlands Epidemiological Society, Dutch Society of Physicians for Respiratory Diseases and Tuberculosis, Scientific Board of the Klosterfrau Foundation Berne, Scientific Board of the European Allergy and Asthma Centre Davos, Scientific Board of ECRHS (European Committee Respiratory Health Survey); American Thoracic Society Conference Planning Committee for the Respiratory Structure and Function (RSF) Assembly.

Invitations to address major conferences
GRIAC members have received 198 invitations to address major scientific conferences, including congresses of the American Thoracic Society, the European Respiratory Society, and the European Association for Allergy and Clinical Immunology.
Section 4.8: Societal Relevance

Societal Quality and Societal Impact

Members of GRIAC participate on the board of the Dutch Asthma Foundation. This encompasses strategy development of new research in the Netherlands, as well as patient oriented activities. The Members of the scientific board are: Prof. HAM Kerstjens, Prof. H. Meurs and Prof. W. Timens. Prof. van Oosterhout was formerly a member of the Advisory Board.

Members of GRIAC spend many evenings and afternoons every year giving lectures in the Netherlands and abroad and giving workshops for patients (organised by members of GRIAC and/or by Dutch Asthma Foundation (NAF), for general practitioners in training (Prof. H.J. Sluiter and conferences for GPs), Pulmonologists, and local GPs. An information meeting for patient-participants in genetics research was held that attracted about 400 attendees. The goal of all these activities is to enhance the knowledge on current developments in asthma and COPD research, as well as to improve patient care and to develop new guidelines for asthma and COPD management. This is also the aim of the international Bronchitis Symposium that are held every five years by GRIAC, the most recent one being in 2009 with an excellent line up of international faculty. Another international symposium, which included both a scientific meeting and a symposium for the general public, was the Fifth Lunteren Symposium entitled: “Smoking as a target in asthma and COPD”. It was devoted to discussing smoking behaviour, smoking cessation, effects of smoking on pathogenesis of asthma and COPD, and effects of smoking on treatment of asthma and COPD.

Members of the GRIAC participate in and/or chair advisory boards in the Netherlands and abroad for different pharmaceutical companies. They are frequently asked for advice in this respect.

GRIAC has developed a new programme for smoking cessation, which has a higher success rate than all other programmes. The topic of smoking cessation and its effect on asthma and COPD is one of the lines of research that receives much attention from society.

Every year, many papers are written in Dutch on asthma and COPD to disseminate the results of GRIAC research to Dutch society. Moreover, some books are being translated and adapted to Dutch guidelines for better accessibility (e.g. pocketbook of COPD and pocketbook of asthma).

Furthermore, GRIAC members have written chapters for medical students, and Groningen has participated extensively in the Dutch Book for Pulmonology (Editorship and writing), the chapter on Pulmonology in the handbook for Internal Medicine. GRIAC always participates in updating morbidity numbers on asthma and COPD in the Netherlands (Volksgezondheid Toekomst Verkenning of the National Health Institute; RIVM).

Dr. J. Gerritsen was appointed president of the European Respiratory Society. GRIAC members participate actively in several assemblies and committees in the ERS, and on several task forces, long-range planning committees (Prof. H.M. Boezen) and Standing Evaluation Committees (Prof. D.S. Postma and Prof. H.M. Boezen). Prof. Postma has been chairperson of the KNAW Foresight committee on the use of biobanks in the genomic era. In addition, GRIAC members participate on the programme and planning committees of the American Thoracic Society.

Within the Pulmonology community, GRIAC participates actively in several sections of NVALT (Dutch Society of Pulmonologists; past-president Dr. P.J. Wijkstra, board member Prof. H.A.M. Kerstjens); within the Epidemiology community Prof. H.M. Boezen has been president of the Netherlands Epidemiological Society (2006-2008) and is currently on the peer review evaluation committee of the MSc and PhD training programmes in Epidemiology of the Dutch Universities; within the Allergology community Prof. J.G.R. de Monchy was chairperson of the Dutch Allergology Society; within paediatrics Prof. E. Duiverman was chairperson of the Dutch paediatric Respiratory Society.

Dr. G.H. Koppelman organises the ‘Publieks Academie’, a series of lectures for the layperson, in which a number of diseases and syndromes are explained to the general public by a series of experts.

GRIAC has participated in the development and world-wide implementation of guidelines for management of COPD (GOLD guidelines, WHO/NIH Van der Molen, Postma, Kerstjens). This also applies to the development of Guidelines for asthma management in the Netherlands (adult and paediatric asthma, Duiverman) and the Dutch guidelines for COPD management (both disease management and medical management (Kerstjens). Kerstjens served as board member of the Dutch foundation for disease management of COPD (SKK) and still serves as board member of the Dutch Alliance of the Lung (LAN). Postma was co-founder of the Dutch Respiratory Society NRS and currently chairs this organisation. Prof Postma is an active member of the Royal College of Physicians in the UK. Van der Molen is Founding President of the International Primary Care Respiratory Group (IPCRG). This was the first initia-
tive to start collaborations all over the world on research and management of asthma and COPD in general practice. Prof. M. Schmidt is a member of the board of the Dutch Pharmacological Society.

Finally, Prof. D.S. Postma is a member of task forces of the NWO (Genomics and TOP grants) and KNAW (vice-chair of Raad Medische Wetenschappen); she was also visiting professor at Harvard University (Boston, USA) by invitation.

**Valorisation**

Research findings have resulted in several patent applications:

- Oosterhout, A.J.M. van; Methods of inducing immunotolerance and compositions for use therein; EPO No. 03075909.6, 2003
- Oosterhout, A.J.M. van; Methods and means to suppress symptoms of an allergic disease; EPO No. 03075908.8, 2003
- Postma, D.S.; Asthma associated gene; US 16.07.01/USP305649, 2004
Section 4.9: Next generation

With regard to the education offered through GUIDE, please refer to the main part of the GUIDE evaluation.

Every two weeks, GRIAC holds research meetings for the entire institute during which internal and external speakers are invited to explore new ideas and challenge the audience. This is also a forum for presenting different types of research to all members of GRIAC. Members of GRIAC participate in very different aspects of asthma and COPD research, including epidemiology, clinical allergology, pulmonology, pharmacology, general practice, and fundamental research in genetics, proteomics, tissue studies, cell cultures and animal models. Lively discussions always take place.

To enhance collaboration and stimulate new areas of research, GRIAC holds a research retreat twice yearly, along with monthly brainstorming sessions on a specific topic.

During the GRIAC retreat, the members of the board of directors, scientific staff and GRIAC post-docs discuss new research developments and explore new collaborations within their research, based on international developments in the field.

Every five years, GRIAC holds a symposium aimed at understanding the differences and similarities between asthma and COPD. This event is well-received internationally. The eighth symposium “Bronchitis VIII” was held from 15-17 June 2009, with excellent international speakers and discussants.

During every defence of a PhD thesis, a top-researcher in a specific research field is invited. He or she is asked to evaluate the thesis and to participate in the PhD defence ceremony. The researcher is also invited to give a lecture. When these external visitors are present, workshops for exchanging ideas are always organised for both senior and junior researchers.

In addition to the centrally organised possibilities for training, GRIAC provides its own training programme. This takes the form of weekly, one-hour meetings for post-docs and PhD students in all disciplines. Senior staff members rotate in participation. In this way, new research projects, initial results, abstracts, presentations on international meetings and final overviews are discussed. Each discipline is present at these meetings. These weekly GRIAC meetings aim to teach different aspects of the approach towards research on asthma and COPD in the various disciplines involved in GRIAC in order to improve the level of interdisciplinary research. Epidemiology and applied statistical courses and courses on genetic epidemiological research and data analysis are also provided by the Department of Epidemiology (Prof. H.M. Boezen, Dr. J.M. Vonk) for participants of GRIAC.
Section 4.10: Viability, SWOT and Future Strategy

Viability
To successfully continue the research within GRIAC, it is essential that it does not rely on only a few individuals. Consequently, younger members increasingly participate in organisation and coordination. This has been initiated to ensure the continuity of the management of GRIAC into the future. Two post-docs have obtained an international post-doc grant from the Dutch Asthma Foundation and have performed research for one year in Pittsburgh (USA) on an animal model implementing gender differences in asthma, and epithelial signal transduction routes in asthma in Toronto, Canada, respectively. One post-doc obtained a Marie Curie Outgoing International Fellowship from the European Community to perform research on the role of caveolae in airway smooth muscle phenotype plasticity. This research was performed at the University of Manitoba in Winnipeg, Canada for two years (outgoing phase) and at the Department of Molecular Pharmacology for one year (return phase). Furthermore, two of the members have received a Veni grant and a tenure track position within GRIAC.

Moreover, we have increased the expertise in different fields of asthma and COPD research within GRIAC. In particular, molecular biology and epidemiology have now been firmly established in GRIAC.

- Prof. A.J.M. van Oosterhout has been appointed Professor in Immunology of Lung Diseases and contributes with both genetical genomics and fundamental immunology. This also provided extra stimulus for recruiting a PhD for molecular biology.
- Prof. M. Schmidt has been appointed Professor within the Rosalind Franklin tenure track system, where she devotes her research on regulatory transduction mechanisms to asthma, COPD and memory deficiencies.
- Prof. A.E.J. Dubois has been appointed Professor in research on food allergy with both clinical and fundamental research, compatible with GRIAC research.
- Prof. H.M. Boezen has been appointed Professor of Epidemiology, with a focus on the role of gene-environment interactions in the onset of asthma and COPD.
- Prof. H. Meurs has been appointed Professor of Immunopharmacology; his research is focussed on airway pharmacology in animal models of asthma and COPD.

SWOT

Strengths
Based on many invited reviews, book chapters and invited lectures at international and national congresses in recent years and on external financial support as well as on the significant output of frequently cited scientific publications and theses, it can be stated that the group has maintained its internationally recognised position. This position is currently supported by a wide range of local, national and international collaborations with academic and industry groups. Longstanding collaborations and strategic alliances have been established. The main theme in the sub-programmes is the fundamental and clinical study of obstructive lung diseases, in particular asthma and chronic obstructive pulmonary disease (COPD) with special emphasis on translational research and effects of disease intervention. The translational research has also been given an additional impulse; the recent advances in genetics together with the expertise already present has enabled high quality research in functional genomics. Unique is the multidisciplinary approach and collaboration in which almost all relevant disciplines in this research area are involved. This is a unique setting in Europe and the world. As such, GRIAC is frequently mentioned as an excellent example of translational medicine, which brings many international researchers to Groningen. For example, all 25 international experts invited to attend Bronchitis 8 (an international meeting that takes place every 4-5 years) immediately accepted. Many research meetings are organised on a structural as well as ad hoc basis. Besides sustaining and further promoting interactions between the staff members of the different disciplines, these meetings specifically offer maximum possibilities for young research fellows to participate in different lines of research and to develop a broad scientific view. For instance, we have initiated monthly interdisciplinary brainstorming meetings for new research in development, and these meetings also inspire new research.

Another important and remarkable feature is the large region from which patients are referred to the university hospital, enabling relatively large studies with patients who have been extensively clinically characterised. Given the stability of the Groningen population, long-term follow up of large cohorts in the population at large, especially in clinical practice, is feasible. This provides unique material for genetic studies and intervention studies on the prognosis of obstructive airway disease. By strongly supporting the interdisciplinary approach towards asthma and COPD, we feel that we are one of the key research groups to successfully reach our goals of better understanding the underlying pathophysiology as well as the management of asthma and COPD.

Weaknesses
The multidisciplinary nature of the group (which is also a strength of the group) is a matter that requires permanent attention. This multidisciplinary nature calls for proper scientific planning and integration of activities under guidance.
of the programme leaders in order to optimally employ the unique expertise and opportunities within the group. Some of the disciplines are represented by only a few permanent staff members, which should be improved to assure the continuity of each discipline. The UMCG could be more helpful in organisation and coordination of the research institutes, providing better administrative support.

Opportunities
The societal impact of this work is considerable in relation to the current problems in healthcare. Asthma is prevalent worldwide, with increasing incidence. COPD is rapidly increasing in incidence and prevalence, especially in women; it is predicted that it will become the third most important cause of mortality in 2015 worldwide. Group members have many local, national and international responsibilities in the advancement of science in the field of asthma and COPD, as well as in the professional training of graduate and post-graduate students, in addition to post-academic teaching. They regularly contribute to meetings with general practitioners, nurses, patients and patient organisations to provide them with insights into new developments in the research on asthma and COPD that can be applied in clinical practice and patient management. GRIAC organises patient evenings to bring the results of the research to the general public. This happens after the finalisation of each study in which patients participate, or at certain time intervals, to keep the participants in the genetic studies informed. These meetings are greatly appreciated and are well attended; the last meeting on genetic research was attended by about 400 participants. Contacts with pharmaceutical companies are being intensified, resulting in new horizons of mutual benefits related to each partner’s research aims. This expanding collaboration provides sufficient synergy for novel approaches. In this framework, group members regularly visit hospital and research laboratories in different parts of the world for training projects and collaborative work. Local collaboration and the local availability of facilities have also expanded: a new Animal Facility recently opened; animal models on asthma and COPD have been broadened and the recent funding by the UMCG of a Mouse Clinic allows for the development of genetically engineered mice for all relevant research purposes. Possibilities for advanced molecular genetics have been greatly expanded in the Dept. of Genetics, and new international collaborations on genetical genomics in the USA and Canada have been initiated. Extensive proteomics work is also possible. Furthermore, much attention has been paid to developing genetic strategies in Groningen, together with other research groups at the University of Groningen.

Recent reports have indicated that the world-wide expertise in integrative pharmacology is rapidly declining – during an era in which the need for this expertise is growing. Groups within GRIAC have developed unique expertise and infrastructure to perform investigations, ranging from molecular biology to the intact organism; this clearly promotes new collaborations with both academia and industry.

Threats
In the Netherlands there is a trend towards research which offers easily envisaged benefits for patients or society, preferably over a relatively short term. A significant part of the research at GRIAC is fundamental in origin, although the sub-programmes over the years have provided many results that were important for patient care. One has to realise that asthma, and especially COPD, are chronic diseases; it can take many years before the impacts of interventions become apparent. Hence, in clinical studies, it often takes much investment of staff before results become apparent and have direct implications. This may be a threat if the increasingly short-term policies – which demand faster applicability – are continued. This will require considerable skills and efforts from the researchers to make the relevance and advantages of the current sub-programmes clear to the public and funding authorities.

Recently there have been severe budget cutbacks in the healthcare system in the Netherlands, affecting University Medical Centres in particular. Some smaller disciplines within GRIAC are especially vulnerable to these budget cuts; they may even threaten their continued existence. This may also pose problems for larger disciplines/departments. Because GRIAC aims at translational research, high quality clinical care with sufficient catchment possibilities for patients is essential. The board of GRIAC will have to stay in contact with the Dean and Board of the UMCG to safeguard our interests as much as possible.

The teaching and clinical load of some members of GRIAC is very high, which impacts the possibilities to develop competitive grant applications and the scientific output.

The available research budget mainly consists of funding from the 3rd and 4th (“soft”) flows of funds, showing the excellent collaboration with industry and non-profit organisations, with some funding from the 1st (“hard”) and 2nd flows of funds. Due to the vulnerability of being partly dependent on funding from a single source like the NAF, more effort will be put into obtaining funding from the 2nd flow of funds (ZON-MW programme grant, ZON-MW fellowships and veni/vidi/vici programme, KNAW fellowships). These efforts have already begun; applications for a clinical fellowship, veni and vici grants and an ERC grant have been submitted, or will be in the near future. It is envisaged that a challenging scientific programme can be maintained for the years to come. The staff of the group is quite stable, but extra efforts should be made to recruit or retain promising PhD students, to retain skilful technical staff and to create career perspectives for permanent staff members.
Future Strategy

Prospects:
In the period since the last self evaluation, GRIAC has been able to continue its positive track and to implement several improvements to the structure and expertise of participants as indicated above. Based on the above overview, the coordinators are confident that GRIAC can be continued successfully.

The next programme period has already started; here are some important findings in 2009:

- Airway epithelial changes in smoking but not in ex-smoking asthmatics. Broekema et al. Am J Respir Crit Care Med. 2009 October. [Epub ahead of print]

Asthma and COPD research takes place in a lively and rapidly changing field. It is expected that new developments will encompass the functional genomics (including proteomics) of asthma and COPD. It is anticipated that a better insight into the risk factors for early development of allergy and asthma will be assessed, both by epidemiological studies and studies on gene-environmental interaction in large cohorts of babies followed up to the age at which formal lung function testing can be performed. Better insights into the nature of severe asthma and exacerbations of asthma and COPD will be acquired in the coming years based on currently ongoing studies. For both asthma and COPD, we will gain better insight into the intricate interplay between epithelial cells and fibroblasts on one hand and their interaction with different inflammatory cell types in the lung and airway smooth muscle cells on the other. With the recognition that the airway smooth muscle cell is a highly plastic cell governed by complex interactions between multiple receptor systems and environmental changes, research will remain focussed on unravelling the interactive mechanisms that determine airway smooth muscle responsiveness and growth in chronic airways disease. Newly discovered genes will be incorporated into our studies on in vitro modification of epithelial, smooth muscle and fibroblast cell cultures.

A focus on the background question of why not all smokers develop COPD will be a first priority in association with the consequences of smoking cessation, and intervention in the progression of inflammation and remodelling. This knowledge is enhanced by studies regarding the effect of smoking on allergy development and asthma progression as well as the effects on treatment response. The former topics will be investigated in animal models and in humans.

We are participating in a 10-year prospective study of smokers at risk for lung cancer. This provides a unique opportunity for further unravelling of the pathophysiology and pathology of COPD, by means of clinical, lung function, radiological, pathological, genetic and proteomic research.

Exacerbations are sometimes life-threatening occurrences in patients with asthma and COPD, which may affect activities of daily living, increase symptoms and reduce quality of life. Research will focus on practical and minimal interventions to prevent these exacerbations, including research on the underlying mechanisms and the associated increase in symptoms. Finally, side effects of drugs will be assessed by questionnaires, which will help to further understand the optimal approach to asthma and COPD management.

An area of importance in paediatric asthma is food allergy, which has recently been shown to be a risk factor for asthma exacerbations requiring ventilation in children. To explore this theme, the recently established food-challenge unit is carrying out double-blind placebo-controlled challenges.
Research in the rehabilitation programme has been recently reinforced with respect to asthma and COPD, and is expected to increase the input to and output of the GRIAC programme. This has been expanded by novel invasive techniques such as applying stents in airway walls, which dramatically improves exercise capacity in emphysema, thus allowing better rehabilitation as well.

The population for genetic analyses in asthma and COPD has been greatly expanded, and will be expanded still further, allowing replication and association studies. In 2003, gene-environment interaction studies were started with a joint effort involving three prospective birth cohorts in the Netherlands (Universities of Utrecht, Rotterdam, Maastricht and Groningen). Functional studies on gene variations in asthmatic and healthy individuals have started, both in cells and in animal studies. Integration of epidemiological results with genetics will provide insight into genetic variants as risk factors for the development, progression or remission of asthma and COPD. Finally, the integration of newly discovered genes with the results of gene expression in relevant tissues that are available and/or cell cultures allows further research into functional relevance. It is envisaged that comparative genomics in animals, cell culture and humans will be initiated.
Table of contents
CHAPTER 5

Centre for Liver, Digestive and Metabolic Diseases
Section 5.1: Objectives and Research Area

Programme Leaders
Prof. F. Kuipers (2003-2008)
Prof. H.J. Verkade and Dr. S.C.D. van IJzendoorn (2009-present)

Mission
The mission of the programme is to define the molecular basis of liver, digestive and metabolic diseases, and to develop new treatment strategies.

Research Area

Background
A common denominator in liver, digestive and metabolic diseases is the disruption of the ‘metabolic flow’ of endogenous and exogenous compounds. Disruption can occur at the interorgan, intercellular and intracellular flow levels. Disturbed metabolic flow exposes cells, in particular liver and intestinal epithelial cells, to abnormal (increased or decreased) levels of these compounds or their metabolites. This can cause cell malfunction or cell death and may result in organ failure and disease at the level of the whole organ. The liver and intestine are functionally coupled organs that are involved in the metabolism, processing and subsequent elimination of a vast number of dietary components and drugs from the body.

Research aims
The previously distinct CLDS sub-programmes Drug targeting and Liver transport and metabolism have been condensed into one revised sub-programme, which is called sub-programme 1, Mechanisms and treatment of metabolic disease. The aim of sub-programme 1 has been to understand, diagnose, and treat inborn and acquired liver and intestinal diseases. This has been achieved through an integrated basic and clinical research approach at a molecular level into the regulation of intracellular and transmembrane transport, and into the metabolic pathways of endogenous, therapeutic and dietary compounds in the various cell populations of the liver and intestine.

In 2007, a new sub-programme, which is called sub-programme 2, Intestinal function and integrity, was initiated to strengthen intestine-focused research at the CLDS. The aim of sub-programme 2 has been to elucidate the genetic and molecular basis of intestinal function (e.g. absorption, transport) and integrity (e.g. barrier function). This was done by means of integrated basic and clinical research on host genetic predispositions and environmental factors, e.g. nutrition and inflammation, which are involved in intestinal disorders. The focus was on celiac disease, inflammatory bowel diseases and intestinal function during liver diseases. By adding this strong sub-programme on intestinal function and integrity (see Sections 5.4 - 5.7), the CLDS programme included both the liver and intestine, the main organs involved in metabolism, which enabled more thorough understanding of their coordinated functions in metabolism, processing and excretion of dietary components and drugs.

Strategy and policy
- Following the retirement of Prof. D. Meijer in 2005 and the appointment of his successors, Prof. G. Groothuis and Prof. K. Poelstra (currently affiliated CLDS members), the sub-programmes Drug targeting and Liver transport and metabolism were condensed into a single, revised sub-programme. This is called sub-programme 1, Mechanisms and treatment of metabolic disease. Through integration and concentration, we were able to enhance the focus and mass of the entire programme.
- With the appointment of Dr. C. Wijmenga (NWO-VICI laureate) as Professor of Human Genetics and full member of the CLDS, state-of-the-art genetic technologies and research have been brought into the CLDS. This has benefited both current sub-programmes.
- The application of molecular physiological and genetic approaches using genetically modified mice has been further enhanced in the CLDS with the arrival of Dr. U. Tietge (NWO-VIDI laureate) and Prof. M. Hofker, who are both world-renowned experts in this area of research. In addition, Prof. M. Hofker’s research on metabolic pathologies, including non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH) and obesity-associated insulin resistance Type II diabetes, strengthens sub-programme 1.
- In 2008, Dr. B. Giepmans was appointed as a full CLDS member. This strengthened the application of cellular imaging using state-of-the-art fluorescent probe technology in conjunction with correlated electron microscopy to visualise and study proteins that play key roles in disease. In 2008, Dr. Giepmans received a EU Marie Curie reintegration grant; he is a former member of the lab of Nobel laureate Roger Tsien.
- Dr. H.J. Verkade was appointed Professor of Paediatric Hepatology and Gastroenterology in 2005.
- Dr. H. Moshage was appointed professor of Experimental Hepatology and Gastroenterology, and his research has shifted towards fatty livers and oxidative stress.
- Dr. S. van IJzendoorn (Cell Biology), Dr. G. Dijkstra (Clinical Gastroenterology) and Dr. D. Reijngoud (Clinical Biochemistry) have all been appointed full members of the CLDS.
Section 5.2: Composition of the Research Unit

Composition of the research unit

The CLDS is flourishing. This is reflected in the increase in total research staff from 48 in 2003, to 77 in 2008. During this period, non-tenured staff (tenure tracks, fellows of the Royal Netherlands Academy of Arts and Sciences (KNAW)) were appointed as tenured staff, with an increase from 3.8 to 7.1 FTE. In addition, non-tenured staff (including tenure tracks, Rosalind Franklin fellows) more than doubled from 2.0 to 4.9 FTE. The number of PhD students in the CLDS also showed a substantial increase, from 34 in 2003 to 51 in 2008 (see Table 5.1; for details, see appendix Section 5.2).

The most significant appointments are listed in Section 5.1.

Table 5.1  Overview of the research staff at the level of programme CLDS

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full professors</td>
<td>3.80</td>
<td>3.30</td>
<td>3.80</td>
<td>4.80</td>
<td>5.70</td>
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<tr>
<td>(n)</td>
<td>(11)</td>
<td>(10)</td>
<td>(11)</td>
<td>(14)</td>
<td>(16)</td>
<td>(20)</td>
</tr>
<tr>
<td>Associate professors</td>
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<td>2.20</td>
<td>2.20</td>
<td>3.40</td>
<td>3.70</td>
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<td>(4)</td>
<td>(7)</td>
<td>(7)</td>
<td>(10)</td>
<td>(11)</td>
</tr>
<tr>
<td>Assistant professors</td>
<td>0.70</td>
<td>1.20</td>
<td>1.20</td>
<td>1.50</td>
<td>1.20</td>
<td>0.80</td>
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<td>(4)</td>
<td>(3)</td>
<td>(4)</td>
<td>(3)</td>
<td>(2)</td>
</tr>
<tr>
<td>Other senior staff</td>
<td>1.10</td>
<td>0.80</td>
<td>0.40</td>
<td>0.40</td>
<td>0.00</td>
<td>0.00</td>
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<td>(2)</td>
<td>(1)</td>
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<td>Non-tenured staff</td>
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<td>1.35</td>
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<td>(2)</td>
<td>(2)</td>
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<td>PhD students</td>
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<td>16.28</td>
<td>21.18</td>
<td>21.18</td>
<td>19.95</td>
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<td>(35)</td>
<td>(37)</td>
<td>(43)</td>
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<td>Employed</td>
<td>19.60</td>
<td>18.03</td>
<td>16.28</td>
<td>21.18</td>
<td>21.18</td>
<td>19.95</td>
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<td>(30)</td>
<td>(34)</td>
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<td>(37)</td>
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<tr>
<td>Non-employed</td>
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<tr>
<td>(n)</td>
<td>(4/11.76%)</td>
<td>(4/11.43%)</td>
<td>(7/18.92%)</td>
<td>(9/20.93%)</td>
<td>(12/26.09%)</td>
<td>(14/27.45%)</td>
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<tr>
<td>Total research staff</td>
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<td>22.68</td>
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<td>27.78</td>
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<td>32.00</td>
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<td>(n)</td>
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<td>(47)</td>
<td>(50)</td>
<td>(59)</td>
<td>(65)</td>
<td>(77)</td>
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</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers also have obligations for patient care. For the sake of simplicity a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD students with an employment contract. For non-employed PhD students (student status), expression in FTE is not appropriate.

Research Funding

During the period 2003 to 2008, the percentage of research staff supported by contract research funds (including those from the Top Institutes Pharma, Food and Nutrition, and the Centre for Translational Molecular Medicine, as well as non-profit foundations) increased from 22% to 45%. This is indicative of an improved interaction between CLDS research and industry and society (see Table 5.2).
Table 5.2  Overview of the research funding at the level of programme CLDS

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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<tbody>
<tr>
<td></td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Funding:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct funding (1)</td>
<td>9.78</td>
<td>7.05</td>
<td>6.90</td>
<td>9.30</td>
<td>10.95</td>
<td>13.23</td>
</tr>
<tr>
<td>(38.45%)</td>
<td>(31.09%)</td>
<td>(31.54%)</td>
<td>(33.48%)</td>
<td>(36.74%)</td>
<td>(41.33%)</td>
<td></td>
</tr>
<tr>
<td>Research grants (2)</td>
<td>10.05</td>
<td>7.13</td>
<td>5.33</td>
<td>4.45</td>
<td>3.80</td>
<td>4.43</td>
</tr>
<tr>
<td>(39.53%)</td>
<td>(31.42%)</td>
<td>(24.34%)</td>
<td>(16.02%)</td>
<td>(12.75%)</td>
<td>(13.83%)</td>
<td></td>
</tr>
<tr>
<td>Contract research (3)</td>
<td>5.60</td>
<td>8.50</td>
<td>9.65</td>
<td>14.03</td>
<td>15.05</td>
<td>14.35</td>
</tr>
<tr>
<td>(22.03%)</td>
<td>(37.49%)</td>
<td>(44.11%)</td>
<td>(50.50%)</td>
<td>(44.84%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total funding</td>
<td>25.43</td>
<td>22.68</td>
<td>21.88</td>
<td>27.78</td>
<td>29.80</td>
<td>32.00</td>
</tr>
<tr>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Expenditures:

<table>
<thead>
<tr>
<th>Item</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel costs (€)</td>
<td>1,076.1</td>
<td>998.8</td>
<td>1,126.9</td>
<td>1,380.2</td>
<td>1,629.6</td>
<td>1,892.0</td>
</tr>
<tr>
<td>Other costs personnel (€)</td>
<td>414.4</td>
<td>384.6</td>
<td>433.9</td>
<td>531.4</td>
<td>627.5</td>
<td>728.5</td>
</tr>
<tr>
<td>Costs non-employed PhD students (€)</td>
<td>63.8</td>
<td>65.4</td>
<td>83.4</td>
<td>104.9</td>
<td>132.2</td>
<td>223.2</td>
</tr>
<tr>
<td>Other costs non-employed PhD students (€)</td>
<td>34.0</td>
<td>34.0</td>
<td>42.5</td>
<td>53.1</td>
<td>65.9</td>
<td>99.9</td>
</tr>
<tr>
<td>Total expenditure</td>
<td>€1,588.3</td>
<td>€1,482.8</td>
<td>€1,686.7</td>
<td>€2,069.6</td>
<td>€2,455.2</td>
<td>€2,943.6</td>
</tr>
</tbody>
</table>

Explanation: The expenses for research include both personnel and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the donation to the provision ‘wachtgelden’ (i.e. the obligation to provide personnel with a reduced salary in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff and other costs such as allowances for child care and commuter traffic. Although non-employed PhD students do not represent research FTE, the costs of these PhD students have been included. Other costs include operational costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

1 Direct funding by the university;
2 Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programmes ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3 Funding for specific research projects obtained from external organisations, such as industry, governmental ministries, European Commission (Framework programmes) and charity organizations.

Strategy and policy

Tenured staff members were appointed to strengthen the existing sub-programme 1 and to initiate a successful and productive new second sub-programme on intestinal function and integrity. Tenure tracks ensure the continuity and high quality of the research programme. Contract research funding ensures a continuing increase in research in the face of expected future cutbacks in government research budgets.
Section 5.3: Research Environment and Embedding

Position and reputation
The CLDS holds a strong national and international position. This is reflected by its structural collaborations: more than 75 with national academia and more than 70 with international academia. These collaborations have resulted in joint/collaborative publications in high-ranking journals. CLDS researchers also maintain more than 30 structural collaborations with industrial partners operating worldwide (including Unilever, Solvay, Danone, Schering Plough, Hoffmann-La Roche, AstraZeneca, Chromos Ltd. and Daichii Sankyo), as well as with non-profit organisations (for details, see appendix Section 5.3).

CLDS researchers are regularly invited to present their work at academic conferences and other events and, in turn, regularly invite leading scientists to present their work at the UMCG. Between 2003 and 2008, CLDS members invited 45 external scientists to present their work (for details, see appendix Section 5.3).

Guest researchers
CLDS members have hosted several guest researchers from the Netherlands and abroad, including four Japanese post-doctoral fellows and tenured staff from the universities of Osaka and Tokyo. These guest researchers from Japan were sponsored by grants from the International Training Programme (ITP) of the Japan Society for Promotion of Science and from Tokyo University. There were also visits from European post-doctoral fellows, funded by an EU grant, a grant from l’Université Catholique de Louvain, and a grant from the Royal Society (the national academy of science in the UK).

Strategy and policy
To promote and strengthen the research environment and embedding within the CLDS, the CLDS participates in national and international study consortia that involve academia and industry (for example, EU funds, IOPs (innovation-directed research programmes), and the Top Institutes Pharma (TIP), Food and Nutrition (TIFN), and the Centre for Translational Molecular Medicine (CTMM)).
Section 5.4: Quality and Scientific Relevance

Most important results per sub-programme
The 5 results highlighted below have set the stage for patents and/or ensuing high quality research.

Sub-programme 1:
- Research in the group led by Dr. K.N. Faber (NWO-VIDI laureate) and Prof. H. Moshage has revealed that the enzyme bile acid-CoA:amino acid N-acyltransferase (BAAT) is highly enriched in peroxisomes in the human and rat liver. This finding reveals a crucial role for peroxisomes in maintaining the enterohepatic cycling of bile salts, i.e., bile salts that are deconjugated by intestinal bacteria and return to the liver need to shuttle through the peroxisome before re-entering the enterohepatic circulation (Hepatology 2007 45:340-348).
- Research in the group led by Dr. S. van IJzendoorn and Prof. D. Hoekstra revealed that a distinct class of proteins that anchor signalling molecules to specific organelles in hepatocytes control the intracellular sorting and trafficking of bile canalicular ABC transporters and sphingolipids, and bile canalicular plasma membrane biogenesis (Mol Biol Cell. 2006 Aug;17(8):3638-50; Mol Biol Cell. 2007 Jul;18(7):2745-54; Bioessays. 2008 Feb;30(2):146-55).
- Research in the group led by Prof. M. Hofker using hyperlipidemic and/or genetically modified mice, indicated that dietary cholesterol, possibly in the form of modified plasma lipoproteins, is an important risk factor for the progression to hepatic inflammation in diet-induced non-alcoholic steatohepatitis (NASH) (Hepatology. 2008 Aug;48(2):474-86).

Sub-programme 2 (initiated in 2007):
- Research in the group led by Prof. C. Wijmenga has performed a genome-wide association study for celiac disease and identified 12 risk variants predisposing to celiac disease (Nat Genet. 2007 Jul;39(7):827-9; Nat Genet. 2008 Apr;40(4):395-402).
- Research in the group led by Prof. C. Wijmenga has resulted in the development of a tag SNP method that is very accurate, and provides an excellent basis for population screening for HLA-risk alleles in celiac disease. This method is broadly applicable in European populations and represents a first step towards providing a cost-effective population screening method for celiac disease (PLoS One. 2008 May 28;3(5):e2270).

Key publications per sub-programme
(for full-text publications, see appendix Section 5.4)

Sub-programme 1:

Sub-programme 2:

High quality publications
About one-third of the research and review articles by CLDS members were published in journals ranking in the top 10% of the CLDS-relevant ISI fields. These journals included Nature Genetics, Gastroenterology, Gut, Hepatology, Journal of Clinical Investigation, Nature Reviews Genetics, American Journal of Human Genetics, Developmental Cell, Traffic and Bioessays. Both the relative and absolute number of publications in the top 10% of journals increased during the period 2003 to 2008. More than 75% of the research and review articles were published in journals that belonged to the top 30% of the relevant ISI fields, including Molecular Biology of the Cell and the Journal of Biological Chemistry. Again, both relative and absolute numbers of publications in the top 30% of journals increased during the period 2003 to 2008, indicating a higher quantity and quality of CLDS research output (see Table 5.3). Four articles published by CLDS members between 2003 and 2008 have been cited more than 120 times, two of which have been cited more than 230 times.

All top publications have been marked in appendix Section 5.5.

Table 5.3  Number of papers published in the best 10% and 30% of relevant disciplines

<table>
<thead>
<tr>
<th>Year</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>(n of articles)</td>
<td>%</td>
<td>(n of articles)</td>
<td>%</td>
<td>(n of articles)</td>
</tr>
<tr>
<td>Belongs to the best 10% of a relevant subject area</td>
<td>30%</td>
<td>(17)</td>
<td>26%</td>
<td>(15)</td>
<td>34%</td>
</tr>
<tr>
<td>Belongs to the best 30% of a relevant subject area</td>
<td>79%</td>
<td>(45)</td>
<td>76%</td>
<td>(44)</td>
<td>76%</td>
</tr>
</tbody>
</table>

Explanation: A ranking for publications present in the on-line database ‘ISI Web of Knowledge’, sub-database ‘Web of Science’ can be calculated and is presented. Papers are categorised based on the journal in which they appear. Approximately 175 subject areas have been designated as ISI fields. The percentages are calculated based on the number of journal titles in the subject area.

Papers published in subject areas relevant to the research programme are included in this analysis. According to the methodology of bibliometric analysis, only papers of the reference types ‘Article’, ‘Note’, ‘Letter’, ‘Review’ and ‘Proceedings paper’ are considered. This implies that references of the type ‘Editorial material’, ‘Book (review)’, ‘Correction’, ‘Meeting abstract’, ‘Conference proceeding’, ‘In memoriam’, ‘News item’ and ‘Biographical item’ etc., are not included.
Section 5.5: Quantity of Scientific Output

Overview of the results
The annual number of peer-reviewed articles rose from 54 in 2003 to 102 in 2008, while the percentage of articles published in journals that ranked in the top 10% and 30% was maintained or even increased. A total of 459 peer-reviewed articles, 27 books and/or book chapters, and two patents were obtained by CLDS researchers between 2003 and 2008 (see Table 5.4; all publications are listed in appendix Section 5.5).

Publication strategy
New research-driven staff with clear clinical interests (e.g. Prof. C. Wijmenga, Prof. M. Hofker, Dr. G. Dijkstra) improved the scientific output. The criteria for full CLDS membership was set by the Dean of the UMCG, and included publishing at least 6 peer-reviewed articles in journals that ranked in the top 30% every 3 years per full member of the CLDS. Failure to meet this minimum requirement resulted in the loss of full membership and associated benefits.

Number of publications

<table>
<thead>
<tr>
<th>Table 5.4</th>
<th>Main categories of research output at the level of programme CLDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Refereed articles</td>
<td>54</td>
</tr>
<tr>
<td>PhD theses</td>
<td>5</td>
</tr>
<tr>
<td>Patents</td>
<td></td>
</tr>
<tr>
<td>Total publications</td>
<td>59</td>
</tr>
<tr>
<td>Books and book chapters</td>
<td>27</td>
</tr>
</tbody>
</table>

Number of PhD students
The number of PhD students in the CLDS shows a substantial increase from 34 in 2003 to 51 in 2008 (see Table 5.5. For details, see appendix Section 5.2).

<table>
<thead>
<tr>
<th>Table 5.5</th>
<th>Number of PhD students</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Number of PhD students per year</td>
<td>34</td>
</tr>
<tr>
<td>employed</td>
<td>30</td>
</tr>
<tr>
<td>non-employed</td>
<td>4</td>
</tr>
<tr>
<td>% non-employed</td>
<td>11.76%</td>
</tr>
</tbody>
</table>
Section 5.6: Earning Capacity

Fund raising strategy and support
The CLDS has been successful in competing for and obtaining prestigious national and international project grants. Almost 90% of the research FTE is through acquired funding, which reflects an excellent fundraising capacity (see Table 5.6). At this time no specific strategy is being followed to further increase the earning capacity of the CLDS.

Results
Highlights
Funded a grant from the Wellcome Trust, Prof. C. Wijmenga performed a genome-wide study with 10,000 celiac disease patients and 20,000 control patients. Wijmenga was able to identify more than 30 genes associated with celiac disease, which could explain approximately 40% of the genetics of celiac disease. Her goal of using this genetic information to trace potential patients came a step closer with these results. With the aid of a recent NIH grant, in collaboration with a group from Colorado (USA) she will test the predictive power of her genetic risk model in a prospective population cohort of 30,000 children who have been followed for 12 years for potential development of celiac disease (the so-called DAISY cohort). Wijmenga is also a partner in a European project that is studying whether gluten tolerance can be promoted by early intervention (PreventCD, www.preventcd.com). For this work, it is even more important to determine as early as possible which newborns are at high risk of developing celiac disease.

Overview of externally funded projects (> €100k)
There were 29 research grants from national and international foundations, industry and national governments (>$13 millions in total). These include NWO ZonMW-VIDI (2x), NWO TOP programmes (2x) and NWO research grants (3x). Funding from NIH R21, Wellcome Trust, MLDS (5x), IOP genomics, and BSIK/NGI has been awarded to CLDS members and cover both sub-programmes of the CLDS:

Sub-programme 1:
- EU (KP6 HEPADIP to Prof. Kuipers in 2006);
- Top Institute Pharma (TIP; to Prof. D. Hoekstra, to Prof. F. Kuipers, and to Prof. R. Vonk);
- Netherlands Organisation of Scientific Research (NWO) - ZonMW VIDI to Dr. K.N. Faber in 2003, NWO-ZonMW VIDI to Dr. U. Tietge in 2005; ZonMW-VENI to Dr. T. van der Heide; ZonMW-VENI to Dr. T. Claudel;
- Diabetes Research Foundation to Prof. C. Wijmenga and Prof. M. Hofker in 2006;
- CTMM PREDICCt to Prof. M. Hofker and Prof. F. Kuipers;
- IOP Genomics to Prof. M. Hofker in 2005;
- Pharmaceutical industry (to Prof. P. Sauer, to Prof. F. Kuipers, and to Prof. D. Hoekstra);
- Dutch Digestive Foundation (MLDS; to Dr. K.N. Faber in 2003 and 2008 and to Prof. H. Moshage in 2003).

Sub-programme 2:
- EU (KP6 PREVENTCD to Prof. C. Wijmenga in 2007);
- Netherlands Organisation of Scientific Research (NWO) - ZonMW Agiko to Prof. C. Wijmenga in 2008, Clinical Fellow Grant to Dr. G. Dijkstra in 2006, NWO VICI to Prof. C. Wijmenga in 2005 (1.25 M€);
- Wellcome Trust to Prof. C. Wijmenga in 2008 (1.1 M€);
- Top Institute Food and Nutrition (TIFN; to Prof. F. Kuipers, to Dr. S. van IJzendoorn, and to Prof. H.J. Verkade in 2008);
- Dutch Digestive Foundation (MLDS; to Dr. S. van IJzendoorn / Dr. E. Rings in 2008);
- Pharmaceutical industries (to Dr. G. Dijkstra).

In addition, the ‘Groningen Expert Centre for Kids with Obesity’ (GECKO), headed by Prof. P. Sauer and financed by an unrestricted grant from Hutchinson Whampoa, has been initiated, in which clinical and basic research is being performed within the framework of the CLDS on the causes and consequences of childhood obesity.
Table 5.6  Fund raising capacity at the level of programme CLDS

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>(FTE)</td>
<td>(FTE)</td>
<td>(FTE)</td>
<td>(FTE)</td>
<td>(FTE)</td>
<td>(FTE)</td>
</tr>
<tr>
<td>Total funding</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>(29.43)</td>
<td>(26.68)</td>
<td>(29.88)</td>
<td>(34.03)</td>
<td>(37.55)</td>
<td>(43.75)</td>
</tr>
<tr>
<td>Allocated funding</td>
<td>12.91%</td>
<td>12%</td>
<td>12.65%</td>
<td>12.93%</td>
<td>15.18%</td>
<td>16.23%</td>
</tr>
<tr>
<td></td>
<td>(3.80)</td>
<td>(3.20)</td>
<td>(3.40)</td>
<td>(4.40)</td>
<td>(5.70)</td>
<td>(7.10)</td>
</tr>
<tr>
<td>Acquired funding</td>
<td>87.09%</td>
<td>88%</td>
<td>87.35%</td>
<td>87.07%</td>
<td>84.82%</td>
<td>83.77%</td>
</tr>
<tr>
<td></td>
<td>(25.63)</td>
<td>(23.48)</td>
<td>(23.48)</td>
<td>(29.63)</td>
<td>(31.85)</td>
<td>(36.65)</td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are funded directly by the University of Groningen and/or the UMCG (allocated funding). To extend their research capacity, they acquire grants via internal and external competition (acquired funding) for non-tenured staff, employed PhD students, non-employed PhD students and in some cases a limited number of staff positions. The fund raising capacity is expressed in research equivalents (in FTE).
Section 5.7: Academic Reputation

Description and overview
CLDS researchers have an excellent academic reputation. This is evidenced by the prestigious awards, prizes, visiting professorships, editorships or participation on editorial boards of academic journals, memberships in academies and participation on the scientific advisory boards of industries and in international academic research institutes. CLDS researchers have founded, organised and/or chaired national and international conferences, and they are regularly invited to address major conferences. CLDS researchers regularly serve as reviewers for many high-ranking journals (including Nature, Science, Gastroenterology, Gut, Hepatology, Journal of Cell Biology, Molecular Biology of the Cell and Journal of Cell Science) and for national, international and European (EC) funding agencies (for all details, see appendix Section 5.7)

Awards and prizes
CLDS members have received 14 honorary memberships and/or prizes, including a Robert Feulgen prize from the Society for Histochemistry (Dr. B. Giepmans) and a NACEE Fullbright Scholarship (Prof. C. Wijmenga).

Editorships in academic journals
CLDS members are editors for or members of the editorial boards of peer-reviewed scientific journals, including:

- The Biochemical Journal (UK) – Prof. D. Hoekstra (Deputy Chairman)
- Biochemistry (USA) – Prof. D. Hoekstra
- Biochimica Biophysica Acta – Molecular and Cell Biology of Lipids – Prof. D. Hoekstra
- Journal of Lipid Research – Prof. F. Kuipers, Prof. M. Hofker
- Journal of Hepatology – Prof. H. Moshage
- International Journal of Inflammation – Prof. H. Moshage
- Liver International – Prof. H. Moshage
- Journal of Clinical Gastroenterology – Prof. H.J. Verkade
- Isotopes in Environmental and Health Studies – Dr. F. Stellaard
- Clinical Genetics – Prof. C. Wijmenga
- Journal of Applied Genetics – Prof. C. Wijmenga

Membership in academies and on scientific boards
CLDS members hold 66 memberships at academies and/or on scientific boards, including various committees. These include:

- Investment Subsidy NWO Large and Medium
- ZonMW-TOP
- Innovational Research Incentives Scheme VIDI) of the NWO
- Diabetes Fund
- Dutch Society of Hepatology
- the Dutch Arterosclerosis Society
- Society of Paediatric Research
- European Lipoprotein Club.

Invitations to address major conferences
CLDS members have received at least 142 invitations to address major scientific conferences. These include:

- Digestive Disease Week (DDW),
- United European Gastroenterology Week (UEWG),
- European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN),
- American Association for the Study of Liver Diseases (AASLD),
- NVGE (Dutch Society for Gastroenterology & Hepatology),
- European Science Foundation (ESF) meetings
- Gordon Research Conferences.
Section 5.8: Societal Relevance

Societal Quality
The increasing prevalence of obesity, type II diabetes, non-alcoholic liver disease/steatohepatitis, celiac disease and other metabolic diseases, particularly in young people, is emerging as a major burden on individual and public health care. Not surprisingly, diseases that involve human metabolism are subject to many lively discussions and debates in our society. Paralleling this development is the emergence of a strong societal emphasis on healthy ageing. Understanding the societal, pathological/physiological and developmental basis of these diseases and, reciprocally, the maintenance of health, is necessary for designing novel strategies to combat or deal with the consequences of these diseases. The focus of the CLDS research programme fits this development perfectly.

Societal Impact
Researchers at the CLDS (Dr. G.P.A. Smit and Dr. D-J. Reijngoud) recently developed a method which makes it possible to screen newborns for metabolic diseases such as MCAD (medium chain acyl-CoA dehydrogenase) deficiency by using tandem mass spectrometry. Over the past three years, screening for MCAD deficiency in the north of the Netherlands has been investigated by means of the heel stick. In this trial project, MCAD deficiency was found to be twice as prevalent as had been predicted, and was detected four times as frequently. At the recommendation of a Health Council of the Netherlands committee, the heel stick has been extended since 1 January 2007 to include screening for MCAD deficiency.

Research involving CLDS researchers (Prof. H.J. Verkade) has resulted in an adaptation of the national vitamin K guideline for newborns, approved by the board of the Dutch Paediatrics Society in September 2009. This adaptation was based directly on research data showing that the current daily dose of 25 micrograms of vitamin K to breast-fed infants in the population fails to prevent bleedings in apparently healthy infants with unrecognized cholestasis because of biliary atresia. This research underlines the fact that event analysis in specific at-risk populations can help to evaluate and improve nationwide prophylactic regimens.

Research within the CLDS contributes to the current liver transplantation and intestine transplantation programme for children. (The UMCG is the national reference centre for intestine and liver transplantations in children). For example, two children who received an intestine transplant in 2008 suffered from a rare, fatal and difficult to diagnose enteropathy called microvillus inclusion disease (MVID). With a 2008 research grant from the Dutch Digestive Foundation (MLDS), Dr. S. van IJzendoorn (Cell Biology), Dr. E. Rings (Paediatrics) and Prof. C. Wijmenga (Genetics) identified new mutations in the MYO5B gene in MVID patients, which will facilitate reliable genetic counselling and prenatal screening.

Regarding the KP6-funded PreventCD study of Prof. C. Wijmenga, if the proposed early dietary intervention results in effective prevention of celiac disease, then this is expected to result in the development of new European guidelines for early nutrition in order to prevent the disease.

Dr. G. Dijkstra of the CLDS participates as principal investigator in clinical trials related to Crohn’s Disease and ulcerative colitis.

Valorisation
Patents:
1. UK0803004, seven new genetic risk markers for celiac disease susceptibility
2. PCT/EP2007/052343, method for determining an HLA-DQ haplotype in a subject
Section 5.9: Next Generation

With regard to the education offered through GUIDE, please refer to the main part of the GUIDE evaluation.

- The CLDS holds an annual meeting during which CLDS PhD students present their work.
- Visiting scientists teach ‘master classes’ in which CLDS PhD students are actively encouraged to participate.
- CLDS researchers are involved in several training courses (embedded in GUIDE) for PhD students. CLDS PhD students are encouraged to attend these courses.
- CLDS researchers actively participate in the Junior Scientific Masters class (JSM), which offers motivated medical students additional opportunities to get involved in scientific research in addition to their regular educational programmes. This special scientific educational programme provides students with the possibility of obtaining an Honours degree in research during the Bachelors phase and/or, by combining their internship with a PhD project, of receiving both their MD and PhD following the Masters phase.
- CLDS researchers actively participate in the Topmaster Medical and Pharmaceutical Drug Innovation programme. In this way, the CLDS is able to offer excellent students from this Topmaster programme the opportunity to get involved in CLDS scientific research.
Section 5.10: Viability, SWOT and Future Strategy

Viability

Resource management.
Resource management focuses on excellence. Programmes are in place to attract excellent staff (Dr. B. Bakker – Rosalind Franklin programme; Dr. K.N. Faber – tenure track programme; Prof. C. Wijmenga – VICI programme and several MD/PhD and Topmaster students).

Available infrastructure/research facilities.
In the previous evaluation, the available infrastructure was judged to be excellent. The CLDS research programme was well-regarded as was demonstrated by the inauguration of new laboratory facilities for the departments of Gastroenterology and Hepatology. In addition, the new animal facility was very important to CLDS research (mouse clinic – head: Prof. M. Hofker). The imaging centre was also used intensively by CLDS members (scientific head: Dr. B. Giepmans). Finally, with the appointment of Prof. Wijmenga as chair of the Department of Genetics, large investments were made in the Genetics infrastructure, facilitating participation in this rapidly developing and innovative field.

Innovative capacity.
The innovative capacity is dependent on the quality of the research staff, the students and the available infrastructure to address complex scientific questions. As outlined above, these conditions are met by the CLDS.

Financial resources.
The fundraising capacity of the CLDS scientific staff is solid (Table 5.6) and therefore the prospects for the CLDS are excellent.

Expertise within the institute.
In recent years many talented young staff scientists have been appointed as professors, associate professors or assistant professors (for details, see Section 5.1), bringing in new expertise.

SWOT

Strengths
- Availability of a focused research environment in which high-level independent scientists with complementary expertise enable synergistic approaches to major research questions in gastrointestinal and metabolic diseases.
- Availability of large patient cohorts for genetic studies (celiac disease, diabetes, inflammatory bowel disease), and participation in LifeLines, a national prospective population cohort of approximately 165,000 people.
- Availability to researchers within the research area of CLDS to cover the entire spectrum of research, including genomics, epidemiology, cell biology, genetically modified cell and animal models, proteomics, metabolomics, stable isotope facilities and population/clinical/translational research in healthy and diseased individuals.
- Complementary expertise within the CLDS.
- Long and successful research tradition, which is attractive to ambitious new/young scientists.
- Availability of state-of-the-art facilities in genetics, proteomics, metabolomics and imaging.
- Expertise in the genetics of intestinal inflammatory disorders.
- Successful completion of high-level physiological studies (for example, using stable isotopes).
- New animal facility.
- State-of-the-art technology for genetics and genomics.
- Advanced tools for mass spectrometry and electron microscopy.
- State-of-the-art technology for fluorescence imaging.
- State-of-the-art tools for proteomics.

Weaknesses
Until recently we were substandard in the following:
- Faculty staff in the research area of systems biology of metabolism.
- Facilities for introducing animal experimentation techniques, including specific genetic manipulations in mice.
- A well-defined and integrated system biology-based approach.
- Due to the successful growth of the CLDS, some groups are accommodated far from others.
- Publications in journals below the top 50-75% in ISI research fields.
Opportunities

- Systems biology, including system genetics.
- Increased interest in healthy ageing, rather than the classic (and continuing) theme of curing disease. The theme ‘Healthy ageing’ also stresses the importance of physiological studies, in which the CLDS has developed a strong reputation.
- Increased interest in longitudinal studies from childhood to old age, involving both disease prevention and disease development. Association of CLDS researchers with the University of Groningen initiative LifeLines.
- Availability of whole genome analysis techniques, combined with the population / Life Lines in the UMCG and top scientists.
- Increased diversion of research money towards scientifically successful groups, in particular to group efforts aimed at synergistically addressing complex metabolic diseases.
- Changes in social patterns, population profiles, lifestyle changes, etc.
- The obesity epidemic, now starting at a young age, has increased the awareness that studying metabolism is essential for preventive and curative strategies.
- Local Events: for example Lifelines, healthy ageing as theme for the university.

Threats

- Some universities already have a stronger resource allocation towards scientifically successful researchers / consortia.
- Availability of competitive post-doc positions within the university.
- The nationwide science budget cuts, and those which are expected, could threaten the scientific climate, for example, with respect to the internal University resources and to the availability of researchers being requested to spend more time on other tasks (education, patient care).
- The recruitment of MDs who are truly translational researchers has been difficult. These researchers are crucial to bridge the different areas of research.

Future Strategy

During the period 2003 to 2008, the CLDS was able to maintain its successful course and to implement significant improvements in its structure and level of expertise. The coordinators are confident that the CLDS research programme can be successfully continued. The CLDS invests in high quality staff and research in order to strengthen the areas of systems biology and genetics. In combination with a focus on predictive disease risk modelling, this is especially important given the increased interest in healthy ageing (as opposed to the classic – and continuing – theme of curing disease). The focused research environment of the CLDS – based on high-level independent scientists with complementary expertise – has proven to be very attractive, and has helped to recruit high quality staff and funding in a competitive market.

In 2009, Dr. A.K. Groen was appointed professor of Paediatrics and Systems Biology and full CLDS member. Dr. B. Bakker (Rosalind Franklin Fellow) was appointed full member of the CLDS to strengthen the field of Systems Biology of Metabolic Diseases. Her research focuses on understanding the complex interplay between lipid and carbohydrate metabolism and the development of predictive computer models for metabolic syndrome and inborn metabolic diseases.
CHAPTER 6

Institute for Transplantation, Immunology and Inflammation
Section 6.1: Objectives and Research Area

Programme Leaders
Prof. Dr. Cees G.M. Kallenberg
Prof. Dr. Maarten Slooff (2002-2009)
Prof. Dr. Jan Maarten van Dijl (since 2009)

Objectives
The mission of TRIO is to define pathways and mechanisms of pathogenesis and tissue damage in patients suffering from disturbed immune homeostasis or infectious diseases as a basis for the rational design of novel strategies for repair and prevention. The overarching objective for all research activities within TRIO is to provide a platform for excellent research on the critical determinants for Tissue Damage and Repair. To achieve our mission and the main objective, TRIO strives to provide a top-quality research environment with excellent intellectual and technological infrastructures.

Research Area
To tackle the central theme of Tissue Damage and Repair, TRIO encompasses the two partially overlapping conceptual research areas “Transplantation” and “Clinical and Applied Immunology”. The research teams associated with TRIO contribute differentially to these areas, depending on their particular research interests. Cooperation between the associated teams is promoted and implemented where appropriate. This has led to an attractive and dynamic research environment with the required critical mass that offers a multitude of opportunities for researchers in all possible stages of their careers. In this report we describe what has been achieved during the current reporting period and how we envisage the future perspectives for research within TRIO.

Transplantation
Transplantation is a major clinical challenge taken up by the UMCG; the ongoing activities accommodate transplantation programmes for kidney, liver, lung, heart, pancreas and small bowel, or combinations thereof. Accordingly, transplantation represents a major conceptual research theme and sub-programme in TRIO. The sub-programme Transplantation is headed by Prof. M.J. Slooff. Four topics are specifically addressed:

Chronic Transplant Dysfunction
(CTD; Hillebrands, A.S.H. Gouw, W.vd Bij, W. van Son)
Transplant arteriosclerosis is one of the key features of chronic transplant dysfunction and, therefore, a major subject of research in kidney, liver and lung transplantation. In the field of kidney transplantation, research in the current period of analysis concentrated on the role of smooth muscle cells and circulating stem cells in the development of transplant arteriosclerosis. Also, the relation with the metabolic syndrome, diabetes and insulin resistance and CTD is analysed. Regarding liver transplantation, the main interests in this field of CTD are graft fibrosis and liver regeneration after transplantation and the role of biliary stem cells in regeneration processes. Determinants for the development of bronchiolitis obliterans after lung transplantation is another point of interest in this field.

Optimisation of donor organs
Within this topic the central theme focuses on improving the quantity and quality of organs retrieved from donors. Efforts to analyse new pathways to improve the number of donors is a continuing subject of investigation and publication. The impact of brain death on the organ quality of kidney, liver, small bowel and lungs is studied by analysing gene expression, stress and inflammatory responses in these organs after retrieval, and by analysing the impact on post-transplant function. Studies concerning optimisation of hypothermic machine preservation for kidneys and liver have led to the development of a new, patented portable perfusion system and several publications drawing attention to the positive effects of machine perfusion of donor organs. The effects of organ retrieval from non-heart-beating donors has been studied in animal models – not only for kidney and liver, but also for lung transplantation – in order to investigate factors that determine the usability of such organs.

Evaluation of clinical transplant programmes
The main focus of the evaluation studies is on improving the quality of the clinical transplant programmes. Topics of interest are long-term survival, determinants for outcome in terms of survival and morbidity, cost effectiveness, quality of life, technical aspects of procedures, diagnostics and monitoring of rejection. Especially in the latter field, interesting studies are being performed concerning the interaction of the levels of viral (EBV) serology, rejection and immunosuppression. Blood loss is a major determinant of post-operative survival and morbidity, especially in liver transplantation. Consequently, this subject is an important research line in liver transplantation. Basic research on this subject has been promoted by establishing a post-graduate tenure track position. Further research has concentrated on the expression...
of heme-oxygenase-1 in hepatic ischemia/reperfusion injury and the molecular mechanisms of donor-related bile duct injury. Clinically, the genesis of non-anastomotic biliary strictures was investigated. The first clinical results of the national small bowel transplantation programme were reported in the literature.

(Stem)Cell transplantation
(P. de Vos, M.C. Harmsen, M.J.A. van Luyn)
(Stem) cell transplantation research focuses mainly on two areas, pancreatic islet transplantation and stem cell transplantation for regenerative purposes. The pancreatic islet transplantation research concentrates on the optimisation of islet-harvesting techniques, structure of the micro capsules, biocompatibility of alginate-PLL capsules, optimisation of survival and function of encapsulated islets, immunoprotection of the encapsulated islets and xenotransplantation of these composites. Stem cell research for regenerative purposes is a relatively new line of research. Factors related to the engraftment of bone marrow-derived stem cells in renal repair are also being investigated as well in myocardial infarctions in rats. The possible role of xenotransplantation of porcine foetal cells in Parkinson’s disease is also investigated.

The subprogramme Clinical and Applied Immunology integrates research on autoimmunity, tumour immunology, inflammation and the roles of microbes in human health and disease. This provides excellent opportunities for interdisciplinary and cross-disciplinary research. The subprogramme Clinical and Applied Immunology is headed by Prof. C.G.M. Kallenberg. The following topics are addressed:

Autoimmunity
Systemic autoimmune diseases are a major, long-term line of research. Here, pathogenetic mechanisms are unravelled in order to design more specific methods of treatment with higher efficacy and fewer side effects. Research on anti-neutrophil cytoplasmatic autoantibody (ANCA)-associated vasculitis represents a major research area. In vitro studies have revealed how ANCA interact with neutrophils and endothelial cells and induce vascular damage, probably in the context of an inflammatory stimulus of infectious origin. However, T-cell mediated autoimmune responses are also very important, particularly in Wegener’s Granulomatosis characterised by granulomatous inflammation in addition to systemic vasculitis. The unravelling of these cell-mediated pathways has resulted in new treatment methods. This group has been strengthened since P. Heeringa, who was awarded a VIDI grant, was appointed as associate professor in 2006. His animal model of MPO-ANCA-associated vasculitis/glomerulonephritis makes it possible to test pathogenic and therapeutic concepts in vivo. In terms of treatment, the group participated in major trials, the most important being the NIH-sponsored RAVE study in which B-cell depletion was shown to be effective. The Groningen group was the only European group invited to participate with a few highly qualified groups from the USA. In the systemic lupus erythematosus (SLE) project, the role of disturbed clearance of apoptotic cells has been further explored as a mechanism for perpetuation of inflammation. Furthermore, patient-oriented translational research has explored (late) morbidity and mortality due to increased sensibility to infections and cardiovascular diseases. The role of immunosuppressives, in particular biologicals, on the response to influenza vaccination has been explored in depth. Sjögren’s syndrome is another systemic autoimmune disease characterised by lymphocytic infiltration and destruction of exocrine glands, in particular salivary and lacrimal tissue, together with extraglandular manifestations. Here, B-cell depletion has been successfully used as a new therapeutic approach, also allowing an assessment of the role of B cells in pathogenesis of the lesions. The availability of biopsy material from the parotid gland before and after B-cell depletion has made it possible to study the effects of this treatment modality at the level of the target origin. Furthermore, the group collaborates with UCLA in an NIH-sponsored study on proteomic and genomic biomarkers in saliva and parotid tissue. Amyloidosis is another systemic disease in which diagnostic procedures (abdominal fat biopsy and radio-labelled SAP – serum amyloid P component) have been further developed and new therapeutic approaches have been tested. Since the UMCG has chosen “Healthy Ageing” as a main focus of research, age-associated alterations of the immune response (immunosenescence) are being studied as one of the underlying factors leading to autoimmunity. The appointment of Prof. A.M.H. Boots to this theme will strengthen this integrated line of research. The Centre for Blistering Diseases, Department of Dermatology, is an international referral and research centre for epidermolysis bullosa and autoimmune bullous diseases. New clues have been found for diagnosis, particularly by immunofluorescence, and the pathogenesis of acantholysis in pemphigus is being unravelled. In heritable epidermolysis bullosa, phenotype-genotype correlations of dystrophic and simplex subtypes are being studied. In addition, a new disease, lethal acantholytic epidermolysis bullosa, has been discovered, and new patients with revertant mosaicism have been described.

Tumour immunology
In the field of tumour immunology great progress has been made in vaccination research in gynaecological tumours. The use of recombinant viral vector systems and virosomes for vaccine development was further explored, particularly in the induction of MHC class I-restricted cytotoxic T-lymphocytes. T-cell responses were studied in patients with pre-malignant and malignant cervical neoplasia; in ovarian cancer, p53-specific T-cell responses were evaluated as a base for P53 immunotherapy. In a phase II trial, the potency of immunisation with a p53 synthetic long peptide vaccine was evaluated in terms of p53-specific immune responses. In vitro targeting of TRAIL as a method to induce apoptosis in tumour cells was explored. Further research was also done on EpCAM (epithelial cell adhesion molecule) as a marker not only for tumours, but also for developing and regenerating tissues. Monoclonal antibodies to EpCAM were explored as a method for tumour detection and apoptosis induction.

**Inflammation**


Therapeutic strategies interfering with the microvascular endothelium in chronic inflammatory diseases is a main line of research. Macromolecular drug targeting devices are being developed; these are directed at disease-associated target epitopes for use in the selective delivery of signal transduction inhibitors that prevail in endothelium under pro-angiogenic and/or pro-inflammatory conditions. Besides immuno-liposomes, antibody and peptide-targeted adenoviruses are under study. Via laser microdissection of endothelial cells followed by gene expression array analyses, in vivo microvascular pharmacologic studies are being performed. A major focus within this theme of inflammation is regenerative medicine. Here, the aim is to define new modalities for the prevention/intervention of renal and cardiovascular diseases through the organ-specific application of smart biomaterials, which is guided by the results of investigations on the micro-environment and molecular and cellular pathways during physiological or pathophysiological tissue repair. For this purpose, stem cells, mediators and biomaterials are being used. The micro-environment is studied in order to define appropriate guiding factors that provide instruction to stem cells upon their administration in vivo. With respect to biomaterials, the foreign body reaction is analysed; in itself, this can also be employed to augment regenerative therapies. Finally, within this theme, reproductive immunology is studied, focusing on the regulation of the immune response by factors associated with reproduction, such as factors produced by the placenta or ova ries. Based on studies on the maternal immune response adapting to pregnancy, changes of immune responses during pre-eclampsia are evaluated. These studies are done both in humans and in rat models.

**Microbes in human health and disease**


As part of the theme "microbes in health and disease", the Molecular Bacteriology and Molecular Virology sections of the Medical Microbiology Department perform fundamental, translational and application-oriented research on bacterial and viral pathogenesis. The main objective is to develop novel approaches for the prevention or treatment of infections caused by important bacterial and viral human pathogens that are especially threatening to very young, elderly or immune-compromised individuals.

The **bacteriological research** addresses the mechanisms that lead to virulence and antibiotic resistance of Staphylococcus aureus and Streptococcus pneumoniae in order to identify novel targets for preventive or therapeutic interventions with novel anti-microbial agents, human monoclonal antibodies or vaccines. Additionally, in ecological studies the dynamics of the human gut microbiota and interactions between bacteria are investigated, not only in relation to disease but also in response to interventions with antibiotics or prebiotics and probiotics. A major theme within the bacteriological studies is the analysis of the secretome, which includes all proteins exported to the cell surface and host milieu. This is important, because the secretome is the main reservoir of compounds that influence human health in negative or positive ways. To obtain deeper insights in the roles of the secretome in bacterial fitness, growth, survival and antibiosis, the non-pathogenic model bacterium Bacillus subtilis is also studied by means of Systems Biology approaches.

The **virological research** addresses viral infections that represent a major threat to human health. These include influenza and other respiratory viruses, Dengue and human papilloma virus (HPV) infections. Research on respiratory viruses is primarily devoted to the development of novel anti-viral vaccines, including the use of reconstituted viral membrane envelopes (virosomes) for efficient cellular delivery of vaccine antigens and adjuvants. In the area of influenza virus vaccines, special attention is given to technologies that can be deployed in case of an emerging pandemic. In collaboration with the Department of Pharmacy, methods for increased vaccine shelf-life and improved vaccine administration are explored. The research on respiratory syncytial virus – a pathogen with exceptionally high prevalence – is also focused on the development of a vaccine based on reconstituted viral envelopes. Research on Flavivirus infections, especially Dengue, is focused on the molecular mechanisms of cell entry and the phenomenon of Antibody-Dependent Enhancement of disease that is observed following heterotypic Dengue-infections. The main objective of
research on tumour viruses is to develop strategies for immunotherapeutic treatment of virus-induced cancers, such as cervical cancer, ovarian cancer and hepatitis C virus-induced liver cirrhosis/cancer. Clinical studies focus on the immunotherapy of ovarian cancer with P53 as the target antigen. An integrative element in the research on bacterial and viral pathogens is the use of epidemiological techniques to investigate and predict the behaviour of these microbes in patient populations and the community.

**Strategy and policy**
During the present reporting period the strategy and organisation of TRIO has been adapted to the needs of the participating researchers. This was achieved by (1) taking organisational measures for streamlining and increasing the coherence of the research programme; (2) further strengthening of translational research activities within TRIO; and (3) strengthening the internal links within TRIO by establishing new research teams.

Note to 1) To streamline the research programme, it was decided to group the research activities into two conceptual areas: Transplantation and Clinical and Applied Immunology. Furthermore, the coherence of the programme has been increased by adapting the leadership in TRIO. This has been achieved by establishing a TRIO Board, which is composed of the coordinators and the section leaders, and by making a clear distinction between principal and associated investigators. The conceptual approach has helped us to bridge gaps between different sections and departments within TRIO, as several research units can contribute to the implementation of the research areas. Thus, cooperation between the research groups is now primarily initiated and organised from these basic units. The tasks of the coordinators and section leaders have been defined as follows.

The TRIO coordinators
- direct the activities within TRIO,
- facilitate the communication between TRIO and GUIDE,
- disseminate relevant information to the PIs,
- define the research priorities in consultation with the Board,
- determine the membership of TRIO,
- promote mutual consistency and collaboration within the research programme,
- indicate possible deficiencies and opportunities within the research profile of TRIO,
- organise meetings for discussing research progress and needs, and
- are responsible for reporting.

The section leaders
- represent the research groups within particular sections of TRIO,
- take care of the bottom-up distribution of relevant information, organise master classes, meetings and workshops,
- indicate challenges and needs concerning the infrastructure (personnel, laboratory space, equipment etc.), and
- supply the necessary information for reporting purposes.

The management and monitoring of research output, research projects and grants is done by the staff of GUIDE.

Note to 3) To strengthen the internal links within TRIO, six new research groups were established:
- Dr G. Molema was appointed full professor in the Life Sciences with a research focus on Endothelial cell function and dysfunction in health and disease in 2004.
- Dr M.J.A. van Luyn was appointed full Professor in Tissue Engineering in 2005.
- Dr R.J. Porte was appointed full Professor of Surgery in 2007.
- Dr C.A.H.H. Daemen was appointed full Professor in Tumour Virology in 2008.
- Two new professors were recruited from outside the UMCG:
- Dr. J.M. van Dijl was appointed full Professor in Medical Microbiology with a research focus on Molecular Bacteriology in 2004.
- Dr M. Peppelenbosch was appointed full Professor in Cell Biology with a research focus on Molecular Cell Biology in 2004.

In conclusion, TRIO is a viable platform for cooperation between research groups with interests in research on transplantation, immunology, inflammatory processes and infectious diseases. This has been achieved by creating a flat organisational structure with clearly defined tasks for coordinators, section leaders and PIs, and by following a concept-based division of the research activities into the two main areas of Transplantation and Clinical and Applied Immunology. Importantly, the cooperative activities within these areas are driven by common interests and complementary capabilities, and they are supported by an excellent infrastructure.
Section 6.2: Composition of the Research Unit

Description of the research unit composition

During the present reporting period, TRIO has experienced a steady increase in the number of tenured and non-tenured staff at all academic levels, demonstrating the fact that TRIO is a healthy and attractive research platform with a strong potential for growth (Table 6.1). Compared to the previous SEP, the tenured staff of TRIO doubled in size from 22 to 43, and the non-tenured staff increased from 7 to 10. Notably, the non-tenured staff includes 2 Rosalind Franklin fellows, and 2 fellows with VIDI grants from the Netherlands research Council NWO. In accordance with the staff expansion, the number of PhD students has more than doubled from 39 to 81. (Table 6.1). Over all, we conclude that TRIO is on the right track with an average of somewhat more than 2 PhD students per tenured member of staff. For details, see appendix Section 6.2.

Table 6.1 Overview of research staff at the level of programme TRIO

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenured staff</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.93</td>
<td>8.35</td>
<td>8.95</td>
<td>10.45</td>
<td>13.45</td>
<td>14.15</td>
<td></td>
</tr>
<tr>
<td>(22)</td>
<td>(27)</td>
<td>(27)</td>
<td>(31)</td>
<td>(41)</td>
<td>(43)</td>
<td></td>
</tr>
<tr>
<td>Full professors</td>
<td>1.85</td>
<td>2.85</td>
<td>3.65</td>
<td>3.95</td>
<td>4.25</td>
<td>4.95</td>
</tr>
<tr>
<td>(6)</td>
<td>(9)</td>
<td>(7)</td>
<td>(9)</td>
<td>(13)</td>
<td>(17)</td>
<td></td>
</tr>
<tr>
<td>Associate professors</td>
<td>3.18</td>
<td>3.00</td>
<td>2.40</td>
<td>3.20</td>
<td>5.60</td>
<td>5.20</td>
</tr>
<tr>
<td>(10)</td>
<td>(9)</td>
<td>(12)</td>
<td>(15)</td>
<td>(14)</td>
<td>(13)</td>
<td></td>
</tr>
<tr>
<td>Assistant professors</td>
<td>0.60</td>
<td>0.60</td>
<td>1.40</td>
<td>2.00</td>
<td>2.80</td>
<td>2.80</td>
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<tr>
<td>(2)</td>
<td>(2)</td>
<td>(4)</td>
<td>(6)</td>
<td>(8)</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>Other senior staff</td>
<td>1.30</td>
<td>1.90</td>
<td>1.50</td>
<td>1.30</td>
<td>0.80</td>
<td>1.20</td>
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<tr>
<td>(4)</td>
<td>(7)</td>
<td>(5)</td>
<td>(4)</td>
<td>(3)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>Non-tenured staff</td>
<td>5.45</td>
<td>4.77</td>
<td>4.77</td>
<td>4.46</td>
<td>5.63</td>
<td>8.78</td>
</tr>
<tr>
<td>(7)</td>
<td>(6)</td>
<td>(6)</td>
<td>(6)</td>
<td>(9)</td>
<td>(10)</td>
<td></td>
</tr>
<tr>
<td>PhD students</td>
<td>19.43</td>
<td>26.08</td>
<td>27.34</td>
<td>26.86</td>
<td>28.70</td>
<td>27.83</td>
</tr>
<tr>
<td>(39)</td>
<td>(51)</td>
<td>(58)</td>
<td>(62)</td>
<td>(65)</td>
<td>(81)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>19.43</td>
<td>26.08</td>
<td>27.34</td>
<td>26.86</td>
<td>28.70</td>
<td>27.83</td>
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<tr>
<td>(32)</td>
<td>(44)</td>
<td>(47)</td>
<td>(45)</td>
<td>(49)</td>
<td>(50)</td>
<td></td>
</tr>
<tr>
<td>Non employed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(7/17.95%)</td>
<td>(7/13.73%)</td>
<td>(11/18.97%)</td>
<td>(17/27.42%)</td>
<td>(16/24.62%)</td>
<td>(31/38.27%)</td>
<td></td>
</tr>
<tr>
<td>Total research staff</td>
<td>31.80</td>
<td>39.20</td>
<td>41.06</td>
<td>41.77</td>
<td>47.78</td>
<td>50.75</td>
</tr>
<tr>
<td>(68)</td>
<td>(84)</td>
<td>(91)</td>
<td>(99)</td>
<td>(115)</td>
<td>(134)</td>
<td></td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers have also obligations for patient care. For the sake of simplicity a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD-students with an employment contract. For non-employed PhD students (student status), expression as FTE is not appropriate.

Strategy and policy

It has been the policy of TRIO to strengthen the scientific standing and coherence of the research programme through a number of strategic appointments of tenured staff. This policy will be continued in the coming years, not so much to expand the number of staff members, but rather to make strategic appointments as replacements for departing members of staff. A pending challenge will be the replacement of Prof. Maikel Peppelenbosch, who was recently promoted to head of the Department of Experimental Gastroenterology at the Erasmus Medical Centre in Rotterdam. Although we regret the departure of Prof. Peppelenbosch, his promotion underpins the fact that TRIO has an important role as an incubator of talented researchers with a high potential for growth. Importantly, staff renewal, as well as excellence and continuity of the research programme, are also ensured through the four tenure track positions within TRIO. As a whole, the TRIO staff has sufficient critical mass to be successful in the competition for external funding provided by national, European and international funding agencies and foundations, and the same is true for the acquisition of resources through contract research (see Table 6.2).
Research Funding
In the period between 2003 and 2008, TRIO’s resources for the appointment of staff have almost doubled. We consider it important that this significant increase mainly relates to the acquisition of substantial external funding through research grants and contract research, the steepest increase being observed for research grants (2.65 FTE in 2003, compared to 6.73 FTE in 2008). This underscores the scientific standing of TRIO as well as the societal and industrial relevance of its research programme (see Table 6.2).

Table 6.2 Overview of the research funding at the level of programme TRIO

<table>
<thead>
<tr>
<th>Year</th>
<th>Direct funding (1)</th>
<th>Research grants (2)</th>
<th>Contract research (3)</th>
<th>Total funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>19.00 (59.76%)</td>
<td>2.65 (8.33%)</td>
<td>10.15 (31.91%)</td>
<td>31.80 (100%)</td>
</tr>
<tr>
<td>2004</td>
<td>25.38 (64.74%)</td>
<td>4.03 (10.27%)</td>
<td>9.80 (24.99%)</td>
<td>39.20 (100%)</td>
</tr>
<tr>
<td>2005</td>
<td>24.94 (60.74%)</td>
<td>3.48 (8.46%)</td>
<td>12.65 (30.79%)</td>
<td>41.06 (100%)</td>
</tr>
<tr>
<td>2006</td>
<td>24.56 (58.81%)</td>
<td>6.68 (15.98%)</td>
<td>10.53 (25.21%)</td>
<td>41.77 (100%)</td>
</tr>
<tr>
<td>2007</td>
<td>27.65 (57.88%)</td>
<td>7.68 (16.06%)</td>
<td>12.45 (26.06%)</td>
<td>47.78 (100%)</td>
</tr>
<tr>
<td>2008</td>
<td>25.73 (50.69%)</td>
<td>6.73 (13.25%)</td>
<td>18.30 (36.06%)</td>
<td>50.75 (100%)</td>
</tr>
</tbody>
</table>

Expenditure (k€)

<table>
<thead>
<tr>
<th>Item</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel costs (k€)</td>
<td>1,520.8</td>
<td>1,946.9</td>
<td>2,199.8</td>
<td>2,286.7</td>
<td>2,797.1</td>
<td>3,150.2</td>
</tr>
<tr>
<td>Other costs personnel (k€)</td>
<td>585.6</td>
<td>749.6</td>
<td>847.0</td>
<td>880.5</td>
<td>1,077.0</td>
<td>1,213.0</td>
</tr>
<tr>
<td>Costs non-employed PhD students (k€)</td>
<td>111.6</td>
<td>114.5</td>
<td>137.6</td>
<td>197.3</td>
<td>251.7</td>
<td>479.6</td>
</tr>
<tr>
<td>Other costs - non-employed PhD students (k€)</td>
<td>59.5</td>
<td>59.5</td>
<td>70.125</td>
<td>99.9</td>
<td>125.4</td>
<td>214.6</td>
</tr>
<tr>
<td>Total expenditure</td>
<td>k€ 2,277.5</td>
<td>k€ 2,870.5</td>
<td>k€ 3,254.5</td>
<td>k€ 3,464.3</td>
<td>k€ 4,251.1</td>
<td>k€ 5,057.4</td>
</tr>
</tbody>
</table>

Explanation: The expenses for research include both personnel and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the donation to the provision “wachtgelden” (i.e. the obligation to provide personnel a reduced pay in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff and other costs like allowances for child care, and commuter traffic. Although non-employed PhD students do not represent research FTE, the costs of these PhD students have been included. Other costs include operational costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

1 Direct funding by the university;
2 Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programmes ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3 Funding for specific research projects obtained from external organisations, such as industry, governmental ministries, European Commission (Framework programmes) and charity organizations.
Section 6.3: Research Environment and Embedding

Position and reputation
TRIO is well-embedded in the national and international scientific community as demonstrated by 90 structural collaborations with international research groups and 47 structural collaborations at the national level (for details, see appendix Section 6.3). These collaborations have resulted in numerous joint scientific publications (see Section 6.4). TRIO researchers also have strong connections with non-profit organisations (11 collaborations with the Gut Flora Foundation, RIVM, Samenwerking Noord Nederland, the Top Institute Pharma and the Top Institute Food and Nutrition) and industry (34 collaborations with companies such as Cellectis, Danone-Numisco, DSM Nutritional Products, Hycult bioscience, Genencor-Danisco, GSK-Oncology, IQ therapeutics, Neurochem Canada, Novartis, Mead Johnson, Medtronic Bakken Res., Mucosia, Mymetics, NIZO-Wyeth, Novo Nordisk, Novozymes, Pepsan, Roche, Solvay Pharmaceuticals, Syncom, Synvalux, TIBOTEC, and the UBC Group). In order to sustain and, where possible, increase these interactions, TRIO has an active outreach policy with respect to publications in international peer-reviewed journals (see Sections 6.4 and 6.5) and presentations at national and international meetings (see Section 6.7).

Overall, we conclude that TRIO provides an attractive research environment for national and international scientific collaborations; it is our intention to further expand this position in the years to come.

Important networks and initiatives:
Top Institute Pharma (TIP) is a public/private partnership that aims to achieve leadership in research and education in areas that are critical for the international competitive position of the pharmaceutical industry. The Institute conducts groundbreaking, cross-disciplinary research and offers advanced training programmes focused on improving the efficiency of the entire process of drug discovery and development (see: www.tipharma.com). TRIO receives major funding through TIP projects T1-215 (Peppelenbosch), T3-103 (Peppelenbosch), T4-213 (van Dijl), and T4-214 (Wilschut). J.M. van Dijl is theme coordinator for TIP Programme 4 on infectious diseases.

Top Institute Food and Nutrition (TIFN)
Top Institute Food and Nutrition (TIFN) is a public/private partnership that generates scientific breakthroughs in food and nutrition. This results in the development of innovative products and technologies that respond to consumer demands for safe, tasty and healthy foods (see: www.tifn.nl). TRIO receives major funding through a TIFN project to P. Heeringa, J.M. van Dijl is a Focal Point for TIFN, and P. de Vos is a project leader for TIFN.

European Research Networks.
European Research Networks. TRIO researchers participate in fourteen RTD research networks in the context of the sixth and seventh Framework Programmes of the EC; a Marie Curie Initial Training Network, and two transnational initiatives coordinated by the European Science Foundation and the organisation for European Systems Biology research in Microorganisms (SysMo). TRIO researchers have leading roles in the establishment and coordination of these European research networks.

BACELL.
Prof. J.M. van Dijl is chairman of the BACELL umbrella organisation (see: www.bacell.eu). Nineteen years of EU funding have placed the European Bacillus community at the forefront of bacterial post-genomics research worldwide. The BACELL umbrella organisation was established to facilitate strong interactions and communication between these programmes. Research centres participating in BACELL have leading positions in the study of dangerous pathogens, including staphylococci, streptococci, Listeria and Bacillus anthracis. The BACELL community is supported and advised by the Bacillus Industrial Platform (BACIP). BACIP includes the largest producers of recombinant organisms and their products worldwide (annual turnover about €2 billion). BACELL and BACIP have submitted several position papers on relevant microbiological topics, like Systems Biology and Synthetic Biology, for consideration by European research policy makers.

Dengue Research Network.
TRIO researchers (J.C. Wilschut and J.M. Smit) are involved in epidemiological research programmes on Dengue virus infections in collaboration with partners in the Academic Hospital in Paramaribo, Surinam, and the University of Carabobo, Valencia, Venezuela.

Mycobacterium ulcerans.
Prof. T. van der Werf has a major role in an international network on Mycobacterium ulcerans infections, also known as Buruli ulcer. His team has published important studies on this topic in major journals (Lancet (2x) and NEJM).
Clinical trial networks
TRIO participates in many multinational clinical trial networks. In the field of systemic autoimmune diseases, Prof. C. Kallenberg participates in a large NIH-sponsored trial on the efficacy and underlying mechanisms of B-cell depletion in ANCA-associated vasculitis. His group also participates in European (EULAR) and international collaborations in the field of Sjö gren’s syndrome (including an NIH-sponsored study on genomics and proteomics in this disease) and Systemic Lupus Erythematosus (including a leading role in an EULAR initiative to assess efficacy and side effects of vaccination in patients under immunosuppression). Strong international collaboration in amyloidosis research has resulted, among other things, in a major clinical trial (NEJM 2007;356:2349-60). Prof. M. Jonkman is leading multi-centre international projects in Autoimmune Blistering Diseases. Transplantation research also has a strong national and international orientation. Prof. R. Ploeg holds a leading position in national and international networks on the various aspects of non-heart-beating donors in organ transplantation and on improvements in organ preservation. A major grant (1,200 k €) was awarded by the Dutch Health Care Insurance Board for a cost effectiveness study comparing the different types of donor grafts.

Guest researchers
In accordance with the general GUIDE policy, TRIO invites distinguished guest scientists to lecture about their research, to enter into scientific discourse with colleagues, to build national and international networks, to participate in master classes and to participate in thesis defences. An overview is given in the table below. During the present reporting period, 64 guest speakers visited TRIO. These speakers were invited to speak in conjunction with workshops, symposia and PhD defences. An overview is provided in appendix Section 6.3

The PIs of TRIO held a major symposium (BACELL 2007) and hosted 74 national and international guest researchers, who presented their work at seminars, meetings and workshops.

<table>
<thead>
<tr>
<th>Institute / year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRIO</td>
<td>2</td>
<td>14*</td>
<td>9</td>
<td>15</td>
<td>13</td>
<td>11</td>
<td>64</td>
</tr>
</tbody>
</table>

* 18 joint lectures together with programme CLDS – noted 9 lectures each

Strategy and policy
To create an attractive and excellent international research environment, the PIs of TRIO are encouraged to participate in national and international scientific networks and, where possible, international grant applications. Such networks include the Top Institute Pharma (4 projects), the Top Institute Food and Nutrition (1 project), and collaborative RTD projects funded through the Framework Programmes of the European Commission (12 projects). The excellent technological and intellectual infrastructures of GUIDE in general, and TRIO in particular, provide the PIs with a strong position to participate in such networks. Preferably, these should include strong interactive links with local (LifeLines) and international cohort studies and biobanking initiatives. It is therefore a policy of TRIO to continue its efforts to sustain a top-level infrastructure.
Section 6.4: Quality and Scientific Relevance

Most important results
In this section, we outline selected results of particular scientific importance, and results that have been very important for the coherence of the TRIO research programme:

1. Transplantation - Chronic transplant Dysfunction
   (CTD; Hillebrands, A.S.H. Gouw, W.vd Bij, W. van Son)
   Chronic transplant dysfunction is a major cause of transplant failure. Both immunological, metabolic and hemodynamic factors are involved. This line of research has identified these factors with implications for treatment (40 publications in peer-reviewed journals, including Hepatology 2005,42:1166; Trends Cardiovasc Med 2005,15:1; Diabetes Care 2005,28:2424; Am J Transpl 2006,6:364; J Am Soc Nephrol 2007,18:165).

2. Transplantation - Optimisation of donor organs
   Due to an increasing demand for organs suitable for transplantation, the research focuses on the impact of the cause of death (cardiac arrest or brain death) on organ quality and the possibilities of pharmacological intervention. In addition, preservation techniques are being improved by investigating the potential of new solutions and machine preservation techniques (47 publications in peer-reviewed journals, including Ann Surg 2003,238:792; Transplantation 2003,76:1150; Kidney Int 2003,64:1874; Hepatology 2006,43:1022; Ann Surg 2007,246:982; Transplantation 2007,84:729).

3. Transplantation - Evaluation of clinical transplant programmes
   Many clinical studies were performed as described in Section 1 (122 publications in peer-reviewed journals, including J Hepatol 2004,4:1017; Transplantation 2006,81:287; Transplantation 2006,82:80; Transplantation 2007,83:29; N Engl J Med 2008,359:1181.

4. Transplantation - Cell and stem cell transplantation
   (P. de Vos, M.C. Harmsen, M.J.A. van Luyn)

5. Clinical and Applied Immunology - Autoimmunity
   Systemic autoimmune diseases have been a major topic of research, in particular focusing on ANCA-associated vasculitis, SLE and Sjögren’s syndrome. In vitro and in vivo experimental studies were performed in addition to clinical studies. Also, research in the autoimmune blistering diseases made extensive progress during this reporting period. Experimental research on diabetes was successful, but this line of research was terminated due to retirement and change of focus (246 publications in peer-reviewed journals, including Arthritis Rheum 2003,48:248; J Immunol 2003,170:3592; Am J Med Gen 2005,77:727; Arthritis Rheum 2007,56:2080; N Engl J Med 2007,356:2349; J Clin Invest 2007,117:1240; Arthritis Rheum 2007,56:3399; Nat Med 2008,14:1018.

6. Clinical and Applied Immunology - Tumour immunology
   In tumour immunology, great progress has been made in vaccination research. A phase II trial addressed the potency of immunisation with a p53 synthetic long peptide vaccine. In vitro targeting of TRAIL as a method to induce apoptosis in tumour cells was explored. Further research was also done on EpCAM (epithelial cell adhesion molecule) as a marker not only for tumours, but also for developing and regenerating tissues. Important work was done at the molecular level by the group of Prof. M. Peppelenbosch who, unfortunately, recently left the UMCG. In addition, promising research is being performed by the group of Prof. G. Molema on targeting tumour endothelium in order to deliver anti-tumour drugs locally. Furthermore, tumour immunological studies were done in Hodgkin’s disease by the group of Prof. S. Poppema (90 publications in peer-reviewed journals, including J Immunol 2004,173:6009; J Biol Chem 2005,280:10025; Cancer Res 2005,65:3380; Blood 2007,110:3310).
Chapter 6  Institute for Transplantation, Immunology and Inflammation

7. Clinical and Applied Immunology - Inflammation
Targeting endothelial cells for drug delivery and regenerative medicine are the main focuses of this research theme. In addition, coagulation studies were performed. Due to the untimely death of Prof. J. van der Meer – the leader of this group – in January 2009, a re-evaluation of this successful area of research was necessary. Within this theme, molecular mechanisms of inflammation have been another topic of study by the group of Prof. M. Peppelenbosch (160 publications in peer-reviewed journals, including Am J Obst Gyn 2003, 188:1073; Hum Gene Ther 2004, 15:433; Nature Materials 2005, 4:568; Circulation 2006, 114:1985; Ann Intern Med 2006, 145:807; Gastroenterology 2006, 12:7621; Nat Cell Biol 2008, 10:1190).

8. Clinical and Applied Immunology - Bacteria in human health and disease
(J.J.E. Bijlsma, H.J.M. Harmsen, G.W. Welling, J.M. van Dijl)

9. Clinical and Applied Immunology - Viruses in human health and disease
In the teams of Prof. J.C. Wilschut, Dr A.L.W. Huckriede, Dr J.M. Smit and Prof. C.A.H.H. Daemen major progress was made in the development of novel vaccines against influenza and other respiratory viruses. Strategies for immunotherapeutic treatment of virus-induced cancers were developed and tested. To initiate clinical evaluation of some of these strategies, a start-up company (ViciniVax), associated with UMCG-RuG, was established. The molecular mechanism of cell entry by Dengue virus was analysed in great detail. Funding for this research was obtained from DFN, Ned. Kanker Bestrijding, NWO, PUU, STW, Ti Pharma, UNY, UTSN and ZonMw (50 publications in peer-reviewed journals, including J. Virol. 2005, 79, 7942-8; Gene Therapy 2006, 13, 400-11; J. Clin. Virol., 2006, 35: 233-43; J. Virol. 2007, 81, 12019-28; PLoS Pathog. 2008, 4, e1000138; Plos Pathog. 2008, 4, e1000244).

Key publications
In this section, we outline the publications that have been crucially relevant for the TRIO research programme. Full text article are provided in appendix Section 6.4.

1. Transplantation - Chronic transplant Dysfunction
(CTD; Hillebrands, A.S.H. Gouw, W.vd Bij, W. van Son)

2. Transplantation - Optimisation of donor organs


3. Transplantation - Evaluation of clinical transplant programmes


4. Transplantation - (Stem)Cell transplantation
(P. de Vos, M.C. Harmsen, M.J.A. van Luyn)


5. Clinical and Applied Immunology - Autoimmunity


6. Clinical and Applied Immunology - Tumour immunology


8. Clinical and Applied Immunology - Bacteria in human health and disease
(J.J.E. Bijlsma, H.J.M. Harmsen, G.W. Welling, J.M. van Dijl)

High quality publications
TRIO aims for high-quality and high-visibility output as shown by the fact that 40% of the TRIO publications were published in the top 10% of journals, which include Ann. Rheum. Dis., Arthritis Rheum., Blood, Brit. J. Cancer, Environ. Microbiol., Inflamm. Bowel Dis., Int. J. Cancer, J. Biol. Chem., J. Mol. Biol., J. Virol., Microbiol. Mol. Biol. Rev., Mol. Microbiol., Nat. Cell Biol., Nat. Materials, Nat. Med., N. Eng. J. Med., PLoS Pathogens, Proteomics, and Trends in Microbiology. Furthermore, 73% of the TRIO publications were published in the top 30% of journals (Table 6.3). It is noteworthy in this context that these percentages have not significantly changed between 2004 and 2008, while the total output of papers has doubled (see Table 6.4). All these top publications have been marked in appendix Section 6.5.

Table 6.3 High quality publications – number of publications in the top 10% and 30% of journals in relevant disciplines

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Belongs to the best 10% of a relevant subject area</td>
<td>40%</td>
<td>37%</td>
<td>40%</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td></td>
<td>(43)</td>
<td>(38)</td>
<td>(63)</td>
<td>(65)</td>
<td>(68)</td>
</tr>
<tr>
<td>Belongs to the best 30% of a relevant subject area</td>
<td>79%</td>
<td>74%</td>
<td>78%</td>
<td>72%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>(85)</td>
<td>(76)</td>
<td>(122)</td>
<td>(124)</td>
<td>(128)</td>
</tr>
</tbody>
</table>

Explanation: A ranking for publications present in the on-line database ‘ISI Web of Knowledge’, sub-database ‘Web of Science’ can be calculated and is presented. Papers are categorised based on the journal they appear in. Approximately 175 subject areas have been designated (ISI fields). The percentages are calculated based on the number of the journal titles in the subject area.
Section 6.5: Quantity of Scientific Output

Overview of the results
The number of refereed publications by TRIO principal investigators has nearly doubled from 112 in 2003 to 213 in 2008. This is a satisfying result in view of the fact that the quality of the TRIO publications has remained constant. On average, tenured staff members have published 4 to 5 refereed articles per year. Notably, the number of PhD theses tripled during the present reporting period. Furthermore, TRIO principal investigators have been involved in 9 patent applications, and have published 65 book chapters. All publications are listed in appendix Section 6.5.

Publication strategy
In accordance with the criteria established for the Faculty of Medical Sciences, TRIO rewards its PIs with a full membership if they publish a minimum of six peer-reviewed articles in the top 30% journals in their field over a period of three years. We consider this a very reasonable requirement. Therefore, failure to comply with this standard results in a loss of the full membership, unless there are pressing reasons to decide otherwise. For the coming period, we would like to attain a further increase in the numbers of publications per PI, but especially an increase in the quality of publications. This can be achieved by making the current TRIO tenured staff more aware of the pressing need to publish in higher impact journals, by taking the quality of publications into account when taking decisions concerning tenure or promotion of staff and, where possible, through the recruitment of excellent new staff members with an established track record of publishing in high visibility journals.

Number of publications:
Table 6.4  Main categories of research output at the level of programme TRIO

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refereed articles</td>
<td>112</td>
<td>121</td>
<td>113</td>
<td>164</td>
<td>198</td>
<td>213</td>
</tr>
<tr>
<td>PhD theses</td>
<td>4</td>
<td>8</td>
<td>8</td>
<td>16</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Patents*</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Total publications</td>
<td>117</td>
<td>131</td>
<td>122</td>
<td>181</td>
<td>215</td>
<td>228</td>
</tr>
<tr>
<td>Books and book chapters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>65</td>
</tr>
</tbody>
</table>

Number of PhD students
The number of PhD students in TRIO has grown steadily from 39 in 2003 to 81 in 2008 (see Table 6.5). This increase can be related to the increase in tenured staff with a fairly constant ratio of 2 PhD students per tenured staff member since 2004. We would consider 3 to 4 PhD students per tenured staff as an optimal average ratio for the coming years.

Table 6.5  Number of PhD students

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PhD students per year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>employed</td>
<td>32</td>
<td>44</td>
<td>47</td>
<td>45</td>
<td>49</td>
<td>50</td>
</tr>
<tr>
<td>non-employed</td>
<td>7</td>
<td>7</td>
<td>11</td>
<td>17</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>% non-employed</td>
<td>17.95%</td>
<td>13.73%</td>
<td>18.97%</td>
<td>27.42%</td>
<td>24.62%</td>
<td>38.27%</td>
</tr>
</tbody>
</table>
## Section 6.6: Earning Capacity

### Fund raising strategy and support

During the reporting period, TRIO has been successful in acquiring external funding, the level varying between 78.5 and 82.15% (Table 6.6). This demonstrates a strong earning capacity, which has been largely created through the participation in national and international research networks. For the coming years, TRIO aims to further increase the level of externally acquired funding to about 90%.

### Results

TRIO principal investigators have succeeded in acquiring the following financial support:

* for explanation, see list of abbreviations

### 5 grants of more than €1.0 million

<table>
<thead>
<tr>
<th>Short description grant</th>
<th>Grant received from*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TI Pharma AntiStaph T4-213</td>
<td>Top Institute Pharma</td>
</tr>
<tr>
<td>Tat machine (van Dijl)</td>
<td>EC FP6</td>
</tr>
<tr>
<td>TeRM – Smartmix (v. Luyn)</td>
<td>MOW</td>
</tr>
<tr>
<td>NIVAREC Novel Influenza Vaccines (Wilschut)</td>
<td>ZonMw</td>
</tr>
<tr>
<td>TI Pharma T4-214 (Wilschut)</td>
<td>Top Institute Pharma</td>
</tr>
</tbody>
</table>

### 10 grants of €0.5-1.0 million

<table>
<thead>
<tr>
<th>Short description grant</th>
<th>Grant received from*</th>
</tr>
</thead>
<tbody>
<tr>
<td>StaphDynamics (van Dijl)</td>
<td>EC FP6</td>
</tr>
<tr>
<td>BaSysBio (van Dijl)</td>
<td>EC FP6</td>
</tr>
<tr>
<td>Kinin receptor activation (Heeringa)</td>
<td>ZonMW</td>
</tr>
<tr>
<td>Designed Targeted Therapy (Hillebrands)</td>
<td>NSN</td>
</tr>
<tr>
<td>Modulating foreign body response (v. Luyn)</td>
<td>MED</td>
</tr>
<tr>
<td>TI Pharma T3-103 (Peppelenbosch)</td>
<td>Top Institute Pharma</td>
</tr>
<tr>
<td>EUREGIO Biotech Business (vd Steege)</td>
<td>EC</td>
</tr>
<tr>
<td>Novel influenza vaccines (Wilschut)</td>
<td>ZonMw</td>
</tr>
<tr>
<td>Virosome carrier systems (Wilschut)</td>
<td>NWO-STW</td>
</tr>
<tr>
<td>RAVE (Kallenberg)</td>
<td>NIH</td>
</tr>
</tbody>
</table>

### 30 grants of €250,000 – 500,000

<table>
<thead>
<tr>
<th>Short description grant</th>
<th>Grant received from*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerulo-Nephritis (Molema/Kallenberg)</td>
<td>DIV</td>
</tr>
<tr>
<td>Myeloma stem cell network (Bos)</td>
<td>EC FP7</td>
</tr>
<tr>
<td>Intestinal bacterial antigens (Bos)</td>
<td>DFN</td>
</tr>
<tr>
<td>Immunotherapy cervical cancer (Daemen)</td>
<td>NKB</td>
</tr>
<tr>
<td>BACELL Health (van Dijl)</td>
<td>EC FP6</td>
</tr>
<tr>
<td>Inhibition plasma hemopexin (Faas)</td>
<td>NSN</td>
</tr>
<tr>
<td>Function of bone marrow stem cells (M.Harmsen)</td>
<td>NSN</td>
</tr>
<tr>
<td>Soft tissue engineering (M. Harmsen)</td>
<td>EC FP6</td>
</tr>
<tr>
<td>Determinants vascular dysfunction (Heeringa)</td>
<td>TIFN</td>
</tr>
<tr>
<td>Therapeutic value of human TRAIL (Helfrich)</td>
<td>NKB</td>
</tr>
</tbody>
</table>

### 46 grants of €100,000 – 250,000

<table>
<thead>
<tr>
<th>Short description grant</th>
<th>Grant received from*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantbare kunstnien (Booiker)</td>
<td>NSN</td>
</tr>
<tr>
<td>EpCAM and cell Dynamics (Booiker)</td>
<td>NSN</td>
</tr>
<tr>
<td>BACELL EuroSCOPE (van Dijl)</td>
<td>ESF EuroCORES &amp; NWO-ALW</td>
</tr>
<tr>
<td>BACELL SysMo (van Dijl)</td>
<td>SysMo &amp; NWO-ALW</td>
</tr>
<tr>
<td>Kinome profiling (Peppelenbosch)</td>
<td>NWO</td>
</tr>
<tr>
<td>Role of CMV (Wilschut)</td>
<td>DFN</td>
</tr>
</tbody>
</table>
Table 6.6  Fund raising capacity at the level of programme TRIO

<table>
<thead>
<tr>
<th>Year</th>
<th>Total funding</th>
<th>Allocated funding</th>
<th>Acquired funding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(FTE)</td>
<td>(FTE)</td>
<td>(FTE)</td>
</tr>
<tr>
<td>2003</td>
<td>100% (38.80)</td>
<td>17.85% (6.93)</td>
<td>82.15% (31.87)</td>
</tr>
<tr>
<td>2004</td>
<td>100% (46.20)</td>
<td>18.08% (8.35)</td>
<td>81.92% (37.85)</td>
</tr>
<tr>
<td>2005</td>
<td>100% (49.31)</td>
<td>18.15% (8.95)</td>
<td>81.85% (40.36)</td>
</tr>
<tr>
<td>2006</td>
<td>100% (53.52)</td>
<td>19.53% (10.45)</td>
<td>80.47% (43.07)</td>
</tr>
<tr>
<td>2007</td>
<td>100% (62.53)</td>
<td>21.51% (13.45)</td>
<td>78.49% (49.08)</td>
</tr>
<tr>
<td>2008</td>
<td>100% (76.0)</td>
<td>18.62% (14.15)</td>
<td>81.38% (61.85)</td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are funded directly by the University of Groningen and/or the UMCG (allocated funding). To extend their research capacity, they acquire grants via internal and external competition (acquired funding) for non-tenured staff, employed PhD students, non-employed PhD students and in some cases a limited number of staff positions. The fund raising capacity is expressed in research FTE.
Section 6.7: Academic Reputation

Description and overview
The PIs of TRIO have an excellent academic reputation, as evidenced by their awards, prizes, editorships in relevant academic journals, memberships on scientific boards and advisory boards, and active participation in national and international conferences. Furthermore, TRIO researchers regularly served as reviewers for high-visibility journals and national and international funding agencies (for all details, see appendix Section 6.7).

Awards and prizes
TRIO members have received the following awards or prizes:
• Bijlsma - Rosalind Franklin Fellowship UMCG (2007)
• van Dijl - UMCG Research Prize (2007)
• Heeringa – VIDI grant NWO (2005)
• Kallenberg – Van Loghum prize, Dutch Society for Immunology (2007)
• Lisman - Young Investigator Awards at the biannual Meeting of the International Society of Thrombosis and Haemostasis (2003)
• Molema - Award from the Polish Ministry of Science and Education, as collaborator on the heme-oxygenase research performed by Dr Jozef Dulak, Krakow University, which was given the Polish Research Award 2006 (2006)
• Rots – VIDI grant NWO (2005)
• Rots - Rosalind Franklin Fellowship UMCG (2007)
• Rots - Aspasia grant NWO (2008)
• Slooff – Teaching Prize Faculty of Medicine UMCG (2003)
• Slooff – honorary doctorate of the Semmelweis University, Budapest, Hungary (2003)

Editors in academic journals
The PIs at TRIO are editors or editorial board members of the following peer-reviewed scientific journals:

• Annals of Transplantation – Slooff (2008-present)
• Autoimmunity Reviews – Kallenberg (2005-present)
• British Medical Journal – Cases – Peppelenbosch (2008-present)
• Clinical Experimental Immunology – Kallenberg (2001-2004)
• Current Genomics – Peppelenbosch (2004-present)
• European Journal of Clinical Investigation – Kallenberg (starting 2009)
• European Journal of Dermatology – Jonkman (2008-present)
• Gut – Peppelenbosch (2007-present)
• Journal of Autoimmunity – Kallenberg (2006-present)
• Journal of Crohn’s and Colitis – Peppelenbosch (advisory board; 2007-present)
• Journal of Dermatology Science – Jonkman (2003-present)
• Journal of Hepatology – Porte (2005-present)
• Journal of Liposome Research – Kamps (2005-present)
• Kidney International – Kallenberg (2003-present)
• Liver Transplantation – Porte (2002-2004) / Slooff (all years)
• LUPUS – Kallenberg (2003-present)
• Microbiology - van Dijl, Associate Editor (1998-2006), Editor (2008-present)
• Open Gastroenterology Journal – Lisman (advisory board; 2008-present)
• Oral Biosciences and Medicine – Vissink (2003-2007)
• Transplant International – Slooff (all years)

Membership in academies and scientific boards
The PIs of TRIO are members of academies and scientific boards, and participate in various committees, including:
• van Dijl - Member of the BACELL steering group (2003-2008), Chairman of BACELL (2006-present)
• Hazenberg - Secretary of the Board of the International Society of Amyloidosis (2004-present)
• Hazenberg - Member of the European Amyloidosis research consortium EURAMY (2006-present)
• Jonkman - European Society for Dermatological Research, board member (2002-2007)
• Jonkman - Dutch Society for Experimental Dermatology, founder, chairman and member (all years)
• Jonkman - International Pemphigus & Pemphigoid Foundation, medical advisory member
• Kallenberg – Member of the EULAR task force on SLE (2006-present)
• Kallenberg – Member of the EULAR task force on Vaccination in RA (2008-present)
• Kallenberg – Member of the Scientific Board of the National Leprosy Foundation (2001-present)
• Kallenberg – Chairman of the Organising Committee of the 7th European Lupus Meeting, Amsterdam May 7-10, 2008.
• Kamps - Secretary Dutch Society of Pharmaceutical Sciences (NVFW; 2008-present)
• Kamps - Board of the Netherlands Platform for Targeted Nanomedicine (2008-present)
• de Leij - Board Dutch Society for Immunology (secretary 2003-2009)
• de Leij - member Board IOP Genomics (2003-present)
• de Leij - member Executive Board TopInstitute Pharma
• de Leij - member Programme Counsel TopInstitute Food and Nutrition
• de Leij - member NWO committee VICI
• Molema – Member of the EU Nanomedicine for Health/Drug Delivery SRA writing group (2006)
• Molema – Member of scientific advisory board of Diatos SA (2007-2009)
• Peppelenbosch – Scientific Board Maag-, Lever-, Darmstichting (2005-present)
• Peppelenbosch – Nederlandse vereniging voor Immunologie (programme committee; 2005-present)
• Peppelenbosch - ALW–VICI Committee member (2007)
• Slooff – Member International Advisory Board Integrated Research and Treatment Centre for Transplantation Medizinische Hochschule Hannover Duitsland (2007-present)
• Slooff – Board Division of Transplantation of the UEMS 2007-2009
• Slooff – Board Division of HPB Surgery UEMS (2008)
• Wilschut - Coordinator of the Netherlands Influenza Vaccine Research Centre (NIVAREC), a consortium comprising the University Medical Centre Groningen, Erasmus Medical Centre, Rotterdam, Netherlands (Prof. A. Osterhaus), and Solvay Pharmaceuticals, Weesp, Netherlands (2004-present)
• Wilschut - Coordinator of collaborative development programme between the UMCG and the Academic Hospital, Paramaribo, Surinam, on "Development of a Dengue Surveillance System in Surinam", funded by the UTSN (Twining Organisation Surinam-Netherlands) on behalf of the Dutch Government (since 2009)

Invitations to address major conferences
The PIs of TRIO have been invited keynote speakers at more than 200 international conferences of major relevance and importance.
Section 6.8: Societal Relevance

Societal Quality

Transplantation
In our ageing society the demand for organ transplantation is steadily increasing. Unfortunately, however, the number of donor organs available for transplantation is not increasing, and many patients die before an organ becomes available. There is a strong need for improving the quality of transplantation and to increase the potential number of organs. This programme, which focuses on optimising donor organs, aims to fulfil this need. Since chronic transplant dysfunction reduces the lifespan of a transplanted organ (and is, in fact, the main determinant), solving this problem is of utmost importance to increase the lifespan of transplanted organs. In this respect, evaluation of the clinical results of organ transplantation is a first step to improve understanding of the shortcomings that still exist. This will be followed by in-depth analysis of clinical problems, which will lead to better protocols to be tested in RCTs. Finally, transplantation will always be an artificial way to restore organ function. The ultimate solution will hopefully lie in regenerative medicine via stem cell transplantation techniques.

Applied immunology
Autoimmune diseases are a major burden to society. Little progress has been made in recent years in the treatment and prevention of these diseases (such as rheumatoid arthritis, diabetes and multiple sclerosis). Better treatment and prevention requires insight into the immunological mechanisms underlying disease development and progression. The current programme, using models for autoimmunity such as ANCA-associated vasculitis and autoimmune blist-ering diseases, aims to unravel these mechanisms in order to design treatment and prevention programmes based on insights into etiopathogenesis.

Inflammation is a key characteristic of many disorders. Basic research into inflammatory processes can open the way for targeted treatment. This is exactly the route that is chosen for drug targeting using, for example, changes in endothelial cells during inflammation as a possibility to deliver specific drugs at inflammation sites. This theme in TRIO overlaps directly with stem cell transplantation; the latter also studies the micro-environment in order to define appropriate guiding factors for stem cells upon their administration in vivo. Moreover, the field of tissue repair, whether or not using biomaterials, is of utmost importance in an ageing society, where disability is increasing and biomaterials are potentially available for repair.

Cancer is still a major cause of death, and the role of the immune system to combat and prevent cancer is as yet still not fully appreciated in clinical medicine. This theme focuses on vaccination for virus-associated tumours, an area of great interest. Also, finding less toxic approaches to cure cancer using immunologic tools that target tumour cells more specifically would be a major step forward in cancer treatment. These areas are actively studied in the TRIO programme.

Microbes in human health and disease.
Modern societies are demanding broader and better health care systems that are available for everyone. Modernisation and innovation in health care are two reasons why the costs for health care systems are currently exploding. Another main reason is that Europe has an ageing society, which is susceptible to bacterial and viral infectious diseases. These factors together will unavoidably lead to even higher costs for health care in the future. If new threats emerge, like untreatable microbial infections and conditions like those in the “pre-antibiotics” era, then they will confront society with major challenges for the decades to come. One of the main goals for society, and for the scientific community, is therefore to fight the emergence of untreatable infections and to find new treatments for them. These challenges for innovation should therefore be met and new approaches taken to identify effective measures against antibiotic-resistant pathogens or pathogens that can cause serious pandemics. Therefore, the objective of this theme within TRIO is the development of novel approaches to prevent and combat bacterial and viral infections, and to find and characterise drug targets for the design of a new generation of antivirals and antibiotics. In addition, novel vaccines and monoclonal antibodies for the prevention or treatment of infectious diseases are being developed.

Societal Impact

Transplantation
As mentioned above, in our ageing society organ failure is an increasing cause of disability or death. Organ transplantation is hampered by the insufficient numbers of donor organs available and the quality of these organs. The TRIO programme aiming at optimising donor organs is an internationally recognised effort to improve the results of organ transplantation. Prolonging the lifespan of a transplanted organ is another important step forward in transplantation. Careful analysis of factors involved in late transplant failure, as done in the TRIO programme, is another way to improve
the outcome. Repair of failing organs via regenerative medicine is a promising approach with a potentially great impact on society. Much research is required to reach this goal. TRIO aims to actively participate in tackling this challenge.

**Applied immunology**

The impact of autoimmune diseases on society is clear from the increasing incidence of diseases like type 1 diabetes, rheumatoid arthritis and multiple sclerosis. TRIO aims to unravel the basic mechanisms underlying autoimmune diseases using some prototype autoimmune disorders. This analysis is being directly translated into clinical medicine by applying the relevant biologicals for targeting of the pathogenetic pathways that underlie the autoimmune process.

Inflammation is a common process in many diseases. Specific targeting of inflammatory pathways instead of “broad” immunosuppression via (high dose) corticosteroids and non-specific immunosuppressives would be a major development for many diseases in which inflammation is a characteristic feature. Drug targeting in inflammation is a key factor in this theme of TRIO.

Using the immune system to combat cancer would have an enormous impact on society. Now that HPV vaccination to prevent cervical carcinoma has started, the TRIO programme is actively exploring possibilities for the prevention of other forms of virus-associated cancers. Targeted treatment based on immunological methods is also being developed. Targeted treatment in all the research areas of TRIO demonstrates the policy of directing the research programme towards the central theme of GUIDE.

**Microbes in human health and disease.**

Viral and bacterial infectious diseases have remained a very significant source of societal disease burden around the world. In terms of Disability Adjusted Life Years (DALYs), bacterial and viral lower respiratory tract infections account for 6.6% of the annual DALYs, or about 3.8 million deaths worldwide. In Europe, lower respiratory tract infections account for 4.01% of the DALYs or about 170,000 deaths. Furthermore, up to one million people die each year from influenza worldwide, but this number could increase to 40-50 million deaths, as exemplified in the 1918-1919 pandemic. In the Netherlands, about 5-20% of the population suffers from influenza each year. The WHO report Priority Medicines for Europe and the World has therefore included five infectious diseases on its list of 19 ‘priority diseases requiring priority medicines’. Two of these diseases are being studied in the context of TRIO: infections with antibiotic-resistant bacteria and pandemic influenza. Antibiotic resistance, enhanced by drug abuse, is developing fast and catching up with us. Therefore, ongoing research within TRIO is aimed at obtaining new insights into the molecular mechanisms of resistance development, new analytical methods and new anti-infectives. As underscored by the current influenza A pandemic, influenza is one of the biggest commonalities of interest with regard to the disease burden worldwide. Therefore, new concepts are needed which increase the effectiveness of influenza therapy or prevention or which reduce the number of complications. Such challenges are addressed by ongoing research in TRIO.

**Valorisation**

The tangible products of research within TRIO will be (i) novel tools, devices and methods for transplantation, and (ii) novel drugs, vaccines, protective antibodies, tools and technology for drug delivery. Knowledge protected by patents and a wide range of tools and technologies for pharmaceutical research and drug innovation can have a variety of applications, leading to economic activities that focus on bringing new drugs to the market, as well as providing services to the international industry. Therefore, the PIs of TRIO are well aware of the necessity to protect and exploit their generated intellectual property. An important development has been the establishment by Prof. J.C. Wilschut of two start-up biotech companies: Virosome Biologicals (2003) and ViciniVax (2009) in Groningen. During the present reporting period, efforts to protect intellectual property have led to a total of 9 patent applications:

- Kamps / Molema - Improved liposomes and uses thereof. EP07115897.6 (2007)
- Kamps - Improved liposomes and uses thereof. WO2009031896 (2008)
- Molema - Method of conjugating therapeutic compounds to cell targeting devices via metal complexes. 05076682.3(2005)
- Popa - Isolation of endothelial progenitor cell subsets and methods for their use. EC: C12N5/06B28P; G01N33/50D2F8; IPC: C12N5/06; C12N5/06 (2006)
Section 6.9: Next Generation

With regard to the education offered through GUIDE, please refer to the main part of the GUIDE evaluation.

For several reasons, TRIO represents an excellent “research incubator” for young, independent scientists. The PIs of TRIO have important roles in the education and training of Bachelors and Masters students at all levels in the Medical Sciences, Pharmaceutical Sciences and Life Sciences. Furthermore, several TRIO PIs participate in the Top-master programme Medical and Pharmaceutical Drug Innovation, which is dedicated to especially talented students. As documented in the previous sections, many PhD students and young post-doctoral researchers are trained by members of TRIO in state-of-the-art techniques for fundamental, translational and clinical research. Exchanging knowledge, ideas and information within TRIO is encouraged through seminars and master classes, to which guest scientists are also invited. In the master classes, PhD students and young post-doctoral research fellows discuss their work with visiting scientists, who have made important scientific contributions in the research areas addressed within TRIO. Furthermore, all PhD students associated with TRIO participate in the PhD training programme of the Graduate School GUIDE. This provides them with complementary skills training, but the students are also encouraged to attend specific scientific or practical skills classes, or even classes on Ethics or the management of intellectual property. Regarding complementary skills, the PhD students learn, for example, how to manage their PhD as a project by defining a work plan and deliverables, and they take classes to develop their communication and writing skills. Furthermore, all PhD students are encouraged to: (i) present their results at national and international conferences and workshops, preferably in the form of oral presentations, but certainly in the form of posters; and (ii) participate in the international Summer Schools held by EMBO, FEBS or NATO. Overall, the Masters and PhD students as well as the young researchers are exposed to expertise beyond the scope of their individual laboratories, which makes TRIO a formidable springboard for their subsequent careers in science, industry and society.
Section 6.10: Viability, SWOT and Future Strategy

Viability
The objectives and research area of TRIO are clearly defined. The topics that are actually addressed are appropriately interrelated, and they have a very high scientific, clinical and societal relevance. Thus, at all possible levels, there is a very clear need for the research done within TRIO. Importantly, the overall quality and quantity of the research output are excellent, and the TRIO principle investigators are able to acquire substantial funding from many different sources at the national and international levels. This excellent earning capacity relates to the strong academic reputation of the TRIO principle investigators and, especially to their proven capacity for innovative research. The acquired funds are invested in top-level infrastructure, with respect to both technological and intellectual resources. Excellent facilities with state-of-the-art equipment are available within TRIO. Consequently, TRIO has evolved into a highly dynamic research incubator for scientific staff, from the early post-doctoral stage, through the tenure-track stage to the tenured stage and, finally, the full professorship. Our personnel management focuses on scientific and clinical excellence. Where needed, we aim for replacement of departing staff with excellent new staff. We therefore conclude that the overall viability of the TRIO research programme is excellent, as are its future prospects.

SWOT

Strengths
- A lively research environment with a broad and relevant scientific scope
- Clear translational and clinical research deliverables with relevance for research on Healthy Ageing, the overarching research theme of the UMCG
- Excellent scientific, technological and intellectual resources
- Excellent overall research output
- Excellent overall earning capacity
- Excellent and attractive facilities for fundamental, translational and clinical research
- Excellent and attractive facilities for training students and staff
- Excellent staff with complementary expertises and proven track records
- High potential for synergistic interactions
- Flat organisation structure
- TRIO is well embedded in the larger UMCG research infrastructure with excellent facilities for animal experiments, microscopic imaging, electron microscopy, flow cytometry, genome sequencing, mass spectrometry and proteomics.
- Excellent support from an experienced graduate school at all possible levels, but especially the PhD training programme, the management and monitoring of research output, and the management of research projects and grants
- Easy access to large patient cohorts, such as the LifeLines programme. LifeLines is a large observational follow-up study in the northern Netherlands that covers three generations (grandparents, parents and children) and currently includes 10,000 volunteers with about 9 years of follow-up. Ultimately, approximately 165,000 volunteers will be included.

Weaknesses
Overall we see no serious weaknesses that could threaten the viability of TRIO in the coming years. Nevertheless, there is room for improvement in the following areas:
- We see a stronger need for implementation of Systems Biology approaches. The first initiatives have been taken, for example in the theme Microbes in Health and Disease, but we should strive for a broader implementation of holistic approaches. A highly relevant initiative was the recent Symposium on Systems Genetics (1-2 October 2009).
- Accommodation in the very distinct buildings on the UMCG campus hampers ‘quick exchanges of information’ (like the daily chat in the coffee room).
- Although the overall output in terms of publications is excellent, not all PIs have contributed equally to this output. The same is true for the acquisition of grants. because TRIO is a dynamic research environment, this makes the organisation somewhat vulnerable to changes in personnel. The coordinators are fully aware of this and will do their utmost best to recruit top scientists to fill any upcoming vacancies.
- There is room for improvement concerning publication of results in high-visibility journals.
- There is room for a higher ratio of PhD students to tenured staff.
Opportunities

- Implementation of Systems Biology, System Genetics and perhaps even Synthetic Biological approaches at all levels of fundamental, translational and clinical research provides formidable new opportunities for major scientific and clinical breakthroughs. This will require additional investments in areas like Proteomics.
- Building a strong research portfolio on Healthy Ageing without weakening the present strengths in topics that are highly relevant for clinical and translational activities within the UMCG.
- Making more effective use of the excellent technological and intellectual infrastructure at the UMCG. Also, the LifeLines programme offers a wide range of opportunities that need to be explored and exploited to the full.
- Making more use of international funding opportunities as provided by the EC Framework programmes, the Human Frontiers Science programme, the NIH and other funding bodies that operate at the European or worldwide levels.
- There are good opportunities for increased publication in high-visibility journals. Likewise, there are more opportunities to obtain funding than are currently being utilised. The challenge here is to mobilise more staff members to acquire top-level funding that will provide them with the possibilities to perform challenging – and sometimes riskier – research.
- Further training/coaching of research staff with respect to the skills they need for writing high visibility publications and acquiring financial resources for their research.
- There are good opportunities for increased publication in high-visibility journals. Likewise, there are more opportunities to obtain funding than are currently being utilised. The challenge here is to mobilise more staff members to acquire top-level funding that will provide them with the possibilities to perform challenging – and sometimes riskier – research.

Threats

- The main threat for all research activities, not only in Groningen, is that the budgets for research are under pressure due to the current economic crisis. To face this threat, PIs within the entire UMCG need to become more competitive with respect to their publication strategy and the acquisition of external funding.
- There is a clear need to acquire more funding for post-doctoral researchers and tenure-track positions. The Rosalind Franklin fellowship programme to enhance the numbers of female staff scientists is a truly wonderful initiative in this respect. However, we need to create more openings for recruiting and retaining excellent young researchers.
- We need to maintain an active personnel policy with respect to making appropriate staff replacements where needed. In this respect, it is relevant to note that “the distance from Amsterdam to Groningen is seemingly longer than the distance from Groningen to Amsterdam”. To overcome this unbalanced perception of distance, we need to keep up our promotional and outreach activities at the highest possible level.

Future Strategy

For the coming years, TRIO aims to further consolidate its competitive position with respect to scientific output and the acquisition of external financial and other resources. As before, strong emphasis needs to be placed on continuously recruiting excellent (young) scientists in anticipation of expected or unexpected vacancies. An important challenge will be to become even more involved in decision making at the local, national and international levels through involvement on the respective governing bodies and boards. The TRIO staff is fully aware of the opportunities, challenges and threats as outlined above, and these will be taken fully into account in any future decisions regarding the course of the Institute. In conclusion, the TRIO coordinators and staff are committed to making TRIO an even more inspiring place for fundamental, translational and clinical research at the highest possible levels.
Table of contents
 CHAPTER 7

Northern Netherlands Oncology Center
Chapter 7.1: Objective(s) and Research Area

Program Leaders
Prof. E.G.E. de Vries, Prof. H. J. Hoekstra

In 2001, the Northern Netherlands Oncology Center (NNOC) had grown so large that it was decided to establish an internal board. This board consists of Prof. R.M.W. Hofstra, Prof. Ph.M. Kluin, Prof. A.G.J. van der Zee and the program leaders; it optimally reflects the various groups active within the center and assists in policy decisions.

Objectives
The aim of the NNOC is to translate more fundamental insights in oncogenesis and tumor behavior from basic research into cancer prevention, improvement of early detection of cancer, and better treatment for cancer patients.

Aims of the four sub-programs
1 Cancer: genes, mutations and their consequences
   • To study cancer susceptibility genes and mutations in these genes, and their direct and indirect involvement in cancer development.
   • To use genetic variation to identify and elucidate molecular pathways that characterize normal and aberrant cell development.

2 Hematopoietic development and hemato-oncology
   • To obtain detailed knowledge about molecular and other mechanisms that determine hematopoietic stem cell renewal and differentiation, with the ultimate goal of deepening our insight into the development of leukemia.
   • To obtain insight into the pathogenesis and evolution of B-cell lymphomas and Hodgkin lymphoma, and to find new tools for diagnosis and targets for therapy.

3 Translational oncology
   • To explore new tools outlined in fundamental research, for innovative classification and diagnostics of cancer.
   • To identify new targets, outlined in fundamental research for innovative cancer therapy.

4 Clinical studies
   • To perform phase I, II and III studies in patients with solid tumors and patients with hematological malignancies in order to improve the treatment results.
   • To detect and prevent short-term and long-term side effects of cancer treatment.

Research Area
Research is performed at the fundamental, translational and clinical levels. Central to the research is the goal of translating fundamental findings into practice in the clinic and vice versa. Therefore, there is a strong interaction between the research foci. The research foci of the four main sub-programs are:

1 Cancer: genes, mutations and their consequences
The detection of cancer-related gene alterations has proven successful in providing powerful diagnostic tools, and is often used for making decisions in clinical management. So far, most studies have focused on single gene alterations. However, with the elucidation of the human genome and the introduction of new technologies, thousands of genes can be screened simultaneously. This will result in new tumor markers or clusters of markers, which might help us to improve our understanding of cancer and our treatment of cancer patients. The aim of our studies is not only to identify such multiple gene alterations, but also to understand the cellular biological effects of these alterations. More basic questions in our research program are related to genomic stability, the roles of quantitative trait loci, and their relationship to cancer development. We exploit induced and naturally occurring genetic variation in order to identify and elucidate molecular pathways that characterize normal and aberrant blood cell development. We use high-end bioinformatics tools to detect and visualize genetic transcriptome networks.

2 Hematopoietic development and hemato-oncology
An important aspect in understanding malignant deregulation in the hematopoietic compartment is the knowledge of the regulatory pathways that control the normal proliferation, differentiation and cell survival of young and aged hematopoietic stem cells. By making use of hematopoietic cells isolated from human cord blood and bone marrow, we are able to perform gene function analysis utilizing various strategies, including retro/lentiviral transduction protocols, RNAi approaches and multicolor flow cytometry. These protocols have also been optimized for acute myeloid leukemia (AML) cells of patients, which also provides the opportunity to study the gain of functions in the malignant counterpart.
Chapter 7  Northern Netherlands Oncology Center

For B-cell lymphomas and Hodgkin lymphoma, recent studies have shown that a distinction of real biological entities and determinants is essential for further improvement in targeted therapy and the clinical outcome of cancer. Although many lymphomas are characterized by primary genetic lesions, it is evident that additional genetic and epigenetic features, as well as mutations and polymorphisms of immune regulatory genes that influence the interaction with the environment – in relation to EBV infection or not – are all instrumental in the behavior of tumor cells. MicroRNAs may be key players in the modification of the expression of a large number of genes that are essential in normal and neoplastic B cells.

3 Translational oncology
Current classification of cancer is still based largely on the morphology of tumor cells, while current cancer diagnostics (e.g. CT/MRI) are primarily based on visualization of the size and shape, and to a lesser extent, the composition of tumors. The identification of more cancer-specific cell biological changes in tumors and/or body fluids and their visualization should lead to improved classification, detection and imaging of cancer. In addition, these cancer-specific cell biological changes should also be exploited to identify unique targets for innovative therapy.

4 Clinical studies
A major challenge is the translation of preclinical data into phase I clinical studies. In addition, phase II studies followed by phase III studies will finally give a true evaluation of new treatment options. Often, more information is required to understand the nature of the different response patterns seen in patients. This requires side studies with a broad variety of techniques to define in more detail the pharmacokinetic analysis, tumor pathology and imaging techniques, etc. With the improving results of anti-cancer treatments and the increasing numbers of long-term survivors, the relevance of and knowledge about the pathogenesis of treatment-induced long-term (and short-term) morbidity is also increasing. This knowledge about the occurrence of side-effects will provide opportunities for tailoring potentially toxic treatment and/or guiding primary and secondary prevention strategies for serious side effects of cancer treatment.

Strategy and policy
In 2005 the Academic Hospital Groningen and the Faculty of Medical Sciences of the University of Groningen merged into one organization: the University Medical Center Groningen (UMCG). The NNOC has many full members working in several departments within the UMCG and their activities are often closely related to patient care. A conference was held in 2004 to optimize the integration between preclinical and clinical research and patient care. At this conference speakers from other centers in the Netherlands presented the various organizational structures for integrated oncology centers, discussed the involvement of researchers and the members of the boards of directors. This resulted in a number of recommendations for a new integrated structure of the organization. In 2007, the organization of the UMCG was divided into 6 sectors (divisions). This major change in UMCG organization has been implemented during the last two years. The sector Oncology is a separate section, and the only one which is specifically disease oriented. This section not only carries out patient care for three medical departments (Hematology, Medical Oncology and Radiotherapy), but also works on the development of the UMCG Cancer Program. This means that tumor boards and research are both gaining an even more integrated position. This will increasingly result in a structured support for research. Data management and serum and tissue collection, among other activities, will be performed in an integrated manner. The aims of the UMCG Cancer Program are to link the pathway from preclinical research to improved health outcomes, by establishing a collective multidisciplinary resource that is accessible to the domains of basic research, clinical research and population application.

Instruments for stimulating excellence in the research program
Within the NNOC, there is an active policy for retaining talented researchers within the graduate school by making use of the Tenure Track system, the Rosalind Franklin program, the pre-tenure track program and the MD-PhD program. This is addressed in more detail in Chapter 7.9, ‘Next Generation’.

As a result of its recruitment and grant writing efforts, the NNOC has been awarded Veni, Vidi and Vici grants, and has recruited clinical fellows and clinician in training for medical specialists (AGIKOs).

Several top researchers from outside the UMCG have been recruited for strategic positions in key areas of expertise, thereby strengthening the scientific staff of the NNOC. They include:

- Prof. R.A. Dierckx, as professor of Nuclear Medicine and Molecular Imaging from Ghent University
- Dr. G.H. de Bock, as associate professor in the Department of Epidemiology, previously with Leiden UMC
- Prof. J.A. Langendijk, as professor of Radiotherapy. He was previously with the VUMC, Amsterdam
- Prof. J.M. Schippers, Radiotherapy, as professor of Radiotherapy, in particular, applied physics particle therapy from the Particle Accelerator Department of the Paul Scherrer Institute in Villigen (Switzerland)
- Prof. O. Sibon, as professor of Cell Biology, in the section Radiation and Stress Cell Biology, from the Department of Biochemistry and Cell Biology, Institute for Cell and Developmental Biology, State University of New York at Stony Brook, Stony Brook, NY, USA
Dr. E.A. Nollen, tenure track at the Department of Genetics, from Hubrecht Laboratory, Center for Biomedical Genetics, Utrecht, the Netherlands.

Dr. F.A. Kruyt, as associate professor of Molecular Cancer Biology in the Department of Medical Oncology. Previously with the VUMC, Amsterdam

Dr. M.A van Vugt, medical biologist, tenure track at the Department of Medical Oncology, from MIT, MA, USA

Internationalization policy
Performing research in an international environment and with good international relationships is considered crucial. The NNOC actively participates in the collaborative GUIDE program with the Medical Faculty Mannheim of the Ruprecht-Karls-University of Heidelberg, as well as with the University of Uppsala. In addition, several Bernouilli bursaries have worked at the NNOC since the agreement between the UMCG and the universities in Beijing was finalized. Apart from these formal frameworks of cooperation between the UMCG and institutions outside the Netherlands there are numerous students who come to the center from abroad to obtain their PhD.

As shown in the appendix of Chapter 7.3, there are numerous significant collaborations between NNOC Principal Investigators (PIs) with centers abroad, resulting in joint publications as well as grants.

Instruments for performing and promoting translational, innovative drug-oriented research
Researchers are encouraged and supported to participate in various public-private consortia, such as TI Pharma, CTMM, DPTE/SCDD and ParelSnoer, and to file patents. Crucial facilities for translational research are available, such as a GMP facility, microPET/CT, microSPECT/CT, a small animal facility and CT/IVIS (fluorescent) scans for both preclinical and clinical optical imaging. The flow cytometry facility has been expanded by the purchase of several cell analyzers and a second high-speed cell sorter.

Synergy between the NNOC and the department of Pharmacy (GUIDE-GRIP)
NNOC members participate in a joint Masters research program (Topmaster Medical and Pharmaceutical Drug Innovation), in which selected Masters students are trained to perform research at the interface of medicine, pharmacy and biomedical sciences. There is also collaboration in joint applications for large-scale initiatives (e.g. Top Institute Pharma (TIP), and the Center for Translational and Molecular Medicine (CTMM)), which have resulted in several shared PhD students and postdocs. For details, see Chapter 7.3.

Specific issues with respect to the 4 subgroups based on the PRC in 2002, and the Midterm Review in 2005

Sub-program 1: ‘Cancer: genes, mutations and their consequences’
The appointment of Prof. C. Wijmenga will further expand the research into the multigenetic origin of diseases. An EU grant on the genetics of colon cancer, awarded to Prof. R.M.W. Hofstra as project leader, will allow further expansion of this sub-program.

Over the past five years, technology for identifying genetic variation has improved enormously. We are now able to screen hundreds of thousands of DNA markers simultaneously, making genome-wide association and comparative genome hybridization studies possible. Furthermore, new sequence technology now makes it possible to sequence entire genomes or exomes. These kinds of studies are currently being performed because we now have all the necessary equipment available at the genome facility, which is located in the Genetics Department.

Sub-program 2: ‘Hematopoietic development and hemato-oncology’
Within this sub-program (as is also shown in sub-program 4), basic and clinical research on hemat-o-oncological diseases is being actively pursued. The reviewer had concerns regarding the hematopoietic cell development research in programs 1 and 2 during the 2003 review process. However, since then each program has developed its own main lines, i.e. genetic genomics in genetically distinct mice populations and gene function analysis in human normal and leukemic cells, respectively. Although STAT5 has relevant cellular functions in leukemic cells and could be used as a target for cellular intervention, recent studies have indicated that BMI1 might be a more relevant factor for leukemic transformation and therefore a more interesting target for intervention. This will be pursued in the years to come.

Sub-program 3: ‘Translational Oncology’
The translational research program has been further expanded. Characterization of tumors with novel tools has been extended, as well as the research on novel targeted drugs. Molecular imaging using PET technology is performed more actively, including novel tracers and is facilitated by the appointment of Prof. Dierckx from Ghent (Belgium) as head of the Department of Nuclear Medicine and Molecular Imaging as well as by major grants. The recent acquisition of a fluorescent camera that can be used in the operation suites now allows leading-edge intraoperative guided surgery, e.g. by using fluorescent labeled antibodies or aspecific dyes for sentinel node detection.
Sub-program 4: ‘Clinical studies’
Numerous local, national and international clinical trials are ongoing, and the study of the long-term effects of cancer treatment has now been expanded to include improved collaboration within the UMCG and with other facilities in the Netherlands. Apart from a focus on optimal patient care, the tumor work groups have been increasingly encouraged to focus more on translational research and clinical studies.
Chapter 7.2: Composition of the Research Unit

Composition of the research unit
Research in the NNOC is characterized by multidisciplinary interactions and by intensive and fruitful collaboration between the four sub-programs within the center. Furthermore, there is extensive collaboration with other groups within the University, particularly the Faculty of Mathematics and Natural Sciences.

Strategy and policy
Membership selection for the NNOC during recent years was based on the selection criteria as recently defined by the Dean: admittance to the research institute as a PI, requiring an average of 6 publications over a period of 3 years, and ranking in the top 30% of the relevant ISI subject area. Based on these criteria, 56 members were selected as PIs. They originated from 20 departments covering the entire domain, from cell biology to clinical care.

The scientific staff of the NNOC (see Table 7.1; for details see appendix Chapter 7.2) has been expanded and strengthened by key appointments, including appointments from abroad. These appointments, listed below have been a very positive addition to the Center:

- Prof. G. de Haan as professor of Cell Biology, in particular Molecular Biology of Stem Cells
- Prof. H.H. Kampinga as professor of Radiation and Stress Cell Biology
- Prof. R.M.W. Hofstra as professor of Human Developmental Genetics
- Dr. E.E.A. Nollen, Genetics Department, received a Rosalind Franklin Fellowship
- Prof. H. Hollema as professor of Oncological Pathology
- Dr. B.L. van Leeuwen, Department of Surgical Oncology, received a Rosalind Franklin Fellowship
- Dr. M.G.Rots, Department of Pathology and Laboratory Medicine, received a Rosalind Franklin Fellowship
- Prof. P.H.B. Willemsen as extraordinary professor, in the evaluation of efficacy and societal aspects of treatment, specifically as related to medical oncology
- Prof. R.A. Dierckxs as professor of Nuclear Medicine and Molecular Imaging
- Dr. G.H. de Bock as associate professor in the Department of Epidemiology
- Dr. J.J. Koornstra as associate professor in the Department of Gastroenterology
- Prof. H.J.M. Groen as professor in Pulmonary Oncology
- Prof. J.A. Langendijk as professor of Radiotherapy. From the VUMC (Amsterdam)
- Prof. H.W. Nijman as professor in Gynecologic Oncology, in particular Immune Therapy
- Prof. M. Mourits as professor in Gynecologic Oncology and Hereditary Predisposition for Gynecological Cancer
- Prof. J.A. Gietema as professor in Medical Oncology, in particular Effect-driven Systemic Therapy
- Prof. J.Th. M. Plukker was appointed as professor of Surgery, in particular Surgical Oncology
- Dr. G.A.P. Hosper was appointed as associate professor in the Department of Medical Oncology
- Prof. A.H. Suurmeijer was appointed as professor of Pathology
- Prof. J.M. Schippers (Radiotherapy), as professor of Radiotherapy, in particular Applied Physics Particle Therapy
- Prof. O.C. Sibon was appointed as professor in Cell Biology, in the section Radiation and Stress Cell Biology
- Dr. F.A. Kruyt as associated professor in Molecular Cancer Biology in the Department of Medical Oncology
- Prof. J.H.M. van den Berg, professor of Pathology
- The major grants obtained by NNOC members have clearly increased the number of PhD students.

Research staff
The tenured staff has increased since 2003 by 21.7% and the number of PhD students has increased by 40%. Not shown in the table below are the numerous technicians who are financed by grants.

Research
Below (Table 7.2) is a representation of funding at the program level. Regrettably, this does not include external grants obtained via the UMCG such as ZonMW grants for which examples are 1) Laparoscopy versus laparotomy in treatment of early stage endometrial cancer: a multi-centre cost-effectiveness study (€400,000); 2) A controlled trial of geriatric liaison intervention in frail surgical oncology patients (€350,000) or major grants such as the €1.2M grant for a positron emission tomograph and microCT for small animal imaging from the NWO. Moreover, the funding obtained with the CTMM grants has not yet been included because they just started running. CTMM Mammoth (PI, UMCG) is a €15 M grant, which includes €2.5 M for the UMCG, CTMM-AIRFORCE gained a grant of €2.3 M for the UMCG, CTMM-Prostate Cancer Molecular Medicine (PCMM) a €2 M grant for the UMCG, Adult Stem Cell program, €2 M grant for the UMCG.
Table 7.1  Overview of research staff at the level of the program NNOC

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
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<tr>
<td></td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>Tenured staff</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>14.75</td>
<td>15.30</td>
<td>15.05</td>
<td>16.25</td>
<td>16.30</td>
<td>17.75</td>
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<td></td>
<td>(46)</td>
<td>(46)</td>
<td>(46)</td>
<td>(51)</td>
<td>(52)</td>
<td>(56)</td>
</tr>
<tr>
<td>Full professors</td>
<td>5.40</td>
<td>5.40</td>
<td>6.25</td>
<td>7.15</td>
<td>7.25</td>
<td>8.65</td>
</tr>
<tr>
<td></td>
<td>(17)</td>
<td>(17)</td>
<td>(20)</td>
<td>(23)</td>
<td>(24)</td>
<td>(28)</td>
</tr>
<tr>
<td>Associate professors</td>
<td>4.65</td>
<td>4.80</td>
<td>4.10</td>
<td>5.0</td>
<td>4.70</td>
<td>4.40</td>
</tr>
<tr>
<td></td>
<td>(14)</td>
<td>(14)</td>
<td>(12)</td>
<td>(15)</td>
<td>(14)</td>
<td>(13)</td>
</tr>
<tr>
<td>Assistant professors</td>
<td>1.70</td>
<td>2.10</td>
<td>1.70</td>
<td>1.10</td>
<td>1.00</td>
<td>1.30</td>
</tr>
<tr>
<td></td>
<td>(6)</td>
<td>(6)</td>
<td>(5)</td>
<td>(4)</td>
<td>(3)</td>
<td>(4)</td>
</tr>
<tr>
<td>Other senior staff</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
<td>3.00</td>
<td>3.35</td>
<td>3.40</td>
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<tr>
<td></td>
<td>(9)</td>
<td>(9)</td>
<td>(9)</td>
<td>(11)</td>
<td>(11)</td>
<td></td>
</tr>
<tr>
<td>Non-tenured staff</td>
<td>13.05</td>
<td>9.23</td>
<td>5.85</td>
<td>7.20</td>
<td>6.30</td>
<td>7.20</td>
</tr>
<tr>
<td></td>
<td>(16)</td>
<td>(12)</td>
<td>(8)</td>
<td>(7)</td>
<td>(8)</td>
<td></td>
</tr>
<tr>
<td>PhD students</td>
<td>47.63</td>
<td>56.38</td>
<td>55.45</td>
<td>56.88</td>
<td>52.68</td>
<td>51.28</td>
</tr>
<tr>
<td></td>
<td>(81)</td>
<td>(92)</td>
<td>(105)</td>
<td>(109)</td>
<td>(110)</td>
<td>(113)</td>
</tr>
<tr>
<td>Employed PhD students</td>
<td>47.63</td>
<td>56.38</td>
<td>55.45</td>
<td>56.88</td>
<td>52.68</td>
<td>51.28</td>
</tr>
<tr>
<td></td>
<td>(77)</td>
<td>(88)</td>
<td>(92)</td>
<td>(91)</td>
<td>(84)</td>
<td>(87)</td>
</tr>
<tr>
<td>Non–employed PhD students</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4/4.9%)</td>
<td>(4/4.35%)</td>
<td>(13/12.38%)</td>
<td>(18/16.51%)</td>
<td>(26/23.64%)</td>
<td>(26/23.01%)</td>
</tr>
<tr>
<td>Total research staff</td>
<td>75.43</td>
<td>80.90</td>
<td>76.35</td>
<td>80.33</td>
<td>75.28</td>
<td>76.23</td>
</tr>
<tr>
<td></td>
<td>(143)</td>
<td>(150)</td>
<td>(159)</td>
<td>(168)</td>
<td>(169)</td>
<td>(177)</td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professors, associate professors, assistant professors and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management tasks. Clinical researchers also have obligations for patient care. For the sake of simplicity, a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD students with an employment contract. The use of FTE for non-employed PhD students (student status) is not appropriate.

Table 7.2  Overview of the research funding at the level of the program NNOC

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
</tr>
<tr>
<td></td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Funding:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct funding (1)</td>
<td>36.73</td>
<td>40.80</td>
<td>40.60</td>
<td>46.20</td>
<td>44.20</td>
<td>44.60</td>
</tr>
<tr>
<td></td>
<td>(48.69%)</td>
<td>(50.43%)</td>
<td>(53.18%)</td>
<td>(57.52%)</td>
<td>(58.72%)</td>
<td>(58.51%)</td>
</tr>
<tr>
<td>Research grants (2)</td>
<td>6.13</td>
<td>7.35</td>
<td>6.65</td>
<td>4.90</td>
<td>4.95</td>
<td>6.65</td>
</tr>
<tr>
<td></td>
<td>(8.12%)</td>
<td>(9.09%)</td>
<td>(8.71%)</td>
<td>(6.10%)</td>
<td>(6.58%)</td>
<td>(8.72%)</td>
</tr>
<tr>
<td>Contract research (3)</td>
<td>32.58</td>
<td>32.75</td>
<td>29.10</td>
<td>29.23</td>
<td>26.13</td>
<td>24.98</td>
</tr>
<tr>
<td></td>
<td>(43.19%)</td>
<td>(40.48%)</td>
<td>(38.11%)</td>
<td>(36.38%)</td>
<td>(34.71%)</td>
<td>(32.76%)</td>
</tr>
<tr>
<td>Total funding</td>
<td>75.43</td>
<td>80.90</td>
<td>76.35</td>
<td>80.33</td>
<td>75.28</td>
<td>76.23</td>
</tr>
<tr>
<td></td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
</tr>
</tbody>
</table>

Explanation: Expenses for research include both personnel and other costs. Personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the donation to the provision “wachtgelden” (i.e. the obligation to provide personnel a reduced pay in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff and other costs such as allowances for child care and travel. Although non-employed PhD students do not represent research FTE, the costs of these PhD students have been included. Other costs include operational costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

Expenditure (k€)

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel costs (k€)</td>
<td>3,553</td>
<td>3,880</td>
<td>3,922</td>
<td>4,180</td>
<td>4,118</td>
<td>4,440</td>
</tr>
<tr>
<td>Other costs personnel (k€)</td>
<td>1,368</td>
<td>1,494</td>
<td>1,510</td>
<td>1,609</td>
<td>1,586</td>
<td>1,709</td>
</tr>
<tr>
<td>Costs non-employed PhD students (k€)</td>
<td>63.8</td>
<td>65.4</td>
<td>141.8</td>
<td>260.2</td>
<td>341.3</td>
<td>446.4</td>
</tr>
<tr>
<td>Other costs - non-employed PhD students (k€)</td>
<td>34.0</td>
<td>34.0</td>
<td>72.3</td>
<td>131.8</td>
<td>170.0</td>
<td>199.8</td>
</tr>
<tr>
<td>Total expenditure</td>
<td>k€ 5,018.4</td>
<td>k€ 5,473.6</td>
<td>k€ 5,645.5</td>
<td>k€ 6,180.8</td>
<td>k€ 6,212.3</td>
<td>k€ 6,795.1</td>
</tr>
</tbody>
</table>
1 Direct funding by the university;
2 Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programmes ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3 Funding for specific research projects obtained from external organisations, such as industry, governmental ministries, European Commission (Framework programmes) and charity organizations.
Chapter 7.3: Research Environment and Embedding

Position and reputation
The Northern Netherlands Oncology Center (NNOC) is one of the research institutes of GUIDE. In the NNOC itself, collaborative projects with various groups are ongoing and have a structural character that is evidenced by the joint publications and PhD research projects.

The participants in the NNOC are appointed from the Departments of Medical Oncology, Hematology, Pulmonary Oncology, Gastroenterology, Radiotherapy, Pediatric Oncology, Otorhinolaryngology and Oral and Maxillofacial Surgery, Gynecological Oncology, Surgical Oncology, Cell Biology, Radiation and Stress Cell Biology, Pathology, Genetics, Medical Biology, Nuclear Medicine and Molecular Imaging and Epidemiology, Epidemiology and Clinical Chemistry.

There are close and crucial collaborations with other groups within the UMCG.

There is extensive collaboration with the Department of Pharmacy of the Faculty of Mathematics and Natural Sciences that has further matured in recent years. This has resulted in joint publications and grants. Examples include the collaborations with the following research groups:

- Analytical Biochemistry of the University of Groningen Research Institute of Pharmacy, including Prof. R. Bischoff for Proteomics, Prof. D.R.A. Uges for Cancer Drug Pharmacokinetics, and Prof. F.A.J. Muskiet for neuroendocrine tumor marker development
- Pharmacokinetics, Toxicology and Targeting, with K. Poelstra for tumor imaging with designed peptide, also as part of the CTMM Mammoth project and with Prof. G.M.M. Groothuis for drug toxicity studies on tumor slices
- Pharmacotherapy & Pharmaceutical Care with J.R.J.B. Brouwers for drug interactions with anticancer drugs
- Pharmaceutical Gene Modulation with H.J. Haisma and M. Rots for gene modulation research
- Pharmaceutical Biology with Prof. W.J. Quax and Dr. R.H. Cool on TRAIL research, also as part of the TiPharma and FP6 EU project.

Members of the NNOC hold various positions in organizations in the Netherlands, including the NWO (Netherlands Organization for Scientific Research)/ZonMw, the Royal Netherlands Academy of Arts and Sciences (KNAW), the KNAW’s Advisory Board on Medical Sciences National Health Council (Gezondheidsraad) and the Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine). They serve as members on scientific advisory boards such as the scientific board of the Dutch Cancer Society. They are members of various societies and serve on many scientific committees at cancer conferences, prize selection committees and peer review panels of FP projects.

NNOC researchers collaborate structurally with Dutch universities, as well as with all university medical centers, with hospitals in Leeuwarden, Zwolle, Enschede, Deventer, Tilburg and Arnhem, with the Dutch Cancer Institute, and the TNO. These collaborations are often organized as part of large-scale national consortia such as the CTMM and TiPharma, the Parelsoener, European consortia within the 6th Framework Program, and large-scale clinical trials.

Strong international collaborations exist with researchers at universities and institutes in the UK, Ireland, Belgium, Germany, Switzerland, Austria, Spain, France, Italy, Finland, Denmark, Portugal, Sweden, the USA, Australia, Japan and China.

The collaborations with companies include frameworks of cooperation with major pharmaceutical companies (Schering-Plough, Novartis, MSD, Roche/Ventana, and Amgen), technology companies (Agilent, Veenstra, Waters Pepsan Kinase Arrays, ImClone Systems, Oncomethylome Sciences, Genentech, Novartis, Schering-Plough, InVivoScribe, and Brainlab) and small and medium-scale enterprises (Triskel Therapeutics, Pamgene, and ISA Pharmaceuticals).

Researchers within the NNOC collaborate with many non-profit organizations, the most important being the Dutch Cancer Foundation, the KIKA, the SKOG and the NWO-ZonNW.

Key collaborations
Three key collaborations per NNOC researcher are summarized in appendix Chapter 7.3

Visitors
The NNOC frequently invites distinguished guest scientists to lecture on their research, to enter into scientific discourse with colleagues, to build national and international networks, to participate in master classes and to participate in thesis defenses. An overview of guest lectures is given in appendix Chapter 7.3.
Chapter 7.4: Quality and Scientific Relevance

Most important results of the four sub-programs

1 Cancer: genes, mutations and their consequences

Our aim is to identify genes and genetic pathways that regulate the development of primitive hematopoietic stem cells into mature blood cells. To this end, we performed screens in genetically distinct strains of mice. We identified FGF1 as an important growth factor that is able to amplify hematopoietic stem cells. We identified the Polycomb group protein Ezh2 as an important intrinsic stem cell regulator, and have since studied multiple PcG genes. We perturbed the expression of these regulators and assessed clonal consequences in in vivo transplantation models.

In recent years we continued the search for mutations in patients suspected of inherited cancers. The most attention was given to Lynch Syndrome. We were able to identify groups of patients who had a high probability of carrying germline variants that predisposed to colorectal and endometrial cancer, for example. Because we identified many variants for which the significance for disease development was unclear (unclassified variants - UVs) we set up functional assays that will help us solve this problem. Moreover, to help diagnostic laboratories that are also struggling with these UVs, we have built a well-visited database that contains all data available on these UVs ([www.mmrmissense.net](http://www.mmrmissense.net)). Finding mutations was a priority, along with counseling and treating patients with inherited cancer syndrome. In close collaboration between people from the lab and the clinicians involved in the daily care for these patients, we paid substantial attention to the development of new treatment strategies.

2 Hematopoietic development and hemato-oncology

Relevant pathways have been identified for stem cell self-renewal and differentiation in normal and leukemic cells by performing gene function analyses with STAT5 and BMI1. Simultaneously, relevant cellular routes involved in the process of enhanced cell death in myelodysplasia have been identified.

The role of EBV in lymphoid malignancy has been explored with emphasis on the role in the pathogenesis of Hodgkin’s disease and the HLA associated genetic susceptibility. Similarly, modifications in immunoregulatory genes have been identified in lymphomas arising in immune sanctuaries.

High-throughput gene expression and microRNA expression studies in relationship to genes such as MYC, NFkB and p53 have resulted in a much better understanding of diseases such as diffuse large B cell lymphoma and Burkitt’s lymphoma. Proteomic research has led to the identification as serum TARC (CCL17) as a promising novel biomarker in Hodgkin lymphoma.

3 Translational Oncology

Target evaluation and prognostic and predictive factors

In several studies, in-depth (drug) target analysis was performed, while their prognostic and predictive roles were also evaluated.

The BRCA2 and its product were implicated in DNA repair and transcriptional regulation. A protein (EMSY) was identified, which binds BRCA2 within a region (exon 3) deleted in cancer. EMSY is capable of silencing the activation potential of BRCA2 exon 3, associates with chromatin regulators HP1beta and BS69, and localizes to sites of repair following DNA damage. It was shown that the EMSY gene is amplified almost exclusively in sporadic breast cancer (13%) and higher-grade ovarian cancer (17%), and that its amplification is associated with worse survival, particularly in node-negative breast cancer.

In early-stage cervical cancer, determination of serum SCC-ag levels allows more refined preoperative estimation of the likelihood for adjuvant radiotherapy than current clinical parameters, and simultaneously identifies patients at high risk for recurrence when treated with surgery only.

On the basis of a large microarray study of stage 3-4 ovarian cancer patients, new clues to genes, pathways, and transcription factors were identified that contribute to the clinical outcome of serous ovarian cancer and might be exploited in designing new treatment strategies.

As part of a randomized adjuvant study of stage 3 colon cancer patients, it was shown that both mutant TP53 and MSI-H are prognostic indicators for disease-free survival, but only TP53 retains statistical significance after adjusting for clinical heterogeneity. In addition, high death receptor 4 (DR4) expression was associated with worse disease-free and overall survival.

Imaging

Nuclear imaging

FDG-PET: The glucose uptake visualization of tumors has earned a proven place for a number of indications based on studies in which the UMCG was instrumental. Up-front FDG-PET in patients with suspected lung cancer was not found to reduce the overall number of diagnostic tests, but it maintains the quality of TNM staging with the use of less invasive surgery.

In recurrent NHL, the secondary clinical risk score in conjunction with the FDG-PET response provides a more accurate prognostic instrument for the outcome of second-line treatment. In patients with melanoma and palpable
lymph nodes, 27% were upstaged as a result of FDG-PET and CT, and treatment changed in one of five patients. FDG-PET and CT are equivalent in upstaging; however, FDG-PET detected more metastatic sites, especially bone and subcutaneous. In addition, new imaging techniques were developed to image neuroendocrine tumors and to visualize tumor-specific targets, including anti-cancer drug targets.

In recent years, UMCG researchers have performed carefully designed, ground-breaking trials in which they used the specific metabolic processes that occur in neuroendocrine tumors. It was shown that 18F-dihydroxy-phenylalanine is superior as a PET tracer in detecting carcinoid tumors, while the 11C-5-hydroxy-tryptophan (5-HTP) PET tracer is superior for islet cell tumor detection. HER2 tumor imaging in patients was proven to be possible, and revealed more lesions in metastatic patients than conventional imaging.

Anatomic imaging
Two major studies for early detection of breast and lung cancer were performed with MRI. MRI appeared to be more sensitive than mammography in detecting tumors in women with an inherited susceptibility to breast cancer. A major drawback of current lung cancer computer tomography (CT) screening regimens is the high rate of suspicious nodules detected, the associated burden of referral and the possibility of overdiagnosis. Therefore, an improved screening strategy is needed. In the largest high-risk sample from the general population (15,822 male and female high-risk current and former smokers aged 50-75 years), a CT screening strategy based only on nodule size and volume doubling time assessment has shown excellent screening test performance.

4 Clinical studies
Clinical trials
Numerous clinical trials are performed as in-house studies as well as part of national and international collaborations. Here we will highlight a number of them.

Solid tumors
Much work has been performed on the role of sentinel node biopsy in staging. An international study in which the UMCG played a pivotal role showed that the sentinel lymph node staging of intermediate-thickness primary melanoma identified patients with nodal disease in whom the survival improved with therapeutic lymphadenectomy. This has led to sentinel lymph node biopsy being a standard staging procedure for primary melanoma. The standard treatment for squamous cell cancer of the vulva is radical excision of the tumor and elective inguinofemoral lymphadenectomy. Although this treatment has good efficacy, only one-third of the patients have regional disease which justifies this lymphadenectomy. In 2008, the international landmark GROINSS-V study showed that sentinel lymph node biopsy in the management of vulva cancer decreased morbidity without compromising loco-regional recurrence rate or survival. As a result, sentinel lymph node biopsy for primary cancer of the vulva became a standard staging procedure.

Based on staging, breast cancer patients are treated with local regional treatment and/or systemic treatment. The role of high-dose chemotherapy was studied in a national randomized high-dose chemotherapy study. The clinical outcome of this pivotal trial showed that high-dose alkylating therapy improved relapse-free survival among patients with stage I/III breast cancer and ≥10 positive axillary lymph nodes. This benefit appeared to be confined to patients with HER-2/neu-negative tumors. There has been an impressive spin-off of studies that addressed the side effects, supportive care, long-term toxicity, psychosocial effects, quality of life, and circulating tumor cells, among other aspects. These studies provided important new insights as to which patients are likely to benefit from high-dose chemotherapy, based on pathological evaluations.

In addition, in a collaborative study the clinical groups at the UMCG showed that a risk assessment model appears to identify febrile neutropenic patients at low risk for bacterial infection. This showed that antibiotics can be withheld in well-defined neutropenic patients with fever.

One paper can be used to illustrate the involvement of NNOC members in phase 1 clinical trials. Here, as part of their early work on angiogenesis inhibition, they demonstrated that the angiogenesis inhibitor ABT-510 has a favorable toxicity profile and linear and time-independent pharmacokinetics with biologically relevant plasma concentrations.

Hematological malignancies
In collaboration with partners EORTC and HOVON, important issues regarding the role of radiotherapy in the treatment of Hodgkin’s disease and dose intense treatments for poor-risk Non-Hodgkin’s Lymphoma were addressed. It was shown that involved field radiotherapy did not improve the outcome in patients with advanced-stage Hodgkin disease who had complete remission after MOPP-ABV chemotherapy. However, in patients with early stage Hodgkin disease chemotherapy plus involved-field radiotherapy should be the standard treatment. In NHL dose intense regimens were tested and it was shown that monoclonal antibody treatment with anti-CD20 significantly improved the treatment results in conjunction with intensive chemotherapy in patients with relapsed
Non Hodgkin Lymphoma. In acute myeloid leukemia, two alternative approaches were used to improve the poor treatment results of AML patients. First, an attempt was made to prime the leukemic stem cell for the effects of chemotherapy by giving a growth factor upfront treatment. This was followed by a more dose-intense regimen that was applied to elderly AML patients. The results showed that the last approach resulted in a significant improvement in overall survival in a subgroup of patients. Additional items that have been studied are (a) dose-intensification in multiple myeloma and AL-amyloidosis which seems possible by using a better risk stratification of patients (b) improving the treatment results of patients with mastocytosis by making use of new kinase inhibitors.

Long-term consequences of cancer treatment
The researchers at the UMCG have made several outstanding contributions in the evaluation and potential prevention of long-term toxicity in cancer patients, with emphasis on breast cancer, testicular cancer, childhood cancer, head and neck cancer and lymphoma survivors. Breast cancer patients diagnosed with breast cancer in the 1990s experienced an excess risk of developing a secondary non-breast cancer, and young patients experienced a high contralateral breast cancer risk, while adjuvant hormone treatment and chemotherapy considerably reduced this risk. Several Dutch epidemiological studies were performed in which NNOC members were instrumental, as well as in-depth studies in germ cell tumors. For example, germ cell cancer survivors following chemotherapy showed gonadal dysfunction, but normal adrenal and thyroid functions were observed. Through its association with BMI, testosterone may play a role in the development of the metabolic syndrome in long-term testicular cancer survivors. It was shown that shared care by pediatric oncologists and family doctors is feasible for long-term follow-up of adult survivors of childhood cancers.

In head and neck cancer patients, it was shown that late radiation-induced toxicity, particularly RTOG (swallowing) and RTOG (xerostomia), had a significant impact on the more general dimensions of HRQoL. These findings suggest that the development of new radiation-induced delivery techniques should not only focus on reduction of the dose to the salivary glands, but also on anatomic structures that are involved in swallowing. In lymphoma studies, the UMCG had an essential role in the EORTC studies on long-term toxicity. One of the findings was that fertility can be secured after nonalkylating chemotherapy for Hodgkin’s lymphoma. In contrast, alkylating chemotherapy has a dismal effect, even after a limited number of cycles.

Key publications for the four sub-programs:
The decision was made to only select papers from those papers with an IF>10

1 Cancer: genes, mutations and their consequences

Hematopoiesis

Cancer syndromes
2 Hematopoietic development and hemato-oncology

Leukemia


Lymphoma


3 Translational Oncology

Target evaluation and prognostic and predictive factors

Imaging

Nuclear imaging


Anatomic imaging


4 Clinical studies

Clinical Trials

Solid tumors


Hematological malignancies


Chapter 7  Northern Netherlands Oncology Center


Long-term consequences of cancer treatment


Appreciation of Scientific Publications

During the period 2003 – 2008, NNOC members published 11 times in the New England Journal of Medicine (IF 50.0), 4 times in Lancet (IF 28.4) 60 times in the Journal of Clinical Oncology (IF 17.2), 8 times in Lancet Oncology (IF 13.3) and 43 times in Blood (IF 10.4). Additionally papers were published in Cell (IF 31.2, one paper), Endocrine Reviews (IF 18.6, one paper), Circulation (IF 14.6, two papers), PLoS Biology (IF 12.7, two papers), Gastroenterology (IF 12.6, four papers), PLoS Medicine (IF 12.2, one paper), Hepatology (IF 11.6, one paper), Current Biology (IF 10.8, one paper), and Gut (IF 10.0, one paper). For an overview of all published papers, see appendix Chapter 7.5. All top-publications (10% and 30%) are summarized in Table 7.3 and have been marked in appendix Chapter 7.5. NNOC papers with an impact factor higher than 10 are summarized in Table 7.4.
Table 7.3  High quality publications – number of publications in the best 10% and 30% of relevant disciplines

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>(n of articles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belongs to the best 10% of a relevant subject area</td>
<td>36%</td>
<td>35%</td>
<td>31%</td>
<td>29%</td>
<td>34%</td>
</tr>
<tr>
<td>(n of articles)</td>
<td>(60)</td>
<td>(77)</td>
<td>(65)</td>
<td>(57)</td>
<td>(67)</td>
</tr>
<tr>
<td>Belongs to the best 30% of a relevant subject area</td>
<td>60%</td>
<td>72%</td>
<td>70%</td>
<td>74%</td>
<td>70%</td>
</tr>
<tr>
<td>(n of articles)</td>
<td>(101)</td>
<td>(157)</td>
<td>(146)</td>
<td>(146)</td>
<td>(140)</td>
</tr>
</tbody>
</table>

Explanation: A ranking for publications present in the on-line database ‘ISI Web of Knowledge’, sub-database ‘Web of Science’ can be calculated and is presented. Papers are categorized based on the journal they appear in. Approx. 175 subject area's have been designated (ISI-fields). The percentages are calculated based on the number of the journal titles in the subject area.

Papers published in the relevant subject area's of the research programme are included in this analysis. According to the methodology of bibliometric analyses, only papers of the reference types 'Article', 'Note', 'Letter', 'Review'; and 'Proceedings paper' are considered. This implies that references of the type 'Editorial material', 'Book (review)', 'Correction', 'Meeting abstract', 'Conference proceedings', 'In memoriam', 'News item', 'Biographical item', etc., are not included.

Table 7.4  High-ranking papers with IF>10

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of articles with impact factor &gt;10</td>
<td>21</td>
<td>18</td>
<td>28</td>
<td>24</td>
<td>26</td>
<td>28</td>
</tr>
</tbody>
</table>
Chapter 7.5: Quantity of Scientific Output

Overview
Table 7.5 shows that the gross increase is about 40% in output refereed articles versus 2003. This increase is paralleled by an over 73% increase in number of theses versus 2003. Over the years during the previous visit there was also a clear steady increase observed. This is also the reason why 2008 compared with 2002 shows even a 43.5% increase in refereed articles, and 116% increase in theses. All publications are listed in appendix Chapter 7.5. Summary of the results:

- During the period 2003-2008, NNOC researchers published numerous book chapters. The three key book chapters per researcher are described in appendix Chapter 7.5
- During the period 2003-2008, eight patent applications were realized. This involved six researchers. Furthermore, in 2009 another three patents were filed. An overview of all NNOC patents from 2003-2009 is given in appendix Chapter 7.5.

Publication strategy
The general strategy is to publish in high ranking journals and especially to accept the challenge of submitting papers to the ISI fields such as “general medicine” and “oncology” which are highly competitive fields with very high impact factors for the best 10%. Submitting papers to other research fields might increase the number of best 10% papers as shown above, but would result in less visibility in the research community and fewer citations.

The NNOC’s program leader, Prof. De Vries, played a major role in the development of the UMCG Research Code. This code offers clear guidance for ethical research issues.

In addition, NNOC members are encouraged to translate research findings into clinical practice and to inform their colleagues and the public in the Netherlands about their findings.

Table 7.5  Main categories of research output at the level of program NNOC

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refereed articles</td>
<td>192</td>
<td>194</td>
<td>243</td>
<td>239</td>
<td>224</td>
<td>226</td>
</tr>
<tr>
<td>PhD-theses</td>
<td>15</td>
<td>16</td>
<td>20</td>
<td>31</td>
<td>31</td>
<td>26</td>
</tr>
<tr>
<td>Patents</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total publications</td>
<td>208</td>
<td>210</td>
<td>263</td>
<td>271</td>
<td>256</td>
<td>254</td>
</tr>
<tr>
<td>Books and Book chapters*</td>
<td>88</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* During the period under review, 28 members contributed to a total of 88 books or book chapters (not corrected for duplicates).

Table 7.6  Number of PhD students

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Employed</td>
<td>77</td>
<td>88</td>
<td>92</td>
<td>91</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td>non-employed*</td>
<td>4</td>
<td>4</td>
<td>13</td>
<td>18</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>% non-employed</td>
<td>4.94%</td>
<td>4.35%</td>
<td>12.38%</td>
<td>16.51%</td>
<td>23.64%</td>
<td>23.01%</td>
</tr>
</tbody>
</table>

* Those who hold a position elsewhere or work on a bursary are defined as non-employed
Chapter 7.6: Earning Capacity

Fund raising strategy and support

Several initiatives have been taken to support funding. Principal researchers are informed about calls for proposals via e-mail, newsletters and meetings. The oncology sections have a special location on their websites which describes oncology-specific funding opportunities.

Meetings are held to discuss experiences and options regarding funding. The Center offers a stimulating environment for discussing grant proposals and for reviewing grant applications by several colleagues, also those not directly involved in the specific application, before grant submission.

Results

Most PIs in the cancer center have a high success rate in acquiring grants. This is shown by grants from sources such as the Dutch Cancer Society, the ZonMW/NWO, the Astma Fonds, the EU, Efficacy Research grants and NIH, Pink Ribbon, Pink Gala, Foundation Vanderes, Von Hippel-Lindau Family Alliance grants, and several industrial partners who provided unrestricted educational grants. In recent years there has been an even greater diversity of grant resources, including NNOC members who serve as PIs for major multicenter grants of CTMM, TI Pharma, Parelsoor and Translational Adult stem cell (TSO) grants etc. These are Dutch government initiatives to foster collaboration between academia and industry. Researchers within the NNOC received NWO grants, which can also be interpreted as an token of esteem: Veni grants (G.A. Huls, MD, PhD, P. van Luijk, PhD, M.A.T.M. van Vugt, PhD, J.J. Schuringa PhD), Vidi grant (J.J. Schuringa and M.G. Rots) and Vici grant to the laureate Prof. G. de Haan (2006) and three Rosalind Franklin fellowships. Twenty-five MD/PhD students worked in the NNOC.

Table 7.7 Fund raising capacity at the program level NNOC

<table>
<thead>
<tr>
<th></th>
<th>2003 (FTE)</th>
<th>2004 (FTE)</th>
<th>2005 (FTE)</th>
<th>2006 (FTE)</th>
<th>2007 (FTE)</th>
<th>2008 (FTE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total funding</td>
<td>100% (79.43)</td>
<td>100% (84.90)</td>
<td>100% (84.85)</td>
<td>100% (95.83)</td>
<td>100% (95.28)</td>
<td>100% (99.73)</td>
</tr>
<tr>
<td>Allocated funding</td>
<td>18.07% (14.35)</td>
<td>17.55% (14.90)</td>
<td>17.27% (14.65)</td>
<td>16.96% (16.25)</td>
<td>16.69% (15.90)</td>
<td>17.80% (17.75)</td>
</tr>
<tr>
<td>Acquired funding</td>
<td>81.93% (65.08)</td>
<td>82.45% (70.00)</td>
<td>82.73% (70.20)</td>
<td>83.04% (79.58)</td>
<td>83.31% (79.38)</td>
<td>82.20% (81.98)</td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are funded directly by the University of Groningen and/or the UMCG (allocated funding). To extend their research capacity, they acquire grants via internal and external competition (acquired funding) for non-tenured staff, employed PhD students, non-employed PhD students and in some cases a limited number of staff positions. The fund raising capacity is expressed in research FTE. Unfortunately no data are provided for the numerous technicians, bench fee and apparatus such as animal PET, funded by external grants.
Chapter 7.7: Academic Reputation

International position and recognition
At both the national and international levels, NNOC members have contributed significantly to the development of their research field. They have taken numerous administrative and editorial roles to promote cancer research in the Netherlands in organizations that include the NWO (Netherlands Organization for Scientific Research), ZonMw, the Royal Netherlands Academy of Arts and Sciences (KNAW), Prof. De Vries is a member), the National Health Council (Gezondheidsraad) and the Nederlands Tijdschrift voor Geneeskunde (Dutch Journal of Medicine).

Members have served on the scientific advisory board of the Dutch Cancer Society, and on several juries for scientific prizes, including the Dr. A.H. Heineken prize for Medicine. NNOC members have also served on the Dutch Health Council or specific subgroups of this council.

At the international level, members have contributed to societies such as the American Society of Clinical Oncology (ASCO), the Society of Surgical Oncology (SSO), the American Association of Cancer Research (AACR), the EORTC, the European Society of Medical Oncology (ESMO), the European Society of Surgical Oncology (ESSO), the International Society for Stem Cell Research (ISSCR) and the International Society for Experimental Hematology (ISEH). They have served on numerous scientific committees at cancer conferences (see appendix Chapter 7.7). In addition members of the NNOC are frequently invited to write articles or chapters in books, to become a member of an editorial board, to give invited lectures and to participate in research grant selection committees.

The international role of members is also illustrated by the presidency of the European Society of Gynecologic Oncology (ESGO) – Prof. A.G.J. van der Zee; chairmanship of RECIST version 2.0 – Prof. E.G.E. de Vries; hosting an International Translational Research Unit for young oncologists by ESMO in 2010; chairmanship of the Head and Neck EORTC cancer group – Prof. J.A. Langendijk; former position as secretary of the EORTC Lymphoma group – Prof. J.C. Kluin-Nelemans; members receiving international awards – the ESSO award to Prof. T. Wiggers, the ESMO award to Prof. E.G.E. de Vries.

This indicates the international acceptance of NNOC members, both nationally and internationally. This international collaboration is also reflected in participation in networks such as the EORTC, the POG, EU networks and the large body of joint publications with colleagues from other countries. In addition, various members of the NNOC participate in strong and valuable international collaborations, which is shown from their joint publications and grants (see appendix Chapter 7.7).

Prominence of the program directors and other research staff
Prof. Dr. Elisabeth G.E. de Vries, MD, PhD, is Professor of Medical Oncology, and head of the Department of Medical Oncology. She was previously a research fellow (1982-1983) at the Department of Medical Oncology, City of Hope National Medical Center, in Duarte, California (USA). She is involved in patient care, teaching, and research. Her research lines are aimed at increasing the sensitivity of tumors to anticancer drugs, and she uses imaging techniques to support this.

Apart from laboratory studies, she performs and coordinates phase I-III studies. She has received numerous grants, including grants from the Dutch Cancer Society and the EU. She has supervised 80 PhD students and published over 631 PubMed listed papers, with 16,320 citations and an H-factor of 59.

Between 1993 and 2000, she served as a member and chairperson on the scientific board of the Dutch Cancer Society. Currently, she is vice-chair on the board of the Dutch Cancer Society. In 2002, she was appointed as a member of the Royal Academy of Arts and Sciences (KNAW). In 2008, she became a Knight in the Order of the Netherlands Lion.

She received the European Society of Medical Oncology (ESMO) award in 2009 and was appointed Fellow of the European Academy of Cancer Sciences. She is active on national committees, the EORTC and program committees at international meetings and is a member of several editorial boards. She currently serves as a member of the Health Council of the Netherlands, and is the chairperson of the Medical Sciences committee of the KNAW.

Prof. Dr. Harald J. Hoekstra, MD, PhD received his surgical and oncology training at the Groningen University Medical Center in Groningen (the Netherlands) and at the Surgery Branch of the National Cancer Institute (NCI) in Bethesda, Maryland (USA). His research is focused on the surgical aspect of combined modality treatment of solid tumors, especially sarcoma, melanoma, and testicular cancer, and the use of new diagnostic imaging techniques in the staging and treatment evaluation of these tumors.

He served on the board of the European Society of Surgical Oncology (ESSO), the Connective Tissue Oncology Society (CTOS), the Dutch Society of Oncology, the Dutch Society of Surgical Oncology and the Dutch Cancer Foundation. He is currently a member of the International Advisory Board of the Society of Surgical Oncology (SSO). He is also a member of various EORTC groups, the Trans-Tasman Radiation Oncology Group (TROG), the Multicenter Selective Lymphadenectomy Trial group, the Selective Lymph Node Working Group, the Dutch Sarcoma Working Party, the Dutch Melanoma Working Party and the Dutch Committee on Bone tumors. He is member of the editorial board of the Annals of Surgical Oncology and the Journal of Surgical Oncology. He has published over 342 PubMed listed papers.
and supervised 30 theses. In addition, he has been involved in various non-profit and fundraising organizations for the treatment of cancer, such as Ride for the Roses.

**Signs of recognition**
During the period 2003-2008, a total of 22 awards were granted to NNOC researchers. In addition, two NNOC researchers received the yearly Research Prize of €100,000 from the UMCG/RUG (Prof. G. de Haan in 2003 and 2006, and Prof. J.H.M. van den Berg in 2008). For details see appendix Chapter 7.7.
Between 2003 and 2008, NNOC researchers were also invited to speak at numerous international scientific events. An overview of all invited lectures is given in appendix Chapter 7.7.

Other indications of academic reputation include: travel awards from the ASH, appearances on Dutch scientific radio and television programs, and chairmanships of national research organizations. These have been listed in appendix Chapter 7.7.
Chapter 7.8: Societal Relevance

Research on important issues
The high incidence of cancer means that most Dutch citizens are confronted with cancer and its consequences, including its societal impact. The NNOC is extensively involved in research which has a major impact on society. In addition, NNOC members are involved in the cancer care for their region, which has 3.4 million inhabitants. There is excellent collaboration with hospitals in the entire region regarding clinical research. Every month, teams from the University Hospital visit the numerous hospitals in the area, perform surgery (gynecological oncology) and have additional videoconferences. This collaboration allows rapid dissemination of novel findings. In addition, NNOC research on the long-term side effects in cancer survivors is currently being translated into tailored recommendations for these individuals. The translational research on new drug development and molecular imaging techniques also show clear examples that are translated to clinical practice, as do the phase 3 studies performed in the NNOC.

The cost related to cancer care is an increasingly bothersome issue in the Netherlands. P.H.B. Willemse has been appointed Professor in the evaluation of the efficiency and societal aspects of treatments, and has played a major role on the BOM committee (Judgment of Oncological Drugs), which develops evidence-based judgments. Members of the NNOC participate in shaping this debate, and will continue to team up with others such as the NFK (Dutch Federation of Cancer Patients).

Societal Impact
Members of the NNOC exert their societal impact by participating in numerous organizations related to health care and health-care research in the Netherlands, including the NWO (Netherlands Organisation for Scientific Research)/ZonMw, the Royal Netherlands Academy of Arts and Sciences (KNAW), the KNAW’s Advisory Board on Medical Sciences, the National Health Council (Gezondheidsraad) and the Dutch Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde). They serve as members on the scientific advisory board and the board of the Dutch Cancer Society. They are involved in the development and modification of numerous Dutch cancer guidelines.

They are not only responsible for the education of medical students, but also for educating pharmacists, biologists, and patient organization groups, among many others.

Members have set up websites for consultation in standard care and trials by medical specialists and patients. (The patient information is largely acquired in collaboration with patient organizations).

These websites include:
http://www.hematologiegroningen.nl/
http://www.medischeoncologiegroningen.nl/
http://www.radiotherapiegroningen.nl/
http://www.umcg.nl/Patienten/ziekten/150264/Pages/borstkanker.aspx
http://www.umcg.nl/Patienten/ziekten/133044/Pages/Prostaatkanker.aspx

In addition, a familial cancer database for worldwide use with R. Sijmons as editor can be found at: http://www.familialcancerdatabase.nl/
A database for worldwide use on unclassified variants in the mismatch repair (MMR) genes which was set up and curated by Rolf Sijmons and Robert Hofstra can be found at: http://www.mmrmisense.info/

NNOC members regularly inform the public by holding public meetings at the institution to report on research, and they participate in the UMCG initiative for the Public Academy and numerous patient organizations. They also collaborate in partnership with the Dutch Cancer Society in the UMCG Cancer Research Funds, which has its own website: www.umcgkankerresearchfonds.nl

Valorization
Valorization is gaining more attention. Members apply for IPs and, as part of ongoing EU, CTMM and TI-Pharma projects, major effort is being put into economic valorization. These major grants will also result in technical benefits for society at large. Several technologies are under development in the field of molecular imaging with PET/intraoperative fluorescent imaging, which will result in toolkits for molecular imaging, for example. Society will benefit from early and optimal access to cancer care at the lowest cost. Several scientific results have been incorporated in patent applications.
Chapter 7.9: Next Generation

With regard to the education offered through GUIDE, please refer to the main part of the GUIDE evaluation.

Objectives and institutional embedding
Teaching PhD students and motivating and reaching students with different backgrounds of oncological research is considered to be a major task of the members of the NNOC.

Structure and content of the program
PhD students
PhD students can participate in various GUIDE courses. In addition, members of the NNOC faculty actively participate in the various courses. PhD students are involved in research meetings at the different departments in which they work, as well as at research meetings of clusters such as the hematology cluster within the NNOC. The research meetings are increasingly being posted on the web with additional relevant information. http://cms.umcg.nl/azgorganisatie/sectord/themas/1109536/1237494.

Expert visits from abroad are often combined with master classes for junior researchers. The students actively participate in journal clubs. In addition, they have ample opportunity to present their own data to colleagues internally, as well as at national and international meetings. The general aim is to give the students the opportunity to present their data at an international meeting during the course of their research.

Training PhD students entails also providing guidance in:
- presentation of new research projects, including discussions on background, content, and expected implications
- presentation of results of current research
- presentation skills and content discussion
- evaluation of the content of abstracts intended for submission to international meetings
- evaluation of content and communication strengths of posters accepted at international meetings
- rehearsal of presentations for international meetings.

PhDs are offered the opportunity to publicly present their data when volunteers have visiting rounds in the UMCG.

Supervision
All PhD students receive regular, intense, individual coaching by the people directly involved in coaching the student. This process is evaluated on a regular basis with AIO progress reports and an extensive PhD student monitoring system, which includes a standardized, extensive analysis after one year. In addition, several PhD students complete part of their PhD project in the laboratory of a collaborating partner abroad. This has often been made possible by grants from the Dutch Cancer Society.

Success rate
Overall, the success rate for PhD students finalizing their thesis is high within the NNOC.

Educational resources
There are a number of special educational opportunities for PhD students within the NNOC. There is a national course in oncology, meant for PhD students and largely financed by the Dutch Cancer Society, for introducing new researchers in the oncology field to the national environment with regard to all aspects of cancer research.

Other aspects
Special attention is paid to the ‘pipeline’ of new researchers and new faculty.

Medical students
Junior Scientific Master (JSM)
An interesting UMCG initiative is the Junior Scientific Master (JSM) class which offers motivated students additional opportunities to become involved in scientific research in addition to their regular medical or dental education. This special educational program provides students with the possibility of obtaining an Honors degree in research during the Bachelors phase and/or, by combining their internship with a PhD project, of receiving both their MD and PhD at the end of the Masters phase. Chairperson of the Junior Scientific Master class is the NNOC member J.C. Kluin-Nelemans. The NNOC has embraced this initiative and coaches numerous MD/PhD students. In addition, as part of the JSM Bachelors Honors trajectory, every year there is a special hands-on science elective, ‘What makes a cell a cancer (stem) cell’, organized by the Departments of Hematology, Medical Oncology, Pediatric Oncology and Gynecological Oncology.
Summer schools
In addition, two international summer schools are held.

- Every other year the International Summer School Oncology in Groningen is organized by the WHO Collaborating Center for Cancer Education/UMCG in collaboration with the International Summer School Oncology of the Medical University of Vienna. UMCG medical students actively participate in the organization of the summer school. The aims are to help students become familiar with cancer care in general health practice, to diminish fear of patients with a malignant disease, and to learn more about cancer-related problems in other countries. A variety of interactive teaching techniques for knowledge, skills and attitude are used. Participants are requested to present a poster on one of these topics.

- There is a yearly UMCG Research Summer School in Palliative Care in collaboration with Cardiff University (UK) and the Universities of Mannheim and Heidelberg (Germany).

Non-medical students
NNOC members teach in the Bachelor program Life Science and Technology. In addition, they are active in the Topmaster program Medical and Pharmaceutical Drug Innovation (MPDI). Students with a variety of backgrounds, including pharmacy, biology, and life sciences, spend their Masters research period in NNOC labs.

MD/PhDs and research
There is concern in the Netherlands that MDs in training to become medical specialists have too little opportunity to be involved in research, either to earn a PhD or as postdocs. After analyzing the problems in the field, the RMW-KNAW (in which NNOC member E.G.E. de Vries was involved) provided the following recommendation: ‘Improve the scientific training of doctors and medical specialists.’

Mandema Stipendia
To address this issue, the UMCG offers the Mandema stipendia (€ 60,000), which enables young physician-scientists (MD/PhD) to combine their specialist training with research and establish their own line of research. Several NNOC members were involved in initiating this initiative. In the NNOC, MDs in training are specifically coached on how to advance their research careers, for example, by supporting them in writing research grants and obtaining research experience abroad.

Flims course. ‘Methods in Clinical Oncology’
This meeting, jointly organized by the European Cancer Organization (ECCO), the AACR and the ASCO, is actively promoted among young oncologists so that they can learn how to execute and write protocols. Eight young UMCG oncologists participated, and NNOC members served on the faculty.

European Translational Research Unit Visit
In the Spring of 2010, the UMCG-Nnoc will host a translational research unit visit for young oncologists. ESMO will select oncologists from abroad to participate on a competitive basis. They, together with young oncologists in the UMCG, will be trained in all aspects of translational oncology. This is supported by an ESMO grant.

Mentor/Mentee program UMCG/RUG for female staff
The UMCG/RUG has set up a successful Mentor/Mentee program for female staff, to which several NNOC members have contributed as mentors.
Chapter 7.10: SWOT and Future Strategy

SWOT

Strengths

Interactions within the NNOC
The NNOC program encompasses more than 15 preclinical and clinical departments, and has 56 full members and numerous postdocs, PhD students, technicians and supporting staff. This is a translational research center with a multidisciplinary approach, which is embedded in GUIDE. In addition, within the NNOC, there is extensive collaboration between preclinical, translational and clinical groups, which permits optimal translational research. There is a stimulating multidisciplinary research environment with a good atmosphere and plentiful opportunities for sharing ideas and receiving comments in sessions such as special group meetings and research meetings.

Research infrastructure and equipment are increasingly being shared by different groups. Two remarkable examples include the newly built small animal facility, and the fact that the labs of Medical Oncology, Hematology, Gynecological Oncology and Pediatric Oncology have shared a newly built, optimally equipped lab since 2003. The newly formed lab is the result of the profound desire of these groups to use a single lab in order to share each other’s expertise and equipment. This has indeed already been shown to result in fruitful collaborations, and is experienced by all as very energizing.

In 2010, the new Outpatient Cancer Center on the UMGC campus will be opened. In this center, medical specialists from various departments will work in teams to evaluate and treat patients with all types of cancer. This team approach will make it possible for many patients to see all of their specialists during a single visit. The NNOC’s knowledge on cancer survivorship issues can now be more easily translated into better care for survivors. In this new outpatient center, they will have access to post-treatment follow-up care, including counseling and monitoring of long-term side effects of treatment. Also housed at this center will be special facilities with a wide range of support services such as social work, an Information Resource Center and data management, and rooms for tumor board meetings. This Cancer Center also hosts the young multidisciplinary Palliative Care team, a group whose shared mission is optimal palliative patient care and evidence based research.

In cooperation with the Dutch Cancer Society, a new fundraising program was started in 2008: the UMCG Cancer Research Fund. The aim of this fund is to more fully involve the population of the Northern region of the Netherlands in the UMCG’s Cancer Research program and to promote the further development of the program.

Interaction with groups in the UMCG beyond the NNOC
NNOC members have several collaborations with other centers within GUIDE and within the Medical Faculty, but there are also other extensive collaborations, specifically with the Faculty of Mathematics and Natural Sciences at the RUG.

The UMCG has decided to place a pivotal focus on ageing in its scientific research, patient care and educational programs. The UMCG is the only university medical center that has chosen to embed healthy ageing and all of its associated aspects in its core tasks on a permanent basis. There are two major UMCG research programs which are the basis of Healthy Ageing related research: the ERIBA and LifeLines.

The European Research Institute on the Biology of Ageing (ERIBA) will operate at the start of the innovation chain. The institute is headed by NNOC member Gerald de Haan. This institute is built around world’s leading scientists in the field of ageing and its associated diseases, and therefore offers a prominent role for cancer research. Each researcher will pursue a specific line of fundamental research.

LifeLines is a large-scale cohort study that will follow 165,000 people for a minimum of 30 years and will record the course of their life and health developments. The aims of LifeLines are to study the extent to which heredity and the circumstances of life play a role in the occurrence of chronic diseases. The size of the cohort in the LifeLines initiative precludes direct cancer research in this cohort. There is Dutch cancer registry in the Netherlands, which is connected to the IARC (International Agency of Cancer Research). Together with this registry, and the availability of a computerized database of all pathology samples (PALGA) evaluated in the Netherlands, this will allow NNOC members to couple these and other data anonymously for research through the IKNO. LifeLines allows comparison with a non-cancer population, e.g. by serving as a healthy control group.

Recently the Healthy Ageing Network Northern Netherlands (HANNN) was founded. In this regional knowledge cluster, research and development are joined in areas related to healthy ageing. The UMCG, universities, educational institutes, companies and regional authorities in the Northern Netherlands are the stakeholders of HANNN.

They have joined forces in order to develop innovative and fundamental breakthroughs which will improve the conditions for a longer healthy life. Three of the five areas that are relevant for oncology are Medical Technology, Care and Cure, and Healthy Lifestyle.

An interesting UMCG initiative is the Junior Scientific Master class, which offers motivated students extra opportunities to become involved in scientific research in addition to their regular medical or dental education. This special educational program provides students with the possibility of obtaining an Honors degree in research during the
Bachelors phase, and/or by combining their internships with a PhD project, of receiving both their MD and PhD at the end of the Masters phase. The chairperson of the Junior Scientific Master class is the NNOC member Prof. J. Kluin-Nelemans. The NNOC has embraced this initiative and coaches numerous MD/PhD students.

**National and international visibility and collaborations**
At both the national and international levels, NNOC members have contributed significantly to the development of their research field. They have participated in numerous administrative and editorial positions to promote cancer research, and have served as members of scientific advisory boards and juries for scientific prizes. At the international level, members have contributed to numerous societies. They serve on numerous scientific committees at cancer conferences. In addition, members of the NNOC are frequently invited to write articles and chapters in books, and to be a member of an editorial board. At the national and the international levels, this demonstrates international acceptance of NNOC members. In addition, various members of the NNOC have strong and valuable international collaborations, which is demonstrated by joint publications and grants (see appendix Chapter 7.3).

**Available patient population and relationship with the clinic**
The UMCG is a large, and in fact only, referral center in a catchment area of 3.4 million people. There is excellent collaboration with hospitals in the entire region for clinical research. Each month, teams from the UMCG visit hospitals in this area to perform surgery (gynecological oncology), and to perform teleconsulting. This collaboration also makes it easy to get patients referred for specific trials. The UMCG has earned continuously high marks for its clinical performance in oncology in the Dutch Elsevier analyses. This perception by the outside world of the performance of the clinical oncology department facilitates initial participation in clinical studies and collaboration with surrounding hospitals.

The patient population in the Northern Netherlands is considered to be a founder population. It is a relatively homogenous population, which makes it potentially interesting for the identification of low penetrance genes, and the relatively low mobility of this population also makes it a very interesting population for collecting relevant clinical data with a long-term follow-up.

**Industry:**
Several groups have an excellent relationship with industry. This collaboration applies to scientific interaction, exchanging ideas, making available investigational drugs for preclinical and early clinical research and grants. This is the case for preclinical as well as clinical groups. A special attraction for industry is the strong translational character of the research and the unique expertise of staff and good facilities for imaging, molecular and otherwise.

**Skill to obtain financial means for research purposes**
In the cancer center, most PIs have a high success rate in acquiring grants from a wide variety of sources.

**Young staff**
Young and enthusiastic researchers have recently been appointed in several groups within the NNOC. The Tenure Track Program has greatly facilitated this process, as it enables the researchers to hone their professional skills and become future staff members. Candidates can be appointed with the understanding that if they perform well, a special full professorship will be considered after 5 years of being an Associate Professor/University Reader. (www.rug.nl/umcg1_shared/PDF/TenureTrackEngels200306.pdf).

The NNOC has access to an interesting ‘pipeline’ of new researchers, but is also actively involved in nurturing this line. The selection, which is based on high marks and the fact that the UMCG is very popular among medical students, is coupled with the fact that many students are interested in oncological research. This allows the NNOC to select the best medical students for research. This is illustrated by the fact that in the MD/PhD program alone, 25 students have already worked at the NNOC. Because many researchers have a pharmaceutical and/or biology background, there are also many pharmacy and biology students at the NNOC. Doctors in training for a medical specialty often get the opportunity, for example through the Dutch Cancer Society, to do preclinical work for one to three years during their training. This allows staff and the MD in training for an oncological specialty to decide whether he/she has the capacity to develop into a staff member. Three promising staff members at the NNOC have received Rosalind Franklin Fellowships.

**Adjustments with key appointments**
Apart from appointments to a professorship within the center, there have also been key appointments from outside the UMCG (see Chapter 7.2).
Weaknesses

Interaction within the center

The strength of the center in performing multidisciplinary research is also a weakness, because focusing the research on specific subjects requires constant attention. A multidisciplinary approach in certain research areas and in certain studies requires long-term, time-consuming follow-up, and results in an enormous amount of research effort before major papers can be written. Luckily, the Faculty of Medicine was able to improve its performance in recent years by increasing the number of active preclinical group members; this will be expanded by the ERIBA initiative. These efforts have already been shown to increase the options for translational research.

Teaching and clinical responsibilities

Because of the nationwide shortage of medical doctors that is foreseen in the future, a larger number of students are being admitted to the Faculty of Medicine. This calls for an increasing effort from staff members to fulfill their teaching responsibilities. In addition, NNOC staff are heavily involved in teaching courses in Life Science and Technology/Biology, where student numbers are also increasing rapidly.

The number of patients with cancer in the Northern Netherlands has increased in recent decades and will increase even more in the future. Therefore, staff at the NNOC will be responsible for a fast-growing number of cancer patients and their families. Especially for medical specialists directly involved in patient care, which account for 62.5% of the PIs in the NNOC, the workload has grown considerably. This, combined with the increasing time required for teaching, means that available research time is constantly under pressure. Given the large number of clinical trials running in the NNOC, the increasing workload related to the execution of clinical trials is felt as a major burden, which is threatening the initiation of new trials.

Personnel

The salary for medical specialists is much higher outside the university medical centers (UMCs). This, together with the workload, requires us to be very competitive in order to attract good people within the NNOC. The peripheral location of Groningen in the Netherlands is often a barrier to attracting talented researchers. Aging of the staff is another point of concern. During the last fifteen years, not enough new staff members have been appointed. However, the relative shortage of preclinical researchers at the NNOC (mentioned in the previous evaluation) has decreased, and future developments as part of the ERIBA are eagerly awaited.

During this evaluation period, the number of full professors has increased, whereas the number of intermediate level staff has decreased (Table 7.1). There appears to be a widening gap between the most senior and the most junior positions, PhD or otherwise.

Administrative support

There is an increasing administrative burden, especially for a large center such as the NNOC, for which there is limited infrastructural administrative support. A stronger incorporation of the NNOC into the Sector Oncology in this respect might reduce this burden. In addition, major effort is currently being put into exploring ways of providing better support for the administrative burden that comes with the execution of clinical trials, especially investigator-driven ones.

Opportunities

Societal relevance

Worldwide, cancer is a major health problem with increasing incidence and prevalence. There is a broad societal interest and involvement in all aspects of oncology and the care for cancer patients. This means that oncological research is actually in the spotlight of societal interest and that this research is considered to be of growing societal relevance. The cost related to cancer care is, a major issue and will continue to be one in the future. P.H.B. Willemse was appointed as Professor in evaluating the efficiency and societal aspects of treatments. The NNOC has participated, and will continue to participate, in shaping this debate.

Genomics, proteomics and bioinformatics

The rapid progress in these techniques and their importance for oncology make it a challenge for the NNOC to participate in these developments. The availability and good management of serum, tissue and databanks are prerequisites for participating in these research fields.

Threats

Finances

There are serious concerns about the future size of grants from governmental organizations and other flows of funds for oncology research. Similar warnings are coming from the UK. The severe economic recession that began in 2008, with its uncertain economic prospects for the coming years, makes a negative effect on the above-mentioned funding likely. In addition, the grant opportunities have changed. In recent decades, the role of the European
Commission as an important financial source for oncology research has increased. The members of the center now make use of a more diverse set of grant opportunities. Moreover, the current financial climate is an additional incentive for the center to put more emphasis on its own fundraising program. This program was made possible by the collaboration with the Dutch Cancer Society (KWF-Kankerbestrijding) that was established in 2008.

**Strategy**

The NNOC has a strong position in cancer research in the Netherlands. In several oncology areas, members of the NNOC are among the worldwide leaders. We are aware of the serious financial constraints we will experience during the coming year. We will therefore aim for a large pallet of funding opportunities. We realize that the challenge for oncology is to aim for value growth rather than a balance with revenue growth and positioning.

Our position as the only tertiary referral center in a large catchment area is unique and allows us to include various categories of patients in clinical trials, preferably led by NNOC members. We will strive to couple innovative translational research to well-defined prospectively collected patient cohorts treated within clinical trials. We are delighted that input of preclinical researchers in the center has been strengthened in recent years. We are determined to attract even more talented young preclinical researchers to the center.

We think that the opening of the outpatient cancer center will facilitate interactions between members tremendously and provide support for translational and clinical trials.

We will continue to strengthen the role of tumor boards, also in relation to research. Despite the increasing clinical burden for the medical specialists, we will still try to allocate research time to the clinicians. In the meantime we want to retain our top referral position for cancer care. This is also one of the reasons why the UMCG wants to obtain a Proton Facility for patient care as soon as possible and why managed clinical networks are being set up with the regional hospitals. We will put even more effort into performing translational research related to phase III multicenter studies. We will continue to spend time on motivating young doctors to advance their careers in oncology.
CHAPTER 8

Biopharmaceuticals: Design, Discovery and Delivery
Section 8.1: Objectives and Research Area

Programme Leaders
Prof. Dr. W.J. Quax
Prof. Dr. H.J. Haisma

Mission statement
The BDDD Division explores innovative approaches oriented towards the early phase of drug development up to the use of these approaches in practice. The focus is on fundamental research towards the discovery and design of bio-pharmaceuticals that as drugs recently have grown enormously in importance as drugs. The division uniquely combines research on drug targeting, drug delivery, biopharmacy and pharmacokinetics. Furthermore, fundamental aspects of biotechnological production processes and dosage forms are studied.

Description of research area
The sub-programme **Pharmaceutical Biology** has as its central aim the study of the living cell as a source of pharmaceutically important products. Natural and directed diversity of micro-organisms, plants and plant cells are explored as a source of natural products, including protein therapeutics. The sub-programme **Pharmacokinetics, Toxicology and Targeting** explores innovative drug delivery tools for the cell-specific targeting of drugs and therapeutic proteins. Specific peptides and protein fragments are studied as homing devices and tools for improving pharmacokinetics. This is combined with research on the in vitro prediction of drug metabolism, transport and toxicity, as well as with pharmacokinetic modelling and simulation. The sub-programme **Pharmaceutical Gene Modulation** focuses on the development of systems for the specific delivery and regulation of genes. These systems should lead to totally new therapies treating the fundamental cause of a disease and not only the symptoms. In order to guide the early stage drug research towards patient therapies a crucial contribution comes from the sub-programme **Pharmaceutical Technology and Biopharmacy** that performs research in the field of dosage forms and their interaction with the living organism. Basic research on the design and development of novel and improved drug delivery systems is combined with research on new processes, equipment and technologies for the production of (biopharmaceutical) dosage forms and their performance. The position of the BDDD programme within pharmaceutical research is schematised below.

Strategy and policy
As the developments in the pharmacy-related aspects of biology and genomics are accelerating at an international level, research in the BDDD programme has further strengthened the orientation towards external collaboration. As demonstrated by the high level of external support (see Table 8.6) the sub-programmes are able to attract significant funding at the national and international level. The programme has a high profile within TI-Pharma with contributions to 7 different projects. The topics vary from novel cancer drugs, novel translational safety biomarkers for adverse
drug toxicity, novel drug formulations, mechanism-based PK-PD modelling to novel flu vaccine formulations. Also the participation in 10 EU research and network projects demonstrates the international academic profile of the groups. The steady growth in external funding has been accompanied by the allocation of several new tenure track positions to the sub-programmes in recent years. International research experience is one important selection criteria for these candidates (see also Section 10). The success of the tenure track system is reflected in the high number of personal grants including VIDI and VICI acquired by this new generation of research staff. As advised by the previous PRC the strategy for valorisation of the research has matured, and licensing activities have gone hand in hand with the creation of a number of spin-off companies by members of the BDDD programme. This has not only led to additional corporate research activities but also to a very significant royalty income to the University, allowing the programme to finance long-term research positions on basic research. The formation of the successful BDDD programme is the tangible result of the recommendation of the previous PRC to organise the research into larger units and to strengthen internal collaboration. This is not only reflected in the increase of the number of jointly acquired grants, but also in the number of joint publications.

Pharmaceutical Biology’ (PB)

The growing understanding of the basic molecular mechanisms underlying diseases has expanded the number of potential targets for therapeutic intervention. Both in-depth pathophysiological investigations and the genomics and proteomics revolution have allowed identification of numerous novel receptors and cell components, for which interacting ligands are sought. Biodiversity and biotechnology are very complementary in providing complex ligand molecules that can be the start of a new therapeutic. Exploiting natural diversity, e.g. plant cells, has a long standing tradition in drug discovery. Novel techniques such as directed diversity and directed evolution are now being explored for creating new leads from secondary metabolites and (poly)peptides. This is the key research area of this programme.

1. The plant biotechnology research line is concentrated on the production of bioactive compounds of natural origin using plant cell cultures and plants. Next to phytochemical analysis, molecular-biological techniques are applied to gain insight into biosynthetic routes and to control the formation of bioactive compounds (pathway engineering). Current projects that involve this work are (i) the production of cytostatic lignans in cell suspensions, organ cultures and plants from Anthisicus sylvestris (ii) the production and isolation of the anti-malaria drug Artemisinin with the use of plants and plant cell cultures from Artemisia annua. One of the goals is to redesign Xanthophillum dendrohorous as minimal cell factory to maximize the production of plant-derived natural terpenoids.

2. The molecular-biological research line concentrates on biotechnologically produced pharmaceutical proteins, enzymes and cell surface receptors. The efficacy of biopharmaceuticals is being improved by the application of new techniques of combinatorial biology, protein mutagenesis and ultimately, computational design. The engineering of more selective cytokine variants is at the core of this research line. New biocatalysts for stereo selective reactions are being engineered including enantioselective proline-based biocatalysts for general alkylation, Michael addition, and aldol reactions.

3. The cell biology research line concentrates on the expression and especially the secretion of pharmaceutical proteins from cells. Protein ligands as potential therapeutics -being macromolecules-present special problems with respect to production. The production of complex natural products is also a huge challenge in the drug development phase, and major bottlenecks are being addressed by developing cell factories.

Changes/modifications/policy

The previous research review was very positive about the profile and achievements of this programme (19.5/20 score). The focus on the biosynthesis of natural products has been intensified with the appointment of Dr. Oliver Kayser in 2004. Dr. Kayser came from Berlin and his arrival has lead to the opening of new avenues of combinatorial biosynthesis in recent years. In 2006 the biocatalysis and protein engineering research was further strengthened with the appointment of Dr. Gerrit Poelarends, who obtained a prestigious VIDI grant in the same year. The research on secretion systems of Gram positive bacteria was carried on by Dr. Jan Maarten van Dijl, who was invited to take up the Chair of Medical Bacteriology in the UMCG. The scientific staff now has achieved the size of one full professor, one associate professor and one assistant professor as was recommended by the previous PRC. This has lead to three very viable research lines with a very successful grant acquisition profile. A significant growth in the number of PhD students in this programme from 11 in 2003 to 22 in 2008 has resulted.

Two novel developments highlight the new directions that were chosen in this programme. The directed evolution and protein design methodology was refined, and the example of an engineered, more selective variant of the apoptosis-inducing ligand TRAIL has obtained major attention, including a publication in PNAS. This has now led to a complete new research line on the design of more effective anti-cancer biopharmaceuticals. A second major development has been the discovery that the group of penicillin and cephalosporin acylases, studied already for many years by us, harbours some very interesting members that can interfere with quorum sensing in pathogenic bacteria. We have shown that the virulence of Pseudomonas aeruginosa can indeed be reduced by quorum quenching and this has resulted in

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1 Principal Investigators: Prof. Dr. W.J. Quax; Prof. Dr. O. Kayser; Dr. G.J. Poelarends
the creation of the very successful Marie Curie Training Network “ANTIBIOTARGET” and a publication in PNAS as most recent highlight.

**Pharmacokinetics, Toxicology and Targeting** (PTT)

Since January 2004, research in the group Pharmacokinetics Toxicology and Targeting has focussed on 3 research lines, (1) drug targeting, (2) human pharmacokinetics & PKPD modelling and (3) drug metabolism & toxicology.

Strategies are being developed for targeting drugs and biologicals such as cytokines, enzymes and prostaglandins to diseased cells in chronic inflammatory and fibrotic diseases (in liver and kidneys) and tumours. New neoglycoproteins and receptor recognizing peptides have been developed, and their therapeutic effects in animal models have been established. Future research activities will focus on the design and development of new receptor-recognizing proteins and peptides for drug targeting purposes, with the aim to design a series of effective cell-selective compounds to target important receptors in fibrosis and tumorigenesis.

Another research interest is human pharmacokinetics, as well as pharmacokinetic-pharmacodynamic (PK-PD) modelling and analysis. Computer programs for PK-PD simulation and population-based data analysis are being developed, both for research on translational modelling and simulation of treatment effects in schizophrenia, and for use in the daily practice of therapeutic drug monitoring.

Innovative in vitro models using human and animal liver and intestinal tissue have been developed to predict human drug disposition, metabolism and toxicity. They are currently applied to the development of biomarkers and elucidation of mechanisms of (idiosyncratic) toxicity, to study regulation of drug metabolism and transport, to study interorgan interactions, and for testing of anti-fibrotic drugs. In addition, studies on the mechanisms of cell damage during cold- and cryopreservation have been initiated, aimed at developing improved preservation methods for transplantation organs as well as tissue for research.

**Changes/modifications/policy**

After the retirement of Prof. Dr. D.K.F. Meijer in 2004, the research line on antiviral drugs was terminated. The acquisition of a new professor, as advised by the previous PRC was interfered by the reorganisation of the faculty. Both Dr. K. Poelstra and Dr. G.M.M. Groothuis were appointed as adjunct professor in 2004 followed in 2009 by appointments to full professor. Dr. J.H. Proost was appointed to associate professor in 2004. Prof. Groothuis has been head of the sub-programme since 2004. Despite the reduction in scientific staff, the group continued to be successful in obtaining new grants, and the total number of employees remained at ca 30-35 members including 10 PhD students. After Prof. Poelstra’s appointment as a VIDI laureate (2001-2005), he obtained a prestigious VICI grant in 2006. In 2008, he went for a 6-month sabbatical to Harvard Medical School, Boston, USA. Prof. Groothuis was registered as toxicologist by the Dutch and European Society for Toxicology during this time.

The collaboration between the sub-programmes Pharmaceutical Gene Modulation and PTT was successfully reinforced, leading to joint publications and grant proposals. In addition, joint projects were started between the PTT sub-programme and those of Pharmaceutical Analysis (Prof. E.M.J. Verpoorte), Pharmaceutical Technology and Biopharmacy (Prof. H.W. Frijlink), and Pharmaceutical Biology (Prof. W.J. Quax). These collaborations have contributed to the coherence of the research programme of GRiP.

The major change in the research of the PTT group in the near future will be the start of a research line on pharmacokinetics and toxicity of biologicals. Biologicals are increasingly applied as drugs and as drug carriers, but the kinetics and toxicity of these biologicals are still poorly understood, and innovative methods need to be developed in order to predict human disposition and safety. Acquisition of a tenure track position in this field is ongoing.

The group will continue to translate its knowledge on drug carriers to the clinical field by extensive testing of new drug carriers in animal models of disease and by continuously seeking collaboration with clinical groups at the UMCG and abroad. In order to keep focus, former projects such as vascular targeting and drug delivery to the kidney will be limited to collaborations (e.g., as partner in European projects).

**Pharmaceutical Gene Modulation** (PGM)

The sub-programme Pharmaceutical Gene Modulation focuses on the development of medicines for the therapeutic manipulation of genes and gene activity. Drugs and delivery forms are being developed for the specific and efficient treatment of cancer and inflammatory diseases. Two research lines can be distinguished.

1. **Modification of gene transcription via gene transfer vectors.**

This is a conceptually new strategy for drug discovery. Gene therapy suffers currently from a lack of efficiency. This research line aims to improve the efficiency by transgene transmission (efficient spread of the gene pro-duct). The transgenes encode for transcription factors or single chain antibodies capable of modulating gene expression of native genes.

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2. Previously named Pharmacokinetics and Drug Delivery. Principal investigators: Prof. Dr. K.Poelstra, Prof. Dr. G.M.M. Groothuis and Dr. J.H.Proost.

3. Principal investigators: Prof. Dr. H.J. Haisma; Dr. F.J. Dekker
This research line is represented by Dr. F. J Dekker, a tenure-track assistant professor, and aims to combine chemical and biological techniques to study gene transcription. Small drug-like molecules are developed using a variety of medicinal chemistry methods. The inhibitors are applied in a reverse chemical genetics approach to study the role of histone acetyltransferases in gene transcription. This will ultimately result in new therapeutic approaches in cancer and inflammatory diseases.

Changes/modifications/policy
The group was created in 2000. Dr. M. Rots (tenure track assistant professor) joint the group in 2001 and left in 2007 to take a position in the UMCG. Dr. A. Bellu (post-doc) was appointed on two sequential EU grants from 2001-2008. Dr. F.J. Dekker joined the group in 2008 as a tenure-track assistant professor. We have attracted highly qualified foreign graduate and post-graduate students to create a multidisciplinary research environment. Collaborations have been set up with local (GUIDE), national and international groups, which have resulted in numerous publications during the past years.

The research in the period 2003-2007 focused on modulation of gene transcription using viral vectors for gene transfer. Several aspects of gene therapy were studied in this period. Currently, this research line is focussed on transgene transmission to overcome the lack of efficiency, which is one of the main bottlenecks in gene therapy. Furthermore, it has become increasingly clear that epigenetic regulation of gene transcription is critical for effective gene therapy. Therefore, a new research line was initiated in 2007 to address this issue by development of small drug-like molecules to modulate the epigenome.

Pharmaceutical Technology and Biopharmacy (PTB)
The nature of modern drug compounds increasingly requires the application of advanced dosage forms to obtain optimal therapeutic efficacy. The rise of biopharmaceuticals such as therapeutic proteins, gene vectors or advanced vaccines, as well as the increase in the number of highly insoluble drugs, has rejuvenated academic research in biopharmacy and pharmaceutical technology over the past decade. This brings challenges that require new approaches in formulation science, production technology and routes of administration.
The sub-programme Pharmaceutical Technology and Biopharmacy is dedicated to fundamental research in the field of dosage forms, their production processes and the interactions of these dosage forms with the living organism. The research objective can briefly be described as “bringing advanced technology from laboratory and production facility to bedside”, which places the group in the centre of the triangle “academic research, industrial research and application in patients”.
The sub-programme has achieved a tremendous expertise surrounding the central theme of pharmaceutical powder technology. As a consequence of this choice, the research focuses on three topics: (1) dosage forms for pulmonary administration (mainly dry powder inhalers), (2) solid oral dosage forms, and (3) the application of sugar glass technology in the formulation of biopharmaceuticals (peptides, proteins, vaccines and gene delivery systems) and highly insoluble drugs (a subject closely linked to nanotechnology). These three research lines exhibit strong synergy. Research is performed on both biopharmaceutical as well as technological aspects, in order to design optimal dosage forms with respect to the technological production, therapeautic efficacy and use by the patient.

Changes/modifications/policy
Following the advice of the previous PRC, both the oral and pulmonary research lines were extended with biopharmaceutical and translational research. This was strongly enhanced by the activities in the sugar glass line. The expertise on rheology was kept in the group with the specialist Dr. Hinrichs, who was financed from industrial income.
Economic valorisation has proven to be a strong point of the group over the past few years. Royalty incomes and milestone payments from products on the market or at the brink of being marketed have accumulated to almost 900 k€ per year (2008) and are likely to rise further in the future. The group currently participates in 1 STW project, 4 TI Pharma projects, 1 BMM project and 1 EFRO project. The group had collaborations with 9 industries in over 12 projects over the past years.
Societal relevance has become another strength of the group’s research. A stable oxytocin injection that can save the live of 125,000 women each year in Africa, a better inhaler for CF patients, and a better preparedness for an influenza pandemic are just three examples of our results.
With regard to the activities in the field of technology, the advice of the previous PRC led to a major shift in activities. The research projects on fundamental powder technology, spheronomisation, and compaction properties of new excipients are no longer core activities. Our efforts are now focussed on gaining a fundamental understanding of production processes (which enables the application of QbD (quality by design), PAT (process analytical technology) and Risk Management) involved in the three research lines of focus. To further strengthen and facilitate the link between
technological and patient-oriented research, we have the strategic intention to fill a current vacancy with a tenure-track assistant professor who has a vast knowledge and experience in biopharmaceutics, translational, and preclinical (safety) research. The development of adequate in situ and in vivo animal models may increase chances for rapid valorisation of our platform technologies.

The international visibility of the group (rated insufficient by the previous PRC) successfully increased through the new strategy. The number of peer reviewed papers and citations are two to three times higher compared to the last reviewed period. Also the number of invitations to speak at major conferences (EUFPS, AAPS, PSWC, ISAM, PBP, etc.) has significantly increased.

Based on the above we consider the future prospects of the group to be bright. Our current IP position guarantees a relative independence from fluctuating funding from the university and allows for independent, fundamental, academic research projects. Our royalty income allowed us to appoint three PhD students recently, who will all work on fundamental questions (formulation and delivery of siRNA, fundamental aspects of complex adhesive mixtures in DPI’s and new strategies for the treatment of pulmonary infections). This will not only increase our academic knowledge base (see previous PRC advice), but also enables the expansion of on new research lines that over the past years proved to attract significant funds both from the second and third money flows.
Section 8.2: Composition of the Research Unit

Description of the research unit composition
The BDDD programme is composed of four sub-programmes that represent a coherent compilation of research expertise in drug development. As the research environment and funding policy for all groups is very similar, only the consolidated figures will be discussed in the remaining sections. This is also in line with the advise of the previous PRC committee, who suggested operation in larger units and development of a joint strategy and policy.

Research staff
The total level of employed research staff showed a healthy growth from 48 to 59 FTE in the period 2003-2008, despite the drop in direct funding from the Faculty of Mathematics and Natural Sciences. A more spectacular growth can be seen in the number of PhD students (from 29 to 39) which is a result of both increased external funding and the introduction of non-employee PhD grants. The increase in external funding is obvious from Table 8.2, which shows that in 2008 80% of the funding came from national research grants (2nd money flow) or EU/contract research (3rd money flow). Note that the decrease in ‘direct funded FTE’ seen after 2003 is partly explained by the fact that employed PhD students are replaced by non-employed PhD students. Details are provided in appendix Section 8.2.

The advise of the previous PRC that the number of tenured staff (see Table 8.1) supported by direct funding should be increased was realised only at the end of 2008, due to a reorganisation in the Faculty in preceding years. In total 3 tenured staff have left the programme due to retirement or promotion, 3 tenure-track assistant professor positions have been filled and 2 tenure-track assistant professor positions are currently being filled. The new staff members entering the programme have fully embraced the opportunities of the tenure-track system and have been very successful in attracting grants and creating their own research lines. In parallel with the growing external funding for research, we have also witnessed an almost doubling of the undergraduate student number, with a concomitant increase in teaching activity from the same tenured staff. Fortunately at the end of 2008, the programme obtained additional funding directly from the board of the university to cope with the increased teaching activity. The current ratio of 39 PhD students over 3.48 FTE tenured staff and 5.81 FTE non-tenured staff is considered challenging and at the upper limit of the desired range.

Table 8.1 Overview of the research staff at the level of programme BDDD

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>Tenured staff</td>
<td>3.10</td>
<td>2.50</td>
<td>2.98</td>
<td>3.08</td>
<td>3.18</td>
<td>3.48</td>
</tr>
<tr>
<td>(8)</td>
<td>(7)</td>
<td>(9)</td>
<td>(10)</td>
<td>(10)</td>
<td>(10)</td>
<td></td>
</tr>
<tr>
<td>Full professors*</td>
<td>1.60</td>
<td>1.90</td>
<td>1.98</td>
<td>1.98</td>
<td>2.38</td>
<td>2.48</td>
</tr>
<tr>
<td>(3+1)*</td>
<td>(3+2)</td>
<td>(3+3)</td>
<td>(3+4)</td>
<td>(3+4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associate professors</td>
<td>0.70</td>
<td>0.00</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>(2)</td>
<td>(0)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td></td>
</tr>
<tr>
<td>Assistant professors</td>
<td>0.80</td>
<td>0.60</td>
<td>0.80</td>
<td>0.90</td>
<td>0.60</td>
<td>0.80</td>
</tr>
<tr>
<td>(2)</td>
<td>(2)</td>
<td>(2)</td>
<td>(3)</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>Other senior staff</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td></td>
</tr>
<tr>
<td>Non-tenured staff</td>
<td>7.52</td>
<td>6.20</td>
<td>5.81</td>
<td>5.58</td>
<td>4.95</td>
<td>5.81</td>
</tr>
<tr>
<td>(11)</td>
<td>(12)</td>
<td>(10)</td>
<td>(9)</td>
<td>(9)</td>
<td>(10)</td>
<td></td>
</tr>
<tr>
<td>PhD-students</td>
<td>15.93</td>
<td>15.23</td>
<td>12.43</td>
<td>10.50</td>
<td>11.55</td>
<td>14.35</td>
</tr>
<tr>
<td>(29)</td>
<td>(28)</td>
<td>(30)</td>
<td>(31)</td>
<td>(35)</td>
<td>(39)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>15.93</td>
<td>15.23</td>
<td>12.43</td>
<td>10.50</td>
<td>11.25</td>
<td>14.35</td>
</tr>
<tr>
<td>(25)</td>
<td>(24)</td>
<td>(21)</td>
<td>(20)</td>
<td>(21)</td>
<td>(22)</td>
<td></td>
</tr>
<tr>
<td>Non employed</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>(4/13.79%)</td>
<td>(4/14.29%)</td>
<td>(9/30.00%)</td>
<td>(11/35.48%)</td>
<td>(14/40.00%)</td>
<td>(17/43.59%)</td>
<td></td>
</tr>
<tr>
<td>Total research staff</td>
<td>26.54</td>
<td>23.92</td>
<td>21.21</td>
<td>19.16</td>
<td>19.68</td>
<td>23.64</td>
</tr>
<tr>
<td>(48)</td>
<td>(47)</td>
<td>(49)</td>
<td>(50)</td>
<td>(54)</td>
<td>(59)</td>
<td></td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers also have obligations for patient care. For the sake of simplicity a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD-students with an employment contract. The term FTE is not appropriate for non-employee PhD students, who have student status.
In between brackets after the + symbol the number of adjunct and extraordinary professors is given.

Table 8.2 Overview of the research funding at the level of programme BDDD

<table>
<thead>
<tr>
<th>Funding:</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct funding (1)</td>
<td>8.68</td>
<td>7.90</td>
<td>6.08</td>
<td>5.18</td>
<td>4.28</td>
<td>4.78</td>
</tr>
<tr>
<td>Research grants (2)</td>
<td>8.25</td>
<td>6.30</td>
<td>5.78</td>
<td>3.05</td>
<td>4.74</td>
<td>7.76</td>
</tr>
<tr>
<td>Contract research (3)</td>
<td>9.62</td>
<td>9.72</td>
<td>9.63</td>
<td>10.94</td>
<td>10.67</td>
<td>11.10</td>
</tr>
<tr>
<td>(including EU)</td>
<td>(31.09%)</td>
<td>(26.34%)</td>
<td>(27.23%)</td>
<td>(15.92%)</td>
<td>(24.06%)</td>
<td>(32.83%)</td>
</tr>
<tr>
<td>Total funding</td>
<td>26.54</td>
<td>23.92</td>
<td>21.21</td>
<td>19.16</td>
<td>19.68</td>
<td>23.64</td>
</tr>
<tr>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
<td>(100%)</td>
</tr>
</tbody>
</table>

Expenditure:

| Personnel costs (k€)        | 1,225.0| 1,160.3| 1,150.1| 1,069.3| 1,133.2| 1,367.4|
| Other costs personnel (k€)  | 471.7  | 446.8  | 442.86 | 411.7  | 436.3  | 526.5  |
| Costs non-employed PhD students (k€) | 63.8  | 65.4  | 129.3  | 146.9  | 183.4  | 303.9  |
| Other costs - non-employed PhD students (k€) | 34.0  | 34.0  | 65.9  | 74.4  | 91.4  | 136.0  |
| Total expenditure            | k€ 1,794.4 | k€ 1,706.4 | k€ 1,788.1 | k€ 1,702.3 | k€ 1,844.4 | k€ 2,333.9 |

Explanation: The expenses for research include both personnel and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the contribution to the provision “wachtgelden” (i.e. the obligation to provide personnel a reduced pay in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff, and other costs like allowances for child care, and commuting. Although non-employed PhD students do not represent research-FTE, the costs of these PhD students have been included. Other costs include exploitation costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

1 Direct funding by the university;
2 Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programmes ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3 Funding for specific research projects obtained from external organisations, such as industry, governmental ministries, European Commission (Framework programmes) and charity organizations.
Section 8.3: Research Environment and Embedding

Position and reputation
Advancements in biopharmaceutical research have become more and more dependent on multidisciplinary collaborative projects. Both nationally and internationally, BDDD members participate in these strategic collaborations. The computational design of protein pharmaceuticals has been investigated in a number of EU projects concentrated around TNF ligand family members. The project acronyms TRISKEL, TRIDENT and TRITAN reflect the special expertise that has been built up in engineering trimeric ligands, of which TRAIL is the paradigm. The special attention of the University of Groningen for the expertise in drug delivery is reflected in the prominent position that the research lines PTT and PTB fulfill in the TI Pharma projects with Prof. Frijlink acting as national coordinator of the area of “Drug Formulation, Delivery, and Targeting”. Drug delivery expertise, with special attention for protein and peptide targeting, is also at the basis of collaborations with SME’s, as exemplified by BioOrion and Triskel Therapeutics. The support of NWO/STW for this activity has been considerable in the past few years with the VICI grant of Prof. Poelstra as most prominent example of this support. Finally, large corporate organisations are expressing a growing interest for collaboration with BDDD members, with respect to research on dosage forms and tissue-based in vitro prediction of pharmacokinetics and toxicology. The international orientation of the BDDD group has resulted in a growing number of international PhD students and guest researchers coming to Groningen (for details, see appendix Section 8.3). A list of the most prominent collaborations is given (see appendix Section 8.3) including an overview of the impact of these collaborations on joint publications. Highlights for each research line are discussed below.

Pharmaceutical Biology
The Pharmaceutical Biology sub-programme has a strong profile within EU research programmes. The long standing collaboration on the TNF ligand, TRAIL, has resulted in intensive staff exchange and joint publications with the laboratory of Prof. Luis Serrano (EMBL-CRG) and Prof. Samali (NUIG-Ireland). The research on antibiotics has resulted in 3 consecutive EU grants, with the most recent an MC network with 12 joint research fellows shared with three institutes in Germany, France and UK. On average, 50% of the publications of PB are international joint publications.

Pharmacokinetics, Toxicology and Targeting
The PTT group has a considerable number of collaborations within GRIP, within the UMCG, and with national and international academic groups. These collaborations are supported by 3 EU, 1 CTMM, 3 TIPharma and 1 TIFood & Nutrition projects, with a total output of more than 90 joint publications between 2003 and 2008. These collaborations were on the development of drug targeting preparations for liver fibrosis and tumours, PKPD modelling for muscle relaxants and schizophrenia, and toxicity and interactions between metabolism and transport of drugs. In particular, the longstanding collaboration with the Department of Surgery (UMCG), on cryopreservation and drug metabolism and transport in human organs, dating from 1984, has resulted in 19 joint publications, and was the basis for 6 PhD theses. The international collaborations with Prof. K.S. Pang (Toronto, Canada) and Prof. S. Friedman (New York, USA) have resulted in almost 10 joint publications.

Pharmaceutical Gene Modulation
This sub-programme has an intensive collaboration on human gene therapy with the University of Alabama (Prof. Curiel) that has resulted in no less than 21 joint publications over the past few years. Prof. Haisma is also strongly involved in the societal debate on gene therapy and its potential impact on gene doping in sports. He has a strong collaboration with the Dutch Doping Authority.

Pharmaceutical Technology and Biopharmacy
The PTB group has developed a strong collaboration with clinical sub-programmes, resulting in new drug administration and formulation concepts that are evaluated in real life. The pulmonary vaccine delivery using sugar glasses was successfully tested and reported in high-profile joint publications. The further development of the sugar glass nanotechnology has been done in collaboration with Solvay Pharmaceuticals, which has resulted in significant license income. In the area of pulmonary delivery, the novel inhalers Novolizer, Genuair and Twincer were successfully tested in the clinic and the collaboration with MEDA has resulted in royalty payments of over 2 M€. Not surprisingly, this sub-programme has a very strong presence within TIPharma.
Section 8.4: Quality and Scientific Relevance

High-quality publications of the BDDD programme

The programme has aimed for a high-visibility profile of its publications over the reporting period. Manuscripts have been published in less specialized, more general, high-impact journals. Even though this implies that papers end up in more highly ranked and more competitive ISI fields, the share of Top 10% and Top 30% publications in these higher ISI fields was maintained and even expanded in recent years (all these Top-publications have been marked in appendix Section 8.5). This has resulted in a clearly improved citation record of the publications from the programme.

To demonstrate the rise in the number of citation/year between 2003 and 2008 is given for the professors of the programme: Quax (100 → 260), Groothuis (107 → 250), Poelstra (78 → 185), Haisma (137 → 237), Frijlink (47 → 153) (Source WoS, ISI). With most of the manuscripts (>65%) ending up in the Top 30% of the fields, it is clear that the quality of the research is highly appreciated by peers. The selection of the most important results and the most eye-catching publications has been made not only to demonstrate quality, but also to highlight the various sub-programmes of the programme.

Table 8.3 High quality publications – number of publications in the best 10% and 30% of relevant disciplines

<table>
<thead>
<tr>
<th>BDDD</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% (n of articles)</td>
<td>% (n of articles)</td>
<td>% (n of articles)</td>
<td>% (n of articles)</td>
<td>% (n of articles)</td>
</tr>
<tr>
<td>Belongs to the best 10% of a relevant subject area</td>
<td>20% (8)</td>
<td>21% (8)</td>
<td>23% (11)</td>
<td>24% (13)</td>
<td>26% (9)</td>
</tr>
<tr>
<td>Belongs to the best 30% of a relevant subject area</td>
<td>65% (26)</td>
<td>53% (20)</td>
<td>73% (35)</td>
<td>54% (29)</td>
<td>68% (23)</td>
</tr>
</tbody>
</table>

Explanation: A ranking for publications present in the on-line database ‘ISI Web of Knowledge’, sub-database ‘Web of Science’ has been calculated and is presented. Papers are categorized based on the journal they appear in and the subject area as designated in ISI-fields (2008 or year of publication). The percentages are calculated based on the number of the journal titles in the subject area.

Papers published in the relevant subject areas of the research programme are included in this analysis. According to the methodology of bibliometric analysis, only papers of the reference types ‘Article’, ‘Note’, ‘Letter’, ‘Review’ and ‘Proceedings paper’ are considered. This implies that references of the type ‘Editorial material’, ‘Book (review)’, ‘Correction’, ‘Meeting abstract’, ‘Conference proceeding’, ‘In memoriam’, ‘News item’, ‘Biographical item’, etc., are not included.

Pharmaceutical Biology

Most important results:

- Enhanced anticancer activity from engineered, more selective variants of the apoptosis inducing ligand, TRAIL, obtained via computational design.
- Quorum quenching acylases reducing bacterial virulence were discovered.
- Enantioselective lipases for chiral drug synthesis were obtained via directed evolution.
- Biotechnological production of podophyllotoxin, the precursor of Etoposide® and Teniposide®, was achieved.
- Secretion of biologically active Interleukin-3 from Bacillus.
- Novel adipyl cephalosporin acylase obtained by directed evolution to be used in cephalosporin synthesis.

Key publications (full-text articles are provided in appendix Section 8.4)

- Sio, C. F., Otten, L. G., Cool, R. H., Diggle, S. P., Braun, P. G., Bos, R., Daykin, M., Camara, M., Williams, P., and Quax, W. J. Quorum quenching by an N-acyl-homoserine lactone acylase from Pseudomonas aeruginosa PAO1, Infect. Immun. 74, 1673-1682.
Chapter 8  
Biopharmaceuticals: Design, Discovery and Delivery


Books


Pharmacokinetics, Toxicology and Targeting

Most important results:
• In vitro system to study drug metabolism and regulation of drug metabolising enzymes and transporters in the human intestine.
• Assessment of genotoxicity, fibrosis and drug-induced toxicity in human liver slices.
• Development of new drug carriers for the Platelet-Derived Growth Factor receptor and its application as a drug carrier to fibroblasts and certain tumour cells.
• Successful treatment of animals with liver fibrosis by targeting antifibrotic drugs to the key cells in fibrogenesis, the hepatic stellate cells
• Demonstration of therapeutic effects of intestinal alkaline phosphatase in animal models of shock and colitis.
• Development of an Iterative Two-Stage Bayesian procedure for PK and simultaneous PK-PD population analysis.

Key publications (full-text articles are provided in appendix Section 8.4)


• Elferink MGL, Olinga P, Draaisma AL, Merema MT, Faber KN, Slooff MJH, Meijer DKF, Groothuis GMM.LPS-induced downregulation of MRP2 and BSEP in human liver is due to a posttranscriptional process. Am. J Physiol Gastrointest Liver Physiol 2004; 287:1008-1016.

Books

Pharmaceutical Gene Modulation

Most important results:

- Targeting of gene expression in specific cancer cells using cancer-selective promoters and bispecific antibodies.
- Higher gene expression of targeted genes in Kupffer cells obtained by scavenger receptor A antagonists such as polyinosinic acid.
- Development of a targeted secreted gene therapy vector containing a TRAIL protein that was highly effective in cancer treatment in vivo.
- Development of new histone acetyl transferase inhibitors.

Key publications (full-text articles are provided in appendix Section 8.4)


Pharmaceutical Technology and Biopharmacy

Most important results:

- The invention of a technology that is able to stabilize oxytocin in aqueous solution, which enables the development of a heat-stable oxytocin injection for third-world countries. This has the potential to save the lives of 125,000 women each year.
- The design and invention of the Twincer® high-dose dry powder inhaler, and the proof-of-concept of the device for pulmonary administration of antibiotics in humans.
- The invention and in vivo validation in man of a platform technology that enables site-specific, pulsatile drug release in the terminal ileum and ascending colon after oral administration (the Colopuls® system).
- The development of a stable powder form of the influenza vaccine (based on sugar glass technology) that can be administered by inhalation (Twincer®) to provide improved immunological protection.
- A Cyclosporin A dry-powder inhalation system for the treatment of lung transplant patients, that is free of the unwanted side-effects of the co-solvents connected to the use of nebulizers.
- The development of a new bottom-up technology to produce nanocrystals.

Key publications (full-text articles are provided in appendix Section 8.4)


Books

Section 8.5: Quantity of Scientific Output

Overview of the results
The number of publications in relation to the total number of FTE-funded staff has been consistently high over the full period. Even in the years 2007 and 2008 with a large inflow of PhD students and the start of many new projects the output has been stable. It is expected (and in fact in 2009 already has been observed) that after a lag phase the experimental results of these new PhD students will increase the output in the next few years. Despite the fact that contributions to book chapters are hardly visible in citation reports, it is considered important for the dissemination and teaching of new research results that members of the BDDD programme contribute to handbooks and textbooks. The programme encourages the protection of crucial inventions in patent applications for the translation of knowledge into societal and economical relevant applications. The total number of 30 patent applications illustrates the awareness among BDDD members of the importance of patent applications. The valorisation of these patents is explained in Section 8.9. The productivity goals imposed by GUIDE are easily met by all the current BDDD PI’s. All publications are listed in appendix Section 8.5.

Table 8.4  Main categories of research output at the level of programme BDDD

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refereed articles</td>
<td>62</td>
<td>66</td>
<td>58</td>
<td>56</td>
<td>58</td>
<td>54</td>
</tr>
<tr>
<td>Books and book chapters</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>PhD theses</td>
<td>2</td>
<td>7</td>
<td>9</td>
<td>14</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Patents</td>
<td>9</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total publications</strong></td>
<td><strong>75</strong></td>
<td><strong>84</strong></td>
<td><strong>72</strong></td>
<td><strong>79</strong></td>
<td><strong>76</strong></td>
<td><strong>68</strong></td>
</tr>
</tbody>
</table>

Number of PhD students
In the period 2003-2008, not only a shift from employee to non-employee PhD positions can be observed. A significant increase in the total number of PhD students is also evident.

Table 8.5  Number of PhD students at the level of programme BDDD

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of PhD-students per year</td>
<td>29</td>
<td>28</td>
<td>30</td>
<td>31</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td>employed</td>
<td>25</td>
<td>24</td>
<td>21</td>
<td>20</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>non-employed</td>
<td>4</td>
<td>4</td>
<td>9</td>
<td>11</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td><strong>total</strong></td>
<td><strong>29</strong></td>
<td><strong>28</strong></td>
<td><strong>30</strong></td>
<td><strong>31</strong></td>
<td><strong>35</strong></td>
<td><strong>39</strong></td>
</tr>
<tr>
<td>% non-employed</td>
<td>13.79%</td>
<td>14.29%</td>
<td>30.00%</td>
<td>35.48%</td>
<td>40.00%</td>
<td>43.59%</td>
</tr>
</tbody>
</table>
Section 8.6: Earning Capacity

The BDDD programme has been extremely successful in attracting external funding for research. As can be seen from Table 8.6 more than 90% of the total funding has been acquired in competition during the reporting period. The national and international visibility of BDDD researchers and the strategic choices for timely research topics are the basis of this success. The low amount of university-allocated funding in combination with the increased teaching obligations of most research staff has been worrisome in the period 2005-2007. However, the recent increase in staff number has allowed the programme to maintain its international position and funding acquisition power. As can be seen from the list of the most prestigious projects, the funding of the research shows a healthy mixture of European Union projects, National Science Foundation (NWO) and industry collaboration sources.

Results

A numerical overview of the acquired and allocated funding is given in research FTE in Table 8.6. The bottom line shows that over the past 6 years yearly between 89% and 92% of the funding has come from external sources and the absolute amount of acquired funding has grown from 30 FTE in 2003 to almost 40 FTE in 2008. Apart from the funding of personnel, investments in infrastructure and apparatus have also been obtained, totalling up to 1.5 M€.

Table 8.6 Fund raising capacity at the level of programme BDDD

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<tbody>
<tr>
<td>Total funding</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Allocated funding</td>
<td>8.84</td>
<td>7.52</td>
<td>8.91</td>
<td>10.68</td>
<td>9.14</td>
<td>8.53</td>
</tr>
<tr>
<td>Acquired funding</td>
<td>91.16</td>
<td>92.48</td>
<td>91.09</td>
<td>89.32</td>
<td>90.86</td>
<td>91.47</td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are funded directly by the University of Groningen and/or the UMCG (allocated funding). To extend their research capacity, they acquire grants via internal and external competition (acquired funding) for non-tenured staff, employed PhD students, non-employed PhD students and, in some cases, a limited number of staff positions. The fund raising capacity is expressed in research FTE.

Overview of external funding obtained (only projects >100 k€ are included)

Pharmaceutical Biology

EU projects

- ExporteRRs: Exploitation of a novel Sec-independent secretion pathway for protein production 1999-2003 (Dr. J.M. van Dijl)
- EvoCatal: Directed Evolution of Enantioselective Biocatalysts 2001-2004 (Prof. W.J. Quax, EU coordinator)
- TRISKEL: Therapeutic Molecules For The Modulation Of Ligand-Receptor Mediated Apoptosis 2001-2005 (Prof. W.J. Quax, EU coordinator)
- NANOFOLEX: Exploiting the secretion machinery of Pseudomonads 2004-2007 (Prof. W.J. Quax)
- EU-FP7 Collaborative Project grant “Metagenomics for bioexploration: Tools and application”, 2008-2013. (Dr. G.J. Poelarends)

NWO/STW/KNAW projects

- Sexual PCR for in vitro evolution of β-lactam acylases, 2001-2004 (Prof. W.J. Quax)
- Production of Human Interleukin-3 and epidermal growth factor by Bacillus subtilis: Exploitation of SRP-mediated secretion, 2004-2008 (Prof. W.J. Quax)
- Innovative research grant (VENI grant) from NWO. Title: “Design and selection of biocatalysts for amination reactions”. 2004-2007 (Dr. G.J. Poelarends).
- Casimir Project Bacillus expression systems 2004-2006 (Prof. W.J. Quax)
• Innovative research grant (VIDI grant) from NWO. “Exploiting catalytic promiscuity: the tautomerase superfamily active site as a scaffold for new biocatalysts”. 2007-2012. (Dr. G.J. Poelarends)
• Rubicon project DARPINS 2008-2010 (Dr. Boersma)
• KNAW project 05-PP-18: Indonesian renewable resources: Jatropha curcas. Project period 2006-2011.

Collaboration with SME and industry
• EUREGIO Biotech: cross-border project to stimulate and support biotech/medtech companies 2001-2007 (Dr. R.H. Cool, Prof. W.J. Quax)
• KOP/EFRO (CRAFT) Project “Drug targeting and delivery”, 2008 –2013 (Prof. W.J. Quax)
• TOP Institute Pharma-project (TIPharma): “TNF ligands in cancer”, 2006 - 2012. (Prof. W.J. Quax)
• Senter Novem TSGE2035: “Cytokine modification for novel therapies” 2002-2005 (Prof. W.J. Quax).
• KOP II project (Kennis Ontwikkeling in Partnerschap): “Decoy receptor production” projectperiode: 2007 -2008. (Prof. W.J. Quax, Dr. R.H. Cool)
• Senter Novem: “Eating Jatropha – Analysing the potential of Jatropha curcas as foodstock for animals” Projectperiode: 2008 - 2012. (Prof. O. Kayser)
• AIF: “Analysis of proteolytic enzymes from Lucillia sericata” Project period: 2007 - 2008 (Prof. O. Kayser with alpha-Biocare GmbH, Düsseldorf, DE)
• AIF: “Combinatorial Biosynthesis of Tetrahydrocannabinol (THC)” Projectperiode: 2006 - 2010 (Prof. O. Kayser with THC-Pharm, Frankfurt a.M., DE)

Other projects
• European DFG-Graduiertenkolleg “Regulatory Circuits in Cellular Systems: Fundamentals and Biotechnological Applications” between Ruhr Universität Bochum and University of Groningen
• Dioraphte Foundation: “Standardised ethanolic Artemisia annua extracts for the treatment of uncomplicated Malaria”: 2008-2010 (Prof. O. Kayser).

Equipment
• In total 1130 k€ external funding for equipment was obtained.

Pharmacokinetics, Toxicology and Targeting

EU projects
• EU: Marie Curie Novel drug targeting strategies to liver and endothelium 2004- 2007, 1 post-doc, 1 PhD student (Prof. K.Poelstra)
• EU grant (FP6-LifeSciHealth pr), Kinases in hepatic and renal fibrosis 2007-2011. 1 PhD student (Prof. K.Poelstra)
• EU: Marie Curie, Depronil, 2008-2011. 1 postdoc (Prof. K.Poelstra)

NWO/STW/KNAW projects
• VIDI grant (NWO): New therapeutic proteins for the treatment of liver fibrosis. 1 assistant professor, 2 PhD students 5 yr (2001-2005) (Prof. K. Poelstra)
• Vici grant (NWO) 2007-2011 (5 yr) 3 PhD students. The design of new cell-selective drugs (Prof. K.Poelstra)
• STW: Drug targeting to the fibrotic liver, Post-doc, PhD student, technician, 2001-2005. Prof. K. Poelstra
• STW Valorisation grant, Phase I and II. A New Cell-Specific Drug Targeting Company 2006-2009 (2yr, 8 m) post-doc (0.4 FTE) (Prof. K.Poelstra)
• STW (Drug targeting) Utilisation of novel receptor recognizing peptides for the cell-specific delivery of anti-fibrotic and anti-inflammatory drugs 2006-2010. 1 post-doc, 1 PhD student (Prof. K.Poelstra)
• ZON/MW programme on Alternatives to animal experiments. Development of an intestine-liver microfluidic biochip for ADME-tox studies. 2006-2010 1 PhD student and 0.6 technician + bench fee (Prof. G.M.M. Groothuis, Prof. E.M.J. Verpoorte)
• STW: New opportunities for ADME and toxicity studies for drugs in human tissue: vitrification of organs slices 2008-2012 (1 PhD student, 1 technician + bench fee) (Prof. G.M.M. Groothuis)
• NWO/Biopartner First Stage Grant BioOrion, a drug targeting company. 2003- 2005 post-doc, technician (Prof. K.Poelstra)
• STW Valorisation grant, Phase I and II. A New Cell-Specific Drug Targeting Company 2006-2009 (2yr, 8 m) post-doc (0.4 FTE) (Prof. K.Poelstra)
• STW (Drug targeting) Utilisation of novel receptor recognizing peptides for the cell-specific delivery of anti-fibrotic and anti-inflammatory drugs 2006-2010. 1 post-doc, 1 PhD student (Prof. K.Poelstra)
• ZON/MW programme on Alternatives to animal experiments. Development of an in vitro system to test the effect and toxicity of anti-inflammatory and anti-fibrotic drugs in human liver. 2002-2007. 1 PhD student (Prof. G.M.M. Groothuis)
• STW: Development and validation of an in vitro system to predict intestinal drug metabolism and toxicity in man. 2002-2007. 1 PhD student, 0.5 postdoc, 1 technician. (Prof. G.M.M. Groothuis)
Collaboration with SME and industry

- NV Organon/Schering-Plough: Development of early markers for drug toxicity, 1996-2010 1 post-doc and 1 technician + bench fee (Prof. GMM Groothuis)
- TI-Pharma: Towards novel translational safety biomarkers for adverse drug toxicity 2008-2012 1 PhD student, 0.25 FTE technician+ bench fee (Prof. GMM Groothuis)
- TI-Pharma: Nanoscience as a tool for improving bioavailability and BBB penetration. 2007-2011 1 post-doc and 0.5 technician + bench fee (Prof. GMM Groothuis)
- TI-Pharma: Mechanism-based PK-PD modelling platform. 2008-2012. 2 PhD students, 1 post-doc + bench fee (Dr. J.H. Proost).
- TiIFN: Miniaturized, microfluidic system as a quantitative, physiologically relevant intestinal screening. 2008-2010, 1.0 post-doc (Prof. G.M.M. Groothuis).
- TransTechPharma, Species difference in metabolism and toxicity of TTP335, 2008-2009. 0.6 FTE postdoc, 0.6 FTE technician and benchfee (Prof. G.M.M. Groothuis)
- Madaus: Pharmacokinetics of silymarine and its components. 2003-2004 (1 yr) 1 postdoc (Prof. G.M.M. Groothuis)
- AM-Pharma Alkaline phosphatise 2005-2007 post-doc (Prof. K.Poelstra)

Equipment
- In total 140 k€ external funding for equipment was obtained.

Pharmaceutical Gene Modulation

EU projects
- European Community, Fifth Framework EC grant nr.QLRT-2001-02059, Tumor Angiogenesis. co-investigator, Prof. H.J. Haisma
- European Community, Sixth Framework EC grant nr.LSHC-CT-2005-518178, Anti-tumor targeting. co-investigator, Prof. H.J. Haisma
- European Community, Marie-Curie European Reintegration Grant to Dr. Dekker, nr MERG-CT-2007-202652, Novel approaches towards understanding of gene transcription using small molecules as tools. 2007-2010

Equipment
- In total 50 k€ external funding for equipment was obtained.

Pharmaceutical Technology and Biopharmacy

NWO/STW/KNAW
- Stabilization of vaccines and virosomes, STW, 2007-2009, technician 3 years

Collaboration with SME and industry

- “Hot medicines” (stabilization of therapeutic proteins), TI Pharma, 2007-2011, 1 PhD student
- Nanoscience as a tool for improving bioavailability and BBB penetration, TI Pharma, 2007-2011, 1 PhD student
- DeQuaPro-PAT (particle interactions, mixing and granulation), TI Pharma, 2007-2011, 2 PhD students
- Efficient eradication of pulmonary (multidrug-)resistant bacteria, TI Pharma, 2009-2011, 0.5 PhD student
- Development of Novolizer/Genuair inhaler, MEDA, Almirall-Sofotec, 2003-ongoing, >3000 k€
- Sugar Glass technology for dissolution enhancement, Solvay Pharmaceuticals 2004-ongoing, > 1200 k€
- Tibotec/Slq, The application of sugar glass technology for siRNA delivery, 2008-ongoing.
- Medspray, Development of a new soft mist inhaler, 2002-2008
- Novartis, testing of eFlow performance, 2006-2008
- Boehringer Ingelheim, Twincer, 2007
- Sankyo, Twincer, 2008

Equipment
- In total 250 k€ external funding for equipment was obtained.
Section 8.7: Academic Reputation

Rewards, awards and prizes
In 2003 Prof. Poelstra was awarded the Galenus Research prize, a national prize for groundbreaking research in pharmacy. In 2006 he was awarded the prestigious VICI grant. The VICI grants are the most substantial grants in the NWO Innovational Research Incentives Scheme. Dr. G.J. Poelarends was awarded a VIDI grant for his work on tautomerase enzymes. In 2008 he reached the interview round of the prestigious ERC starting grant competition. Three theses received an extra judicium: Dr. J. Prakash received a cum laude grade from the RUG and Dr. E.G.E. van de Kerkhof received the prize for the best thesis in toxicology in 2007 from the Dutch Society for Toxicology. Dr. Y. Boersma won the 2006 FIGON PhD student competition and in 2007 she was awarded a RUBICON fellowship by NWO. Prof. D.K.F. Meijer received in 2004 the prestigious Achievement Award from Japan. Prof. W.J. Quax received the distinguished researcher award from the ITB Bandung and Prof. H.W. Frijlink in 2008 received the Astellas European Foundation Basic Science Award 2008. The full list of awards and prices is given in appendix Section 8.7.

Editorships in academic journals
Prof. Quax is associate editor of "Microbiology" and editorial board member of the "Journal of Biotechnology". Prof. Groothuis was editorial board member of the journal "Hepatology". Prof. Haisma is editorial board member of "Tumour Targeting" and associated editor of "Current Gene Therapy". Prof. Frijlink is editorial board member of "Pharmaceutical Development and Technology". The full list is given in appendix Section 8.7.

Membership of academies and in scientific boards
Several of the members have been involved in organising pharmaceutical research at the national level (Prof. Meijer and Prof. Quax are founding members of FIGON, Prof. Frijlink is currently on the executive board). This has resulted in the creation of the national funding programme TiPharma with a prominent presence of BDDD members in the projects and among the “chairs” (Prof. Frijlink). Prof. Poelstra and Prof. Quax both served on selection committees for the NWO “Vernieuwingimpuls” funding programme for individual scientists, Prof. Poelstra on the Vidi committee, and Prof. Quax as chair of the Veni committee. In addition, BDDD members are frequently asked to take a seat in the scientific advisory boards of both SME and large corporate organisations. Prof. Haisma is a member of the ZonMW committees translational gene therapy and translational research. The full list is given in appendix Section 8.7.

Invitations to address major conferences
The appendix of Section 8.7 shows that members from each of the research lines are frequently invited to contribute to international conferences.
Section 8.8: Societal Relevance

Societal Quality

The translational character of the research is very high and the members of the BDDD group are well aware of how BDDD research can impact clinical and societal needs. A few examples can illustrate this interaction.

- Novel technology for designing proteins leads to more effective biopharmaceuticals. A receptor-specific variant of TRAIL was shown to be superior in an ovarian cancer animal model and a clinical development plan has now been drafted in collaboration with industry. This responds to a societal need for novel therapeutics for difficult to treat cancer types.
- The research towards Anthriscus as a source for podophyllotoxin contributes to a sustainable production system for the widely used chemotherapeutic agents Etoposide® and Teniposide®.
- The drug targeting line has significant societal impact based on clinical studies with alkaline phosphatase performed by spin-off companies. Phase I and Phase IIa clinical trials with alkaline phosphatase include studies in patients with: (i) septic shock, (ii) ulcerative colitis, (iii) acute kidney injury, (iv) coronary artery bypass graft surgery and (v) rheumatoid arthritis. First results show an increased survival of patients with sepsis (see press releases at www.am-pharma.com and www.alloksys.eu).
- The research on in vitro ADME-tox contributes to the reduction of animal use and the better prediction of human ADME-tox by developing in vitro technologies with human tissues. The group has gained a national and international reputation in the field of pharmacokinetic modelling, drug targeting and in vitro ADME-tox research with human tissue slices, and is one of the leading groups in The Netherlands on alternatives to animal experiments.
- The computer programme MwPharm has been developed and is continuously updated. It is marketed by the spin-off company Mediware BV. MwPharm is recommended by the Dutch Association of Hospital Pharmacists (NVZA), and is used in many hospitals for therapeutic management of individual patients in daily practice, including dose regimen calculations, dose adjustment by therapeutic drug monitoring, population pharmacokinetic analysis, optimal sampling strategies, and pharmacokinetic-pharmacodynamic modelling.
- The invention of a proprietary technology that is able to stabilize oxytocin in aqueous solution. The absence of a heat-stable oxytocin injection causes the death of 125,000 women due to postpartum haemorrhage in sub-Sahara Africa every year (solving this problem is number 5 on the U.N.’s millennium development goals). The introduction of a heat-stable oxytocin injection based on our invention has the potential to save these 125,000 lives per year.
- The stabilization technology of influenza vaccine that was developed by the department enables stockpiling of this vaccine for years at ambient temperatures. Moreover, the pulmonary administration of these vaccines was demonstrated to provide improved immunological protection as well as cross-protection. Both aspects can be highly relevant in the framework of pandemic preparedness activities.

Societal Impact

There is a strong visibility and interaction of the BDDD members with various societal developments.

- Prof. H.J. Haisma is strongly involved in the public debate on gene therapy and gene doping through publications in Dutch newspapers and interviews on radio (Radio1, Teleac, BBC World Service) and television (Zembla, NL Sport, VPRO, VARA, TV-Noord, Canvas).
- Prof. Frijlink was at the basis of the development of an innovative, highly stable dosage form of Oseltamivir for the Dutch government. In the framework of the pandemic preparedness activities of the Dutch government, over 40 million dosages (accounting for 4 million treatments) were produced and stockpiled.
- The newly developed Twincer® high-dose inhaler for antibiotics not only increases the therapeutic efficacy and quality of life for patients suffering from cystic fibrosis (first marketed in Australia), but also enables the treatment of patients that suffer from infections with antibiotic-resistant TB, a rapidly growing problem in many countries in Africa and Central-Asia.
- Prof. Quax is an active member of Dutch Life Science seed fund organisations that stimulate the creation and support of spin-off companies. This has resulted in a dozen of successfully operating companies in recent years.
- Prof. Poelstra and Prof. Meijer were active in starting up the spin-off company PharmA-Aware, with an initial investment of 7 M€. Meanwhile, the company has merged with AM-Pharma, with alkaline phosphatase as their lead compound. The total investments in personnel in this company have now increased up to approximately 25 million euro. AM-Pharma together with Alloksys Life Sciences is now conducting clinical trials in patients with coronal artery bypass surgery.
- In 2003, BiOrion Technologies BV was founded based on a patent describing new drug carriers for growth factor receptors. The total investment in this company was 750 k€. Clinical trials with a new drug targeting construct are now in preparation. The Financial Economic Magazine selected BiOrion in the Top 5 of the Dutch most innovative start-ups (FEM Business 16 June 2007).
• Prof. Frijlink's group contributed to the formulation of two EMEA-guidelines: Guideline on the pharmaceutical quality of inhalation and nasal products [EMEA/CHMP/QWP/49313/2005 Corr. 21 June 2006 (EMEA / Health Canada)], and Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD) in adults and for use in the treatment of asthma in children and adolescents [CPMP/EWP/4151/00 Rev. 1, 1 August 2009]. These guidelines receive much attention from the pharmaceutical industry. They determine the demands of inhalation products and clinical trials with inhalation products. Work of the group on inhalation products has resulted in a revision of European Pharmacopoeia monograph Inhalanda.

Valorisation
The BDDD programme has been extraordinarily successful over the reporting period in the economic valorisation of its knowledge. The translational character of the research in the programme provides an excellent starting point for different modes of valorisation. With contributions to 31 patents over the past period (see Table 8.4) the awareness of the importance of intellectual property (IP) in the drug development chain has been amply demonstrated. The PTB group, which performs fundamental (and applied) research on concepts close to the market has been extremely successful in licensing its IP to various companies, who have been able to bring products to the market based on technologies developed by the group. Currently, this generates an income for the university of more than 700 k€ per annum, a sum that is likely to grow in the future. Furthermore, the results from the new research lines have attracted the interest of pharmaceutical industry, and a structural income in the form of milestone payments is already generated. The expected total sum of royalty and milestone payments will be over 3000 k€ in the next 5 years. Since this is non-designated income, this will form a solid guarantee for the fundamental academic research activities in the group. Recently, royalty income was used to appoint three PhD. students. These students will all work on fundamental academic research questions. This will not only increase our academic knowledge, but also strengthen other related research projects. Finally, we have found that industry prefers to continue collaboration during the development phase, which again increases the capacity available for research.

The start of and cooperation with three spin-off companies (AM Pharma and BioOrion, from the drug targeting activities in the PTT group, Triskel Therapeutics from the PB group) forms the basis for the valorisation of research in the PTT, PGM and PB group. With research programmes that generate concepts in early drug research, the start of spin-off companies is a more logical strategy for valorisation. On the one hand, it opens the possibility to develop new products based on the group’s intellectual property, whereas on the other hand the ongoing cooperation between the group and the spin-offs assures a significant strengthening of the research in the department. Not only did these companies create additional research capacity in the groups, they were also very instrumental in obtaining governmental grants, which again increased the possibilities for innovative research in the different sub-programmes.
Section 8.9: Next Generation

With regard to the education offered through GUIDE, please refer to the main part of the GUIDE evaluation.

PhD level

PhD students of the BDDD programme are strongly encouraged to actively participate in the GUIDE training programme and to qualify for the GUIDE certificate. With 26 candidates (out of 43) that received the certificate in the past period, the BDDD programme has the highest rate of participation of PhD students in the GUIDE programme. BDDD researchers actively participate in the Topmaster Medical and Pharmaceutical Drug Innovation both in lecture courses and in training projects. The programme offers scholarships to a select group of excellent students recruited at an international level. Staff members are either week-coordinator, give lectures or supervise research projects within the MPDI master programme. In the past years > 10 Topmaster students enrolled in a research projects with one of the BDDD PI’s and many of them have continued in a PhD position within the institute representing the next generation of researchers.

Inspiration for increasing the international attractiveness of the PhD training also comes from the participation in the Marie Curie Training Network programme ANTIBIOTARGET and the involvement in the European Graduiertenkolleg “Regulatory Circuits in Cellular Systems”. At the national level PhD students and postdoctoral researchers that are funded through the TI Pharma participate in dedicated courses related to project management, drug development or intellectual property management.

Prof. Poelstra is a member of the Programme Committee of the Honors College, which has started this year, and this is a new opportunities to identify and motivate the top 5-10% best students. Simultaneously, the students will come into close contact with the research activities within BDDD at an early stage of their career.

Career Tracks in Science

A new and for the Netherlands revolutionary tenure-track system was introduced by the Faculty of Mathematics and Natural Sciences at the University of Groningen in 2002. The system is a transition from a permanent-staff-oriented policy to a career-driven human resources system. All PI’s from the BDDD programme have been incorporated into the system and all new academic staff positions are filled according to this system. The system contributes to the attractiveness of the University of Groningen as exemplified by its 4th position on the Best Places to Work 2009 (International Academic Institutions) in "The Scientist" ranking. Young talent gets the opportunity to develop an independent research line, and grow into the next-generation leaders in science.
Section 8.10: SWOT and Future Strategy

SWOT

Strengths:
- The unique embedding of the BDDD sub-programmes within UMCG premises enables highly interactive translational research (“from bed to bench to bedside”).
- Strong international collaboration resulting in highly innovative research concepts funded by the EU.
- Large diversity in financial sources, with a large number of grants from 2nd and 3rd money stream (NWO, TI Pharma, BMM, EFRO).
- The strong collaboration with structural biology, microbiology, organic chemistry and chemical engineering groups in Groningen has immediate impact in biopharmaceuticals and drug delivery research.
- Strong societal interest in research results generates income from products that are on the market or close to being introduced.
- Young staff with very good potential for further development and growth (Career paths in science, tenure-track system).
- The synergy between different parts of the BDDD programme and the Faculty of Medical Sciences in the research school GUIDE offers unique research collaborations and unique PhD training.

Weaknesses:
- Small group of scientific staff in comparison to the acquired funding (1 to 10 ratio).
- The budget of the Faculty of Mathematics and Natural Sciences lacks flexibility to follow the growth of Pharmacy.

Opportunities:
- New trends in drug development, including personalized medicine and biologicals offer novel opportunities for research on drug targeting, drug monitoring, reduction of drug toxicity and process engineering.
- Increasing societal attention for alternatives to animal experiments, both nationally as well as internationally.
- Further expansion of research towards biopharmacy and in vivo research (both in animal and man).
- The opening of an in-house GMP facility at UMCG offers great potential for rapid delivery of a proof-of-concept and concomitant opportunities for fast valorisation of our research (Prof. Frijlink is on the supervisory board of this facility).
- Successful start of work on formulation and delivery of siRNA.

Threats:
- The low direct funding limits potential to acquire certain grants, due to the matching requirements of some granting organisation.
- The career-driven personnel strategy can destabilize the staffing of specific fields of expertise.
- Career perspectives in the pharmaceutical industry may deprive academia from young high potential research talent.
- The strong growth in student number will ask attention of staff at the expense of research time.

Future strategy
The availability of a dynamic research environment in the BDDD programme with high quality independent scientists that have complementary expertises proves to be very attractive and aids in the competition to recruit high level staff and funding. Despite the limited amount of direct funding the PIs are able to attract substantial funding from many different sources at the national and international levels. This excellent earning capacity relates to the strong academic reputation of the BDDD PIs and, in particular, their unique position for bridging pharmacy and translational research. The limited amount of direct funding is used to attract three new tenure track assistant professorships that will further enforce the focus on chemical biology and distribution and kinetics of biopharmaceuticals allowing the programme to further contribute to translational research. The active coaching of young researchers in the tenure track system will guarantee the rise of new leaders creating an excellent research climate for the long future.
CHAPTER 9

Synthesis & Analysis
Section 9.1: Objective(s) and Research Area

Programme leader
Prof. Dr. R.P.H. Bischoff

Mission statement
The programme S&A combines expertise in analytical chemistry with that in medicinal chemistry and biomonitoring. The programme performs preclinical and clinical studies in order to translate fundamental new chemical entities and analytical methods into clinical practice. Bioinformatics plays an important role in this process covering molecular modelling of drug-protein structures as well as processing of hyper-dimensional data from ‘omics’ experiments. The programme forms the link between chemistry and biomedicine within GUIDE.

General
The programme Synthesis & Analysis (S&A) experienced difficult conditions during recent years. Firstly, as result of a reorganisation policy, the faculty decided to discontinue the research group Medicinal Chemistry. This decision was taken under great pressure caused by the financial deficits of the faculty of Mathematics and Natural Sciences (FMNS) anticipating the retirement of Prof. Håkan Wikström (in 2006) and the associated professors Dr. Cor Grol (in 2009) and Dr. Durk Dijkstra (in 2010). GRIP disagreed with this decision as Medicinal Chemistry is considered core business of the pharmacy curriculum as well as of the research mission. Secondly, the research group Biomonitoring & Sensoring decided to diminish its research activities in 2004 when the head of the group (and only permanent staff member) Prof. Ben Westerink was appointed as director of the Groningen Research Institute of Pharmacy (GRIP). In addition it was agreed to discontinue the group in 2010 at the occasion of the retirement of Westerink. Thirdly, the research group Pharmaceutical Analysis decreased in size and is now considered below the critical mass for a full member of GUIDE. The group is therefore listed as an associated member of GUIDE and is not included in this evaluation.

As result of these modifications the programme S&A does not longer function as independent research programme and assessment of this programme is not considered appropriate at the present time. We therefore propose to the Peer Review Committee to evaluate the sub-programme Analytical Biochemistry, which is currently the motor of the S&A division.

In this chapter we focus on the research group Analytical Biochemistry. Several tables, in addition, give an overview of the programme S&A as a whole. The position of the S&A division within the pharmaceutical research is schematised below.
Chapter 9  Synthesis & Analysis

Description of the research area of the group Analytical Biochemistry

The research group Analytical Biochemistry of the Groningen Research Institute of Pharmacy (GRIP) of the University of Groningen focuses on the analysis of biological macromolecules with special emphasis on proteins and peptides according to the following research lines.

1. Analysis of Biomarkers
   The biomarker discovery research line is pursued in collaboration with a number of clinical and informatics research groups in the context of large national and international (European) projects. The line is divided into the following main areas: a) discovery of biomarkers for pulmonary disease, notably Chronic Obstructive Pulmonary Disease (COPD), b) discovery of biomarkers for cancer (cervical cancer, prostate cancer), c) discovery of biomarkers for neurological disorders (multiple sclerosis) and d) discovery of biomarkers for obesity and diabetes type II.

2. Data Processing and Analysis (Dr. Peter Horvatovich)
   The bioinformatics research line is closely related to the analytical activity of the research group and focuses on pre-processing and analysis of mass spectrometry-derived ‘omics’ data. In collaboration with IBM we are developing complete data pre-processing pipelines for LC-MS data used in biomarker discovery projects with a focus on the development of novel algorithms to correct for non-linear retention time shifts in complex LC-MS data sets with high concentration variation. In collaboration with chemometrics and statistics groups we are involved in development and assessment of classification methods. In addition we are developing a framework to integrate newly developed tools, including data management software, using local and national computation infrastructures. Our activity is embedded within national bioinformatics initiatives, such us the Netherlands Bioinformatics for Proteomics Platform, The Netherlands Bioinformatics Center (NBIC) and the Netherlands Proteomics Center (NPC).

3. Chemical Proteomics
   This research line focuses primarily on activity-based profiling of metalloproteases comprising members of the matrix metalloprotease (MMP) and the membrane-bound “A Disintegrin and MetalloProtease” (ADAM) families. Another focus is the development of novel stable isotope labelling reagents for proteins, peptides and metabolites. These projects are based on close collaborations with the organic chemistry group of Prof. Overkleeft (Leiden University). We are furthermore investigating the possibilities of combining electrochemical reactions with mass spectrometry to simulate Phase-I metabolic reactions and to promote peptide and protein cleavage. Our research on post-translational modifications focuses on oxidative stress and notably the analysis of nitro-tyrosine-containing proteins and peptides.

Changes/modifications/policy

The focus on the bioinformatics research line has been intensified in January 2008 with the appointment of Dr. Peter Horvatovich as tenure track assistant professor in the area of processing and analyzing ‘omics’ data (research line 2).

The biomarker research line (no.1) is entering a phase from biomarker candidate discovery to biomarker candidate validation. Notably our research project about cervical cancer has led to the discovery of promising candidates that we are currently validating in larger sets of tissue and serum samples. The bioinformatics research line (no. 2) is expanding with a strong embedding in the Netherlands Proteomics and the Netherlands Bioinformatics Centers and forms a crucial support for our biomarker projects. We are actively expanding the chemical proteomics research line (no. 3) into the area of metabolomics as well as into the area of protein post-translational modifications.

The research group Analytical Biochemistry has acquired significant external funding (see section 6) on the order of 5,900 k€ between 2003 and 2008. Some of these grants included investments into mass spectrometry, HPLC equipment amounting to approximately 2,700 k€.

The group has also invested considerably in informatics infrastructure to foster developments in proteomics-related bioinformatics in the group. There are ongoing activities to acquire another cutting-edge MS instrument for quantitative LC-MS/MS analysis of low-molecular weight compounds (metabolites) and for quantitative proteomics in the context of a new systems biology institute (grant applications pending). We realize that continuous investments in this rapidly developing field are needed and will pursue our investment strategy based on external funding.
Section 9.2: Composition of the Research Unit

Programme Synthesis and Analysis (S&A)

The programme S&A consists of four research groups/sub-programmes:
- Analytical Biochemistry
- Biomonitoring and Sensoring (reduced activity since 2004)
- Drug Design (to be established in 2010)
- Medicinal Chemistry (closed in 2005)
- Pharmaceutical Analysis

We present an overview of the Division S&A in the form of two tables: research staff and funding of the programme. Subsequently we focus on the research group Analytical Biochemistry for reasons given in section 1.

In Table 9.1 the research staff of the S&A programme is shown (for details, see appendix Section 9.2). The programme experienced a reduction in tenured research staff between 2003-2008 due to reorganization of the Faculty FMNS (closure of the Medicinal Chemistry group in 2005). This situation will be amended in 2010 with employment of a new professor in Drug Design (hiring campaign ongoing).

| Table 9.1 Overview of research staff at the level of the programme S&A |
| --- | --- | --- | --- | --- | --- | --- |
| Year | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 |
| FTE | FTE | FTE | FTE | FTE | FTE | FTE |
| (n) | (n) | (n) | (n) | (n) | (n) | (n) |
| Tenured staff | 4.34 | 4.34 | 4.34 | 2.84 | 2.44 | 2.44 |
| (13) | (14) | (13) | (9) | (9) | (8) |
| Full professors * | 1.54 | 1.64 | 1.64 | 1.24 | 1.24 | 1.24 |
| (4+1) | (4+1) | (4+1) | (3+1) | (3+1) | (3+1) |
| Associate professors | 1.40 | 1.40 | 1.20 | 0.40 | 0.40 | 0.40 |
| (4) | (4) | (3) | (1) | (1) | (1) |
| Assistant professors | 1.20 | 1.00 | 1.10 | 0.80 | 0.40 | 0.40 |
| (3) | (3) | (3) | (2) | (2) | (1) |
| Other senior staff | 0.20 | 0.30 | 0.40 | 0.40 | 0.40 | 0.40 |
| (1) | (2) | (2) | (2) | (2) | (2) |
| Non-tenured staff | 4.01 | 5.13 | 4.05 | 3.61 | 0.90 | 2.40 |
| (7) | (7) | (5) | (5) | (3) | (4) |
| PhD-students | 7.00 | 7.70 | 7.53 | 7.00 | 6.14 | 7.00 |
| (16) | (17) | (20) | (19) | (18) | (14) |
| Employed | 7.00 | 7.70 | 7.53 | 7.00 | 6.13 | 7.00 |
| (12) | (12) | (14) | (11) | (13) | (10) |
| Non employed | ---- | ---- | ---- | ---- | ---- | ---- |
| ---- | (4/25.00%) | (5/29.41%) | (6/30.00%) | (8/42.11%) | (5/27.78%) | (4/20.57%) |
| Total research staff | 15.35 | 17.17 | 15.92 | 13.45 | 9.47 | 11.84 |
| (36) | (38) | (39) | (34) | (30) | (26) |

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers have also obligations for patient care. For the sake of simplicity a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD-students with an employment contract. For non-employed PhD students (student status), expression as FTE is not appropriate.

* In between brackets after the + symbol the number of adjunct and extraordinary professors is given.
In Table 9.2 the funding of the programme S&A is shown. Direct funding by the University of the S&A programme has decreased sharply by about 60% of the value in 2003 due to the closure of the medicinal chemistry group and other cost savings measures of the faculty FMNS. Part of this decline has been compensated by research grants (increase of more than 4-fold between 2003 and 2008). Income via the third money stream (contract research) has remained constant over the years.

Table 9.2  Overview of the research funding at the level of the programme S&A

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Direct funding (1)</td>
<td>11.62</td>
<td>12.19</td>
<td>10.54</td>
<td>7.27</td>
<td>4.02</td>
<td>4.69</td>
</tr>
<tr>
<td>Research grants (2)</td>
<td>0.90</td>
<td>0.90</td>
<td>1.60</td>
<td>2.53</td>
<td>3.48</td>
<td>3.95</td>
</tr>
<tr>
<td>Contract research (3)</td>
<td>2.83</td>
<td>4.08</td>
<td>3.78</td>
<td>3.65</td>
<td>1.98</td>
<td>3.20</td>
</tr>
<tr>
<td>Total funding</td>
<td>15.35</td>
<td>17.17</td>
<td>15.92</td>
<td>13.45</td>
<td>9.47</td>
<td>11.84</td>
</tr>
<tr>
<td>Expenditure:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel costs (k€)</td>
<td>843.8</td>
<td>988.8</td>
<td>956.6</td>
<td>764.2</td>
<td>549.7</td>
<td>703.1</td>
</tr>
<tr>
<td>Other Costs – Personnel (k€)</td>
<td>324.9</td>
<td>380.7</td>
<td>368.3</td>
<td>294.3</td>
<td>211.7</td>
<td>270.7</td>
</tr>
<tr>
<td>Costs non-employed PhD students (k€)</td>
<td>63.8</td>
<td>81.8</td>
<td>95.9</td>
<td>113.3</td>
<td>59.7</td>
<td>57.0</td>
</tr>
<tr>
<td>Other Costs - non-employed PhD Students (k€)</td>
<td>34.0</td>
<td>42.5</td>
<td>48.9</td>
<td>57.4</td>
<td>29.8</td>
<td>25.5</td>
</tr>
<tr>
<td>Total expenditure</td>
<td>k€ 1,266.5</td>
<td>k€ 1,493.8</td>
<td>k€ 1,469.7</td>
<td>k€ 1,229.2</td>
<td>k€ 850.8</td>
<td>k€ 1,056.3</td>
</tr>
</tbody>
</table>

Explanation: (1) Direct funding by the university; (2) Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programs ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’); (3) Funding for specific research projects obtained from external organizations, such as industry, governmental ministries, European Commission (Framework programs) and charity organizations.

The expenses for research include both personnel and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the donation to the provision “wachtgelden” (i.e. the obligation to provide personnel a reduced pay in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff and other costs like allowances for child care, and commuter traffic. Although non-employed PhD students do not represent research-FTE, the costs of these PhD students have been included. Other costs include exploitation costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

Research group Analytical Biochemistry

Research staff

The sub-programme/research group Analytical Biochemistry is comprised of one full professor (Prof. Dr. R.P.H. Bischoff), one assistant professor (Dr. P.L. Horvatovich, tenure-track), two research technicians, one teaching assistant and 0.5 FTE secretary. All other members of the group are funded by external grants except for one graduate student that forms part of the start-up package of Dr. Horvatovich. The future success of this research unit is thus strongly dependent on acquiring external funding, an activity that has been quite successful in recent years.

The research group forms part of a number of large national research consortia such as the TopInstitute Pharma, the Netherlands Proteomics Center and the Netherlands Bioinformatics Center. The head of the unit (Bischoff) is presently chairman of the Analytical Chemistry section of the Dutch Research Organization (NWO) and actively involved in setting up a new TopInstitute in Analytical Sciences (Business Plan available to the committee upon request). Our strategy is to continue acquiring funding from different sources, such as the Dutch Technology Foundation (STW), which is presently funding 3 PhD positions in the group, and publicly-funded charities (e.g. the Dutch Cancer Society KWF). To maintain investment in the rather costly infrastructure and thus to stay at the forefront of the development in proteomics and related disciplines, we are applying for grants from the medium-size (up to 900 k€) investment funds from NWO (joint application with the MS core facility and 5 other research groups of the FMNS and FMW faculties) and via large, national research initiatives (e.g. a new grant focusing on establishing an Institute for Systems Biology in...
Groningen). As we are strongly focused on analytical methods development, we maintain close contacts with research-oriented large and medium-size companies (e.g. Agilent Technologies and Spark Holland).

Table 9.3 gives an overview of the research staff of the Analytical Biochemistry group. The table emphasizes that most of the research in the group is conducted by PhD students that are funded by external sources. The appointment of an assistant professor in 2008 will allow us to develop the bioinformatics research line further, which is indispensable for our ‘omics-related’ research. Presently (November 2009), the research group has 9 PhD students (8 externally funded).

In Table 9.4 the funding of the research group Analytical Biochemistry is shown. Direct funding of the Analytical Biochemistry group by the University has decreased dramatically between 2003 and 2008 to less than 30% of its original level with an all-time low in 2007. This has been largely compensated by external research grants, the value of which now exceeds funding received from the University. The group has improved its scientific standards over this time period (57.5% of all publications are in the top 10% of the respective ISI field), despite this extremely difficult environment.

Table 9.3 Overview of the research staff at the level of the sub-programme Analytical Biochemistry

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>Tenured staff</td>
<td>1.40</td>
<td>1.20</td>
<td>0.90</td>
<td>0.60</td>
<td>0.60</td>
<td>1.00</td>
</tr>
<tr>
<td>(4)</td>
<td>(4)</td>
<td>(3)</td>
<td>(2)</td>
<td>(2)</td>
<td>(3)</td>
<td></td>
</tr>
<tr>
<td>Full professors</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
</tr>
<tr>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>Associate professors</td>
<td>0.40</td>
<td>0.20</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>(1)</td>
<td>(1)</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
<td>(0)</td>
</tr>
<tr>
<td>Assistant professors</td>
<td>0.40</td>
<td>0.40</td>
<td>0.30</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(0)</td>
<td>(0)</td>
<td>(1)</td>
</tr>
<tr>
<td>Other senior staff</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
<td>(1)</td>
</tr>
<tr>
<td>Non-tenured staff</td>
<td>2.70</td>
<td>3.15</td>
<td>2.25</td>
<td>2.03</td>
<td>0.68</td>
<td>1.35</td>
</tr>
<tr>
<td>(4)</td>
<td>(4)</td>
<td>(3)</td>
<td>(3)</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
</tr>
<tr>
<td>PhD-students</td>
<td>2.80</td>
<td>3.50</td>
<td>2.63</td>
<td>2.28</td>
<td>2.80</td>
<td>3.50</td>
</tr>
<tr>
<td>(4)</td>
<td>(6)</td>
<td>(7)</td>
<td>(7)</td>
<td>(7)</td>
<td>(7)</td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>2.80</td>
<td>3.50</td>
<td>2.63</td>
<td>2.28</td>
<td>2.80</td>
<td>3.50</td>
</tr>
<tr>
<td>(4)</td>
<td>(5)</td>
<td>(4)</td>
<td>(4)</td>
<td>(4)</td>
<td>(4)</td>
<td></td>
</tr>
<tr>
<td>Non employed</td>
<td>0.00%</td>
<td>16.67%</td>
<td>28.57%</td>
<td>42.86%</td>
<td>42.86%</td>
<td>28.57%</td>
</tr>
<tr>
<td>(0/-)</td>
<td>(1/-)</td>
<td>(2/-)</td>
<td>(3/-)</td>
<td>(3/-)</td>
<td>(2/-)</td>
<td></td>
</tr>
<tr>
<td>Total research staff</td>
<td>6.90</td>
<td>7.85</td>
<td>5.78</td>
<td>4.91</td>
<td>4.08</td>
<td>5.85</td>
</tr>
<tr>
<td>(12)</td>
<td>(14)</td>
<td>(13)</td>
<td>(12)</td>
<td>(11)</td>
<td>(12)</td>
<td></td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers have also obligations for patient care. For the sake of simplicity a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD-students with an employment contract. For non-employed PhD students (student status), expression as FTE is not appropriate.
Table 9.4 Overview of the research funding at the level of the sub-programme Analytical Biochemistry

<table>
<thead>
<tr>
<th>Funding:</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
<td>FTE</td>
</tr>
<tr>
<td>Direct funding (1)</td>
<td>6.00</td>
<td>5.35</td>
<td>3.28</td>
<td>2.23</td>
<td>0.60</td>
<td>1.70</td>
</tr>
<tr>
<td>(FTE)(%)</td>
<td>86.96</td>
<td>68.15</td>
<td>56.71</td>
<td>45.46</td>
<td>14.72</td>
<td>29.06</td>
</tr>
<tr>
<td>Research grants (2)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.40</td>
<td>1.85</td>
<td>2.55</td>
</tr>
<tr>
<td>(FTE)(%)</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>8.15</td>
<td>45.40</td>
<td>43.59</td>
</tr>
<tr>
<td>Contract research (3)</td>
<td>0.90</td>
<td>2.50</td>
<td>2.50</td>
<td>2.28</td>
<td>1.63</td>
<td>1.60</td>
</tr>
<tr>
<td>(FTE)(%)</td>
<td>13.04</td>
<td>31.85</td>
<td>43.29</td>
<td>46.38</td>
<td>39.88</td>
<td>27.35</td>
</tr>
<tr>
<td><strong>Total funding</strong></td>
<td>6.90</td>
<td>7.85</td>
<td>5.78</td>
<td>4.91</td>
<td>4.08</td>
<td>5.85</td>
</tr>
<tr>
<td><em>(FTE)(%)</em></td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Expenditure:

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Personnel costs (k€)</td>
<td>367.2</td>
<td>421.1</td>
<td>326.4</td>
<td>276.80</td>
<td>217.8</td>
<td>330.2</td>
</tr>
<tr>
<td>Other costs personnel (k€)</td>
<td>141.4</td>
<td>162.1</td>
<td>125.7</td>
<td>106.6</td>
<td>83.9</td>
<td>127.1</td>
</tr>
<tr>
<td>Costs non-employed PhD students (k€)</td>
<td>0</td>
<td>16.4</td>
<td>29.2</td>
<td>33.6</td>
<td>25.6</td>
<td>19.0</td>
</tr>
<tr>
<td>Other costs - non-employed PhD students (k€)</td>
<td>0</td>
<td>8.5</td>
<td>14.9</td>
<td>17.0</td>
<td>12.8</td>
<td>8.5</td>
</tr>
<tr>
<td><strong>Total expenditure</strong></td>
<td>k€ 508.6</td>
<td>k€ 608.1</td>
<td>k€ 496.1</td>
<td>k€ 434.0</td>
<td>k€ 340.0</td>
<td>k€ 484.8</td>
</tr>
</tbody>
</table>

Explanation: The expenses for research include both personnel and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the donation to the provision “wachtgelden” (i.e. the obligation to provide personnel a reduced pay in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff and other costs like allowances for child care, and commuter traffic. Although non-employed PhD students do not represent research-FTE, the costs of these PhD students have been included. Other costs include exploitation costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

1 Direct funding by the university;
2 Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programmes ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3 Funding for specific research projects obtained from external organisations, such as industry, governmental ministries, European Commission (Framework programmes) and charity organizations.
Section 9.3: Research Environment and Embedding

The research group Analytical Biochemistry has enhanced its reputation in the field of bioanalytical chemistry and bioinformatics. Although being rather small when compared to other programmes within GUIDE, it maintains a high scientific profile. The group leader (Bischoff) is presently chairman of the NWO study group Analytical Chemistry, that recently assembled more than 200 fellow researchers at its national meeting. Interactions and collaborations with a number of research programmes within GUIDE (notably GRIAC and Oncology) as well as with leading academic centers in the Netherlands and across Europe (see below), assures the sustainability of the groups research, which depends to the largest extend on external funding. The recent appointment of Dr. Horvatovich as assistant professor (tenure-track) has enhanced the scope of the research group. Next to grants from the Netherlands Proteomics and Bioinformatics Centers, Horvatovich recently (in 2009) was one of three scientists in the Netherlands that received the “light path” price to establish a high-speed computational network for proteomics research in the Netherlands (http://www.rug.nl/farmacie/onderzoek/basiseenheden/bioanalyseentoxicologie/news).

The Analytical Biochemistry group participates in 3 projects of the TopInstitute Pharma, a centre of excellence in pharmaceutical research in the Netherlands as well as in projects from the Netherlands Proteomics and Bioinformatics Centers, two other accredited centres of excellence. As chairman of the NWO study group in Analytical Chemistry, Bischoff participates actively in preparing funding for a new TopInstitute in Analytical Sciences. Other funding sources comprise the Dutch Technology Foundation (NWO-STW), the Dutch Cancer Society (KWF) and the European Union. While funding from external sources cannot be taken for granted, especially in the present economic environment, we expect that the broad spread of funding sources of the group will allow for a sustained development.

Key collaborations
Three key collaborations are summarized in the appendix Section 9.3

Visitors
The S&A frequently invites distinguished guest scientists to lecture on their research, to enter into scientific discourse with colleagues, to build national and international networks, to participate in master classes and to participate in thesis defenses. An overview of guest lectures is given in appendix Section 9.3.
Section 9.4: Quality and Scientific Relevance

All published papers of the programme S&A are listed in appendix Section 9.5. All top-publications (10% and 30%) in this appendix have been marked.

High quality publications of Analytical Biochemistry
The research group/sub-programme Analytical Biochemistry has strived to increase its research profile and visibility, since its start in 2001. Over the reporting period 2003-2008, the principal investigator increased his citation score from 80 to 212 annually (source Scopus). The group strives furthermore to publish its results in high-ranking journals, rather than trying to augment the number of publications. This is emphasized by the fact that of the 40 publications authored or co-authored by the principal investigator over this time period, 57.5% are in journals ranked amongst the top 10% of their respective ISI field and 95% are in journals ranked amongst the top 30%. Bischoff was furthermore nominated to the editorial advisory board of the Journal of Proteome Research (publisher: American Chemical Society), which is considered number 2 of all proteomics journals at present.

Most important results of Analytical Biochemistry
• Development and application of an integrated analytical system for the activity-dependent analysis of matrix metalloproteases (2007).
• Development and application of a novel two-dimensional alignment procedure for complex LC-MS data sets (2007).
• Development and patenting of an immobilized trypsin reactor for rapid on-line digestion (2005).

Key publications Analytical Biochemistry
Journal articles:

Books and book chapters:
• Govorukhina, N. Biomarker Discovery for Cervical Cancer. Methods and Approaches; VDM Verlag Dr. Müller, Saarbrücken, Germany: 2008; pp 1-151.
Section 9.5: Quantity of Scientific Output

Overview of the results
Despite severe cuts in the finances of the S&A programme resulting in a steep decline in university-funded positions, the scientific output has been largely maintained, which is noteworthy when considering that one major research group (Medicinal Chemistry) out of 4 in the programme has been closed and a second (Biomonitoring and Sensoring) is winding down due to the retirement of the PI in 2010. Notably the Analytical Biochemistry group has contributed to this strong, high-quality output, which is well above the GUIDE criteria in terms of publications in the top 10 or top 30% journals of the respective ISI field when ranked according to their impact factor.

The programme S&A contributes also to dissemination of knowledge in form of book chapters and books as well as through communications in non-scientific journals and through interviews.

In Tables 9.5 and 9.6 an overview is given of the scientific output of the programme S&A and of the research group Analytical Biochemistry.

All publications of the sub-programme S&A are listed in appendix Section 9.5.

<table>
<thead>
<tr>
<th>Table 9.5</th>
<th>Main categories of research output at the level of programme S&amp;A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Refereed articles</td>
<td>35</td>
</tr>
<tr>
<td>Books and Book chapters</td>
<td>3</td>
</tr>
<tr>
<td>PhD-theses</td>
<td>2</td>
</tr>
<tr>
<td>Patents</td>
<td>0</td>
</tr>
<tr>
<td>Total publications</td>
<td>40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 9.6</th>
<th>Main categories of research output at the level of sub-programme Analytical Biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Refereed articles</td>
<td>7</td>
</tr>
<tr>
<td>Books and Book chapters</td>
<td>0</td>
</tr>
<tr>
<td>PhD-theses</td>
<td>0</td>
</tr>
<tr>
<td>Patents</td>
<td>0</td>
</tr>
<tr>
<td>Total publications</td>
<td>7</td>
</tr>
</tbody>
</table>

Number of PhD students
In Tables 9.7 and 9.8 an overview is given of the PhD students of the programme S&A and of the research group Analytical Biochemistry.

<table>
<thead>
<tr>
<th>Table 9.7</th>
<th>Number of PhD students at the level of programme S&amp;A</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Number of PhD-students</td>
<td>16</td>
</tr>
<tr>
<td>employed</td>
<td>12</td>
</tr>
<tr>
<td>non-employed</td>
<td>4</td>
</tr>
<tr>
<td>% non-employed</td>
<td>25.00%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 9.8</th>
<th>Number of PhD students the level of sub-programme Analytical Biochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Number of PhD-students</td>
<td>4</td>
</tr>
<tr>
<td>employed</td>
<td>4</td>
</tr>
<tr>
<td>non-employed</td>
<td>0</td>
</tr>
<tr>
<td>% non-employed</td>
<td>0.00%</td>
</tr>
</tbody>
</table>

The number of PhD positions increased between 2003 and 2005 due to a number of externally funded research projects. This number was sustained until 2008 and is presently at 9 PhD students (November 2009), of which 1 is funded by the university (11.1%).
Section 9.6: Earning Capacity

The sub-programme Analytical Biochemistry has been very successful in acquiring external funding for its research amounting to a direct input of about 5.9 M€ (funding for the overall projects, in which the group is involved, is estimated to be a factor 5-10 larger corresponding to 87 FTE total).

In collaboration with other proteomics-oriented research groups we have now access to the following instrumentation:

<table>
<thead>
<tr>
<th>Instrumentation</th>
<th>Value (new) k€</th>
<th>Year of acquisition</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>chipLC-triple quadrupole</td>
<td>310</td>
<td>2008</td>
<td>Bischoff Lab</td>
</tr>
<tr>
<td>chipLC-QTOF</td>
<td>438</td>
<td>2006</td>
<td>Bischoff Lab</td>
</tr>
<tr>
<td>capLC-ion trap</td>
<td>234 (US $)*</td>
<td>2003</td>
<td>Bischoff Lab</td>
</tr>
<tr>
<td>chipLC-ion trap**</td>
<td>361</td>
<td>2002</td>
<td>Bischoff Lab</td>
</tr>
<tr>
<td>nanoLC-QStar</td>
<td>750***</td>
<td>2004</td>
<td>MS core facility</td>
</tr>
<tr>
<td>MALDI-TOF (DE-Pro)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nanoLC-Orbitrap</td>
<td>750****</td>
<td>2009</td>
<td>Poolman Lab</td>
</tr>
<tr>
<td>nanoLC-MALDI-TOF/TOF (ABI 4800 and 4700)</td>
<td></td>
<td></td>
<td>Poolman Lab******</td>
</tr>
</tbody>
</table>

* according to exchange rate of Aug. 27, 2009 (164 k€)
** chip cube installed in 2005 (value: 50 k€)
*** joint investment with Prof. Vonk (UMCG)
**** joint investment with Prof. Poolman and Prof. Feringa (RUG)
***** no financial contribution by Analytical Biochemistry but access through collaborations.

The position of the group has depended almost entirely on the success of the group leader to acquire funding, since other senior staff was reduced during reorganization of the faculty FMNS. Only recently has there been appointment of Dr. Horvatovich as assistant professor (tenure-track). Dr. Horvatovich is starting to contribute to the acquisition of external funding, which should make the group less vulnerable. Funding allocated by the university is presently only about 14% (see ‘allocated funding’ in Table 9.9), which exerts enormous pressure on the group, due to a concomitant high teaching load. Integration of the Analytical Biochemistry group in a number of national centers of excellence and the future perspective of a closer collaboration with locally implemented, international industry promise to provide increased stability of the financial position of the group in order to maintain its place in the international research arena.

In Table 9.9 a numerical overview of the acquired and allocated funding is given in research FTE. The bottom line shows that over the past 6 years 80% to 86% of the funding has come from external sources and the absolute number of acquired funding has been stable at 7-8 FTE. Apart from the funding of personnel, investments in infrastructure and equipment have been obtained by external funding, totalling about 2 M€. Planned large-scale projects in systems biology and the TopInstitute of Analytical Sciences (presently under review) is expected to allow the group to maintain its international position.

Table 9.9 Fund raising capacity at the level of sub-programme Analytical Biochemistry.

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>% (FTE)</td>
<td>% (FTE)</td>
<td>% (FTE)</td>
<td>% (FTE)</td>
<td>% (FTE)</td>
<td>% (FTE)</td>
<td>% (FTE)</td>
</tr>
<tr>
<td>Total funding</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>(6.90)</td>
<td>(8.85)</td>
<td>(7.53)</td>
<td>(6.91)</td>
<td>(5.58)</td>
<td>(6.85)</td>
<td></td>
</tr>
<tr>
<td>Allocated funding</td>
<td>20.29%</td>
<td>13.56%</td>
<td>11.96%</td>
<td>8.69%</td>
<td>10.76%</td>
<td>14.60%</td>
</tr>
<tr>
<td>(1.40)</td>
<td>(1.40)</td>
<td>(0.90)</td>
<td>(0.60)</td>
<td>(0.60)</td>
<td>(1.00)</td>
<td></td>
</tr>
<tr>
<td>Acquired funding</td>
<td>79.71%</td>
<td>86.44%</td>
<td>88.04%</td>
<td>91.31%</td>
<td>89.24%</td>
<td>85.40%</td>
</tr>
<tr>
<td>(5.50)</td>
<td>(7.65)</td>
<td>(6.63)</td>
<td>(6.31)</td>
<td>(4.98)</td>
<td>(5.85)</td>
<td></td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are funded directly by the University of Groningen and/or the UMCG (allocated funding). To extend their research capacity, they acquire grants via internal and external competition (acquired funding) for non-tenured staff, employed PhD-students, non-employed PhD-students and in some cases a limited number of staff positions. The fund raising capacity is expressed in research FTE.
### Table 9.10 Overview of external funding obtained by the sub-programme Analytical Biochemistry.

<table>
<thead>
<tr>
<th>Project code</th>
<th>Time period</th>
<th>Funding source</th>
<th>Funding* (in k€)</th>
<th>Personnel*</th>
<th>Personnel for the entire project / programme</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPC 6150</td>
<td>2003-2007</td>
<td>NWO-STW</td>
<td>353</td>
<td>1 PhD student</td>
<td>2 PhD students</td>
</tr>
<tr>
<td>RUG 2004-3165</td>
<td>2004-2007</td>
<td>Dutch Cancer Society</td>
<td>374</td>
<td>1 postdoctoral researcher</td>
<td>1 postdoctoral researcher</td>
</tr>
<tr>
<td>LSHC-CT-2004-503011</td>
<td>2005-2008</td>
<td>EU-Strep</td>
<td>174</td>
<td>1 researcher</td>
<td>12 FTE</td>
</tr>
<tr>
<td>HPRN-CT-2002-00189</td>
<td>2003-2006</td>
<td>EU Marie-Curie RTN</td>
<td>207</td>
<td>1 postdoctoral researcher</td>
<td>7 FTE</td>
</tr>
<tr>
<td>Bilk 03015</td>
<td>2005-2008</td>
<td>Netherlands Proteomics Center</td>
<td>750</td>
<td>1 postdoctoral researcher</td>
<td>4 FTE</td>
</tr>
<tr>
<td>Biorange 2.2.3</td>
<td>2006-2010</td>
<td>Netherlands Bioinformatics Center</td>
<td>175</td>
<td>1 PhD student</td>
<td>7 FTE</td>
</tr>
<tr>
<td>TAC 7047</td>
<td>2006-2010</td>
<td>NWO-STW</td>
<td>621</td>
<td>2 PhD students</td>
<td>4 PhD students</td>
</tr>
<tr>
<td>T1-108</td>
<td>2008-2012</td>
<td>Ti-Pharma</td>
<td>520</td>
<td>1 PhD student</td>
<td>13 FTE</td>
</tr>
<tr>
<td>T2-105</td>
<td>2008-2012</td>
<td>Ti-Pharma</td>
<td>484</td>
<td>1 postdoctoral researcher</td>
<td>11 FTE</td>
</tr>
<tr>
<td>D4-102</td>
<td>2007-2011</td>
<td>Ti-Pharma</td>
<td>825</td>
<td>1 PhD student</td>
<td>6 FTE</td>
</tr>
<tr>
<td>08008</td>
<td>2008-2012</td>
<td>NWO-STW</td>
<td>460</td>
<td>1 PhD student</td>
<td>4 FTE</td>
</tr>
<tr>
<td>E 4.2</td>
<td>2009-2013</td>
<td>Netherlands Proteomics Center</td>
<td>220</td>
<td>1 PhD student</td>
<td>7 FTE</td>
</tr>
<tr>
<td>E 1.3</td>
<td>2009-2013</td>
<td>Netherlands Proteomics Center</td>
<td>220</td>
<td>1 PhD student</td>
<td>6 FTE</td>
</tr>
<tr>
<td>SP5.12.2.1</td>
<td>2008-2010</td>
<td>Netherlands Bioinformatics Center</td>
<td>118</td>
<td>1 scientific programmer</td>
<td>5 FTE</td>
</tr>
<tr>
<td>MiddelGroot</td>
<td>2004</td>
<td>NWO ZonMW</td>
<td>375</td>
<td>Mass spectrometers</td>
<td>---</td>
</tr>
</tbody>
</table>

* mentioned numbers concern only funding/personnel for the Analytical Biochemistry group.
Section 9.7: Academic Reputation

Recognition of the group as a leader in its field is emphasized by the numerous invitations to present plenary and keynote lectures at international meetings, chairmanships of sessions at international meetings and the recent decision to appoint Bischoff as chair of the 30th edition of the prestigious International Symposium on Proteins, Peptides and Polynucleotides (ISPPP), which will be held together with the 8th European Symposium on Biochemical Engineering Science in Bologna (Italy) in September 2010.

Academic reputation - Rewards and prizes
In 2003 Prof. Bischoff was awarded with the Agilent Award for Creativity and Innovation in Laboratory Teaching.

<table>
<thead>
<tr>
<th>S&amp;A researcher</th>
<th>Prize</th>
<th>Given by</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bischoff</td>
<td>Recipient of the Agilent Award for Creativity and Innovation in Laboratory Teaching</td>
<td>Agilent Technologies</td>
<td>2003</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

Academic reputation – Editorships in academic journals
Prof. Bischoff is executive editor of the Journal of Chromatography B and member of the editorial advisory board of the Journal of Proteome Research.

<table>
<thead>
<tr>
<th>S&amp;A researcher</th>
<th>Journal</th>
<th>Year(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bischoff</td>
<td>Executive Editor: Journal of Chromatography B (Elsevier Science)</td>
<td>2003- present</td>
</tr>
<tr>
<td></td>
<td>Editorial Advisory Board: Journal of Proteome Research (American Chemical Society)</td>
<td>2007- present</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Academic reputation – Memberships of Academies and in Scientific Boards
Prof. Bischoff is chairman of the Analytical Chemistry section of the Dutch Scientific Organization (NWO) since 2007. Since 2005 he is board member of the Netherlands Proteomics Platform.

<table>
<thead>
<tr>
<th>S&amp;A researcher</th>
<th>Academy or Scientific Board</th>
<th>Year(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bischoff</td>
<td>Chairman: Dutch Scientific Organization (NWO); Analytical Chemistry section</td>
<td>2007- present</td>
</tr>
<tr>
<td></td>
<td>Board member of the Netherlands Proteomics Platform</td>
<td>2005- present</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Academic reputation – Invitations to address major conferences
Prof. Bischoff is a frequently invited lecturer at international conferences.

<table>
<thead>
<tr>
<th>S&amp;A researcher</th>
<th>Congres, City, Country</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bischoff</td>
<td>Vellore Institute of Technology, Vellore, Tamil Nadu, India on the occasion of the inauguration of the Centre for Bioseparations Technology</td>
<td>2005</td>
</tr>
<tr>
<td></td>
<td>HPLC 2006, San Francisco, USA</td>
<td>2006</td>
</tr>
<tr>
<td></td>
<td>Roswell Park Cancer Institute, Buffalo, USA</td>
<td>2008</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>

Academic reputation – Other proofs

<table>
<thead>
<tr>
<th>S&amp;A researcher</th>
<th>Other proofs</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bischoff</td>
<td>External expert for the European Network of Excellence GA2LEN on Asthma and Allergy; Geneva, Switzerland</td>
<td>2004</td>
</tr>
<tr>
<td></td>
<td>Chairman of the Biomarker and Biosensing Discipline, TopInstitute Pharma</td>
<td>2005</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>46</td>
</tr>
</tbody>
</table>
Section 9.8: Societal Relevance

Biomarker research has the potential to deliver better diagnostic and prognostic tools to the health care professionals to improve therapy and to provide the most effective and adequate treatment to individual patients. As such the results of this research line may ultimately contribute to improved health care and reduced spending on ineffective or inadequate medical treatment. As indicated by the number of translational projects, in which the group is involved, there is a strong understanding of the need to translate fundamental research results into clinically useful applications. This is illustrated by projects funded by the TopInstitute Pharma, the European Union, the Dutch Technology Foundation and the Dutch Cancer Society, some of which are outlined below.

• A number of biomarker candidates for cervical cancer has been discovered by tissue proteomics using laser microdissection in collaboration with Dr. Luider from the Erasmus Medical Center in Rotterdam and Prof. van der Zee from the University Medical Center Groningen. These marker candidates are presently being validated and translated into serum diagnostic tests for the early detection of cervical cancer.
• A novel, ultra-fast trypsin reactor has been developed as part of a project funded by the Dutch Technology Foundation. This reactor has been patented together with Agilent Technologies, a company specializing in cutting-edge analytical equipment and applications in the life sciences.
• Novel inhibitors of metalloproteases are being developed in collaboration with Prof. Overkleeft (Leiden University) to enhance specificity. In addition inhibitors are being modified to allow incorporation of radioisotopes for in vivo monitoring of metalloprotease activity (collaboration with the Nuclear Medicine Department of the University Medical Center Groningen).
• Novel biomarker candidates are being pursued in a TI-Pharma-funded project in collaboration with industry and a number of research groups combining proteomics, metabolomics and NMR. First results in animal models of multiple sclerosis are promising and studies in drug-treated animals will commence in early 2010.
• The development of data processing algorithms in cooperation with Dr. Suits from the IBM T.J. Watson Research Center (USA) has resulted in a number of software applications that are presently being implemented on the national life science computing network (LifeScience GRID, SARA computing facilities) to facilitate use by non-experts in the ‘omics’ community. This development is driven by Dr. Horvatovich as part of his ‘light path’ award.

The reach of the Analytical Biochemistry group into the society can also be judged from the list of companies that are involved in one or more of the projects listed in Table 9.11.

Table 9.11 Industrial collaborators as part of funded projects.

<table>
<thead>
<tr>
<th>Industrial collaborators as part of funded projects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nycomed B.V. (Altana)</td>
</tr>
<tr>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>Schering Plough</td>
</tr>
<tr>
<td>Solvay</td>
</tr>
<tr>
<td>PRA International</td>
</tr>
<tr>
<td>TNO</td>
</tr>
<tr>
<td>SparkHolland</td>
</tr>
<tr>
<td>Agilent Technologies</td>
</tr>
<tr>
<td>Philips</td>
</tr>
<tr>
<td>ESA</td>
</tr>
<tr>
<td>Bruker</td>
</tr>
<tr>
<td>Ionics</td>
</tr>
<tr>
<td>Dionex</td>
</tr>
<tr>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Plant Research International</td>
</tr>
<tr>
<td>Innoprac Diagnostics</td>
</tr>
<tr>
<td>CanAg Diagnostics AB</td>
</tr>
<tr>
<td>Pfizer</td>
</tr>
</tbody>
</table>
Section 9.9: Next Generation

With regard to the education offered through GUIDE, please refer to the main part of the GUIDE evaluation.

The S&A programme contributes to the education of young professionals through the training of PhD students, postdoctoral researchers as well as by taking part in master’s and bachelor’s programmes. Throughout the evaluation period there has been an average of 16 PhD students per year in the division. The research groups Analytical Biochemistry and Pharmaceutical Analysis participate in the national training network ANAC for PhD students working in analytical chemistry research groups in The Netherlands. ANAC is organized under the auspices of the Dutch Scientific Research Organization (NWO) and the Dutch Chemical Society (KNCV) (http://sac.kncv.nl/anac-(aiot-network).12022.lynkx). The research group Analytical Biochemistry is furthermore involved in the TopMaster’s programme Medical and Pharmaceutical Drug Innovation (MPDI) that is organizationally associated with the Faculty of Medical Science as well as in the Junior Scientific Masterclass organized by the same faculty. The Analytical Biochemistry group contributes in addition to the International Master’s class on Behavioral and Cognitive Neurosciences that runs under guidance of the Faculty of Mathematics and Natural Sciences. The Analytical Biochemistry group has participated in a Research and Training Network (RTN) of the European Union (Marie Curie action) on molecular imprinting, in which a number of postdoctoral researchers and PhD students from different European countries worked together. Finally PhD students and postdoctoral researchers that are funded through the TopInstitute Pharma participate in dedicated courses related to project management, drug development or intellectual property management.

PhD students that finished their studies in the Analytical Biochemistry group have all found positions in industry, major hospitals or as postdoctoral researchers without delay. Most often, PhD students found employment prior to defending their dissertation. Dr. Horvatovich, who started as a postdoctoral researcher in the group, has been promoted to the tenure-track assistant professor level and is currently supervising 3 PhD students and one scientific programmer.

The programme S&A contributes significantly to the education of young professionals, some of which have the potential to follow an academic career. Incentives for reintegrating these PhDs in the future structure of the programme will depend strongly on the funding environment and the strategy of Pharmacy, GUIDE, the FMNS faculty and the university as a whole. Participation in initiatives such as the planned institute for Systems Biology, the center for ageing research ERIBA and the various TopInstitutes will allow the next generation of researchers to prosper and develop as part of the programme.
Section 9.10: Viability, SWOT and Future Strategy

Viability

The S&A programme experienced a very difficult period due to discontinuation of the Medicinal Chemistry group, the difficulties in funding the Pharmaceutical Analysis group and the perspective of closing down the Biomonitoring & Sensoring group in 2010 at the occasion of the retirement of Prof. Westerink.

However perspectives for the S&A programme have brightened recently with the planned restart of the Medicinal Chemistry group with a full professor position in Drug Design, which includes a tenure-track position. We anticipate that this will reactivate the programme and increase its scientific output, funding capacity and output in terms of highly educated professionals (masters and PhDs) in this important discipline at the interface between chemistry, pharmacy and medicine. Regarding the Pharmaceutical Analysis group, an action plan is in preparation to improve the external funding of the research.

Future strategy

The Analytical Biochemistry group will enhance its focus on biomedical research collaborations (e.g. with GRIAC), an extension of its enabling technology developing activities and the bioinformatics research line. It will strive to be integrated in future, major research initiatives in Groningen (ERIBA, systems biology), nationally (TI Analytical Sciences) and internationally (EU-funded projects). Valorization of research results is part of the future strategy based on the further development of biomarker candidates, implementation of results from bioinformatics research and new technologies.

Based on the personnel plan of the Groningen Research Institute of Pharmacy, we also envisage to start a long-term collaboration with PRA International, a multinational company focusing on bioanalytical chemistry, with the appointment of Dr. van der Merbel as extraordinary professor in the group in 2010.

The future strategy of the S&A programme relies first and foremost on restarting the Medicinal Chemistry group by filling in the vacancies for a full professor in Drug Design, and the related tenure track position, with strong candidates, and on the strategy of the Pharmaceutical Analysis group to increase its ‘earning capacity’.

Still a programme with 3 research groups is on the small side and we must strive to add another chemically-oriented research group to this programme to fill the void left by closure of the Biomonitoring and Sensoring group.

It is the conviction of the programme leader that the S&A programme should only continue if all groups receive adequate funding over the coming years. Otherwise, we propose to close the programme and to associate the groups with other GUIDE divisions.

SWOT

Strengths

- Embedding of the Analytical Biochemistry research group in a biomedical environment forms an ideal situation for biomarker research and its translation into clinical practice. Close collaboration with informatics/statistics groups reinforces the data processing/statistics research line of Dr. Horvatovich.
- Integration of the Analytical Biochemistry research group in large multi-center research projects is favourable to gene-rating high-quality output as well as to forming future consortia to apply for research funding.

Weaknesses

- The funding environment of the faculty is poor and does not allow adequate support for common infrastructure (e.g. the mass spectrometry core facility). Sustainability and expansion thus depend to almost 90% on external funding.
- The high teaching load of researchers in the programme makes it very hard to find the time for initiating new research lines and acquiring funding.

Opportunities

- Discoveries in the biomarker area open possibilities for commercial developments. Close contact with industry creates options for joint funding. Start up of new integrated research centers (e.g. center for Healthy Ageing, Systems Biology institute) opens possibilities for future, sustainable investments.
- Reopening of the Medicinal Chemistry group opens opportunities for collaboration, joint research projects and ultimately increased scientific output.

Threats:

- Risk of a significantly changing funding landscape due to the general financial crisis (e.g. less public funding for research; less financial support from industry) may threaten investment-intensive research.
Groningen Research Institute of Pharmacy (GRIP)
Programme leader
Prof. Dr. B.H.C. Westerink, scientific director of GRIP.

Essential points
In the period 2003-2008 GRIP’s permanent staff was reduced by around 14%. At the same time the influx of undergraduate pharmacy students almost doubled. Despite these circumstances, we are proud that GRIP’s scientific output has remained stable and that the number of PhD students has actually increased from 57 in 2003 to 72 in 2008.

The scientific and societal impact of the institute’s research is clearly visible in the content of many of research projects as well as in a number of products and activities that have reached the market. There is a growing income from royalties and licenses on intellectual property obtained from original research conducted in GRIP. Our research programme benefits strongly from these resources. The impact of valorisation is further demonstrated by a respectable list of spin-off companies.

In the self evaluation of the preceding period (1996-2001), we expressed the ambition to become a top drug research institute in Europe. In the year 2009 we feel that the majority of GRIP’s sub-programmes have made significant progress to reach this goal.

This Addendum aims to highlight GRIP as an entity and to give additional information on its sub-programmes.

Table of contents
1. Introduction
2. Mission, policy and coherence of GRIP
3. The sub-programmes of GRIP
4. Research staff
5. Earning capacity
6. Embedding and academic reputation
7. Scientific output
8. Societal relevance and valorisation
9. SWOT analysis
10. Policy and future strategy
Section 1: Introduction

Currently GRIP numbers ten active sub-programmes (Table 1), each representing research groups within the institute. Each group is headed by a full professor (chairperson), who is the programme leader. The scientific director of GRIP bears final scientific responsibility and is accountable to the Board of the Faculty of Mathematics and Natural Sciences (FMNS).

Table 1 Survey of GRIP’s research groups

<table>
<thead>
<tr>
<th>Sub-programme (research group)</th>
<th>Chairperson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical Biochemistry (AB)</td>
<td>Prof. Dr. R.P.H. Bischoff</td>
</tr>
<tr>
<td>Biomonitoring and Sensoring (BS)*</td>
<td>Prof. Dr. B.H.C. Westerink</td>
</tr>
<tr>
<td>Drug Design (DD) (under construction)</td>
<td>vacancy</td>
</tr>
<tr>
<td>Molecular Pharmacology (MP)</td>
<td>Prof. Dr. H. Meurs</td>
</tr>
<tr>
<td>Pharmaceutical Analysis (PA)*</td>
<td>Prof. Dr. E.M.J. Verpoorte</td>
</tr>
<tr>
<td>Pharmaceutical Biology (PB)</td>
<td>Prof. Dr. W.J. Quax</td>
</tr>
<tr>
<td>Pharmaceutical Gene Modulation (PGM)</td>
<td>Prof. Dr. H.J. Haisma</td>
</tr>
<tr>
<td>Pharmaceutical Technology and Biopharmacy (PTB)</td>
<td>Prof. Dr. H.W. Frijlink</td>
</tr>
<tr>
<td>PharmacoEpidemiology and PharmacoEconomics (PE2)</td>
<td>Prof. Dr. L.T.W. de Jong-van den Berg</td>
</tr>
<tr>
<td>Pharmacokinetics, Toxicology and Targeting (PTT)</td>
<td>Prof. Dr. G.M.M. Groothuis</td>
</tr>
<tr>
<td>Pharmacotherapy and Pharmaceutical Care (PPC)</td>
<td>Prof. Dr. J.J.de Gier</td>
</tr>
</tbody>
</table>

Survey of GRIP’s research groups (in alphabetical order) with the abbreviations used to annotate them and their chairpersons. The groups Biomonitoring and Sensoring, and Pharmaceutical Analysis are not included in this evaluation (indicated with an *).

In this self evaluation the GRIP sub-programmes are clustered along the lines of the GUIDE programmes. The groups Pharmaceutical Biology (PB), Pharmaceutical Gene Modulation (PGM), Pharmaceutical Technology and Biopharmacy (PTB), and Pharmacokinetics, Toxicology and Targeting (PTT) are discussed in detail in the chapter entitled Programme Biopharmaceuticals: Discovery, Design and Delivery (BDDD) (Chapter 8).

Details of the sub-programme Analytical Biochemistry (AB) can be found in the chapter entitled Programme Synthesis & Analysis (S&A) (Chapter 9). The programme S&A also comprises the groups Biomonitoring and Sensing (BS) and Pharmaceutical Analysis (PA), but they are not included in this self evaluation because they are not being reviewed. Biomonitoring and Sensing will be discontinued in 2010 (though part of its activities will be housed in the spin-off company Brains-on-line). The Pharmaceutical Analysis group is below critical mass at present. Note that the group Medicinal Chemistry was discontinued in 2006, but efforts are underway to revive this important pharmaceutical research area again in the form of a new sub-programme Drug Design.

The group Molecular Pharmacology (MP) is presented in the chapter of the Groningen Research Institute of Asthma and COPD (GRIAC) (Chapter 4). The groups PharmacoEpidemiology and PharmacoEconomics (PE2) and Pharmacotherapy and Pharmaceutical Care (PPC) are described in the self evaluation of the Graduate School for Health Research (SHARE). These groups will be evaluated within those research environments. Brief information about these groups is also included in this Addendum.

In this Addendum we describe the mission, policy and coherence of GRIP as an institute for integrated multidisciplinary pharmaceutical research. In addition, we present some details of the three sub-programmes (Molecular Pharmacology, PharmacoEpidemiology and PharmacoEconomics, and Pharmacotherapy and Pharmaceutical Care) who are not part of the programmes BDDD and S&A. Furthermore we pay attention to the issues of research staff, earning capacity, scientific output, societal relevance and valorisation for the entire institute. This section ends with a SWOT analysis, future perspectives and plans.

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1 The group Drug Design (DD) is currently under construction, with a vacancy for a chairperson. It replaces the Medicinal Chemistry group which was discontinued in 2006 due to the reorganization of the Faculty of Mathematics and Natural Sciences (FMNS).
Section 2: Mission, policy and coherence of GRIP

Pharmaceutical research is multidisciplinary and plays a major role in life sciences. It bridges chemistry, biology and physics on the one hand and the medical sciences on the other. Because of GRIP’s embedment in the Faculty of Mathematics and Natural Sciences (FMNS) and its physical proximity to the University Medical Center Groningen (UMCG), this unique position can be fully exploited, as evidenced by the many intra- and interfaculty collaborations.

Mission
The mission of GRIP is:
1. to perform internationally recognized advanced research at the frontiers of knowledge in the pharmaceutical sciences;
2. to amalgamate advanced research and education in order to deliver professional pharmacists and pharmaceutical researchers to society.

Policy
Drug development
Pharmaceutical sciences encompass the entire field of drug development and drug use. At the cradle of the drug development process, target finding and lead finding are major research topics. Genomics and proteomics are increasingly involved in finding disease-specific biomarkers that may identify new targets. In the early phase, scientists in GRIP design and perform small-scale (bio)synthesis of candidate drugs and determine their pharmacological and toxicological profiles. Next steps in the development process include research on drug formulation, bioavailability, drug delivery, pharmacokinetics and production processes. Analytical aspects are essential throughout. Once a new drug has passed the clinical testing phases, it is admitted for registration. From this stage on, the domains of pharmacotherapy, pharmacoepidemiology, pharmacoeconomics and pharmaceutical care prevail. Interactions and continuous feedback between all phases make the development process dynamic.

GRIP’s research policy
GRIP’s research ambition is to contribute to the entire field of the pharmaceutical sciences, from basic areas such as chemical analysis and synthesis to pharmaceutical practice and patient-oriented research. This policy is reflected in the sub-programmes of the various sub-programmes in GRIP. As all groups are also responsible for teaching, a close and stimulating interaction between their research activities and the educational programmes can be realized.

Figure 1. Interactions and coherence between the GRIP research groups.
Coherence
The coherence of GRIP research is evident when viewed in terms of the drug development process: rational drug design, mechanism of action, analysis, delivery and engineering, and drugs in practice (Figure 1).

Rational drug design
New drug targets are identified on the basis of increased insight into the pathophysiology, including the molecular background, of various diseases. Based on these targets, rational drug design and development can deliver completely new generations of drugs with improved effectiveness and safety profiles. In addition, novel therapeutic strategies to treat previously untreatable may result. The molecular biology tool box, combined with proper bioinformatics, provides new opportunities for target finding and validation of experimental drugs. The fields of genomics and proteomics are thus increasingly important in innovative drug research.

Proteins are by far the most widely used drug targets, and modulating their activity is at the heart of modern drug discovery. In-depth protein research is essential for understanding biological disease mechanisms and to assess drug action and target finding. The sub-programmes Analytical Biochemistry (head: Prof. Dr. Rainer Bischoff) and Pharmaceutical Biology (head: Prof. Dr. Wim Quax) are positioned at the heart of this domain. Both groups are rapidly growing and are a source of expertise of modern technologies.

The central aim of the sub-programme Pharmaceutical Biology is focused on the study of the living cell as a source of pharmaceutically important products. Natural and directed diversity of micro-organisms, plants and plant cells are explored as a source of natural products, including therapeutic proteins. Modern molecular biology and genetic techniques are applied to create biological systems producing structurally complex and enantiopure molecules. Novel techniques such as directed diversity and directed evolution are now being investigated for creating new leads for experimental medicines. A research line on plant biotechnology applies pathway engineering to control the formation of bioactive compounds.

The Analytical Biochemistry group is strongly embedded in a biomedical environment. The national and international background of the group’s work enabled a considerable investment in quantitative LC-MS/MS equipment and proteomics-related bioinformatics. The biomarker research line is pursued in collaboration with a number of clinical and informatics sub-programmes, in the context of large national and international (European) projects. This research line is now graduating from pure biomarker candidate discovery to biomarker candidate validation. Promising candidates are evaluated in larger sets of tissue and serum samples. The bioinformatics research line is closely related to the analytical activity of the sub-programme and focuses on pre-processing and analysis of mass spectrometric related ‘proteomics’ data.

The sub-programme Pharmaceutical Gene Modulation (head: Prof. Dr. Hidde Haisma) focuses on the development of novel strategies for gene regulation and the specific delivery methods needed for therapeutic interventions. Strategies for modification of gene transcription using small drug-like molecules or viral vectors are being developed for the specific and effective treatment of cancer and inflammatory diseases. This approach is directed at fundamentally new therapies treating the pathology of the disease, and not only its symptoms.

Knowledge of drug targets is the basis for the development of novel active compounds. Apart from natural sources, chemical synthesis – aided by computer modelling methods – remains a key activity for drug discovery and production. It is expected that the new sub-programme Drug Design will play a central role in computed-assisted design and synthesis of experimental drugs.

Mechanisms of action
At present, pathophysiological processes are being interpreted more and more at the genetic, molecular and cellular levels, and molecular pharmacological methods play an important role in translating this new insight into new medicines. The research performed in the Molecular Pharmacology group (head: Prof. Dr. Herman Meurs) is an excellent example of this approach. The group is strongly oriented towards receptor pharmacology and molecular interventions in cellular signalling networks related to the pathophysiology of chronic diseases such as asthma, COPD, Alzheimer and cardiovascular diseases. Various in vitro and in vivo model systems and a unique expertise and infrastructure to perform investigations from the molecular biology level all the way to the intact organism and to translate animal model findings to human cells and tissue are available. In addition, novel pharmacological findings are incorporated into clinical research, particularly in the framework of GRIAC (e.g. pharmacogenetics).

The Biomonitoring and Sensoring group (head: Prof. Dr. Ben Westerink) is developing sophisticated in vivo monitoring methods that are applied to various pathophysiological animal models in drug efficacy evaluations. The group has made a significant contribution to the developments the microdialysis technique both in animal models as well as...
in clinical studies. After the retirement of Prof. Westerink, in 2010, a number of the research topics will be harboured in the successful spin-off company Brains-on-line.

**Analysis, delivery and engineering**

Advances in fast-track technologies including microchip-based liquid handling will enable drug research to maintain the ever-increasing pace of developments in related fields. The research of the Pharmaceutical Analysis group (head: Prof. Dr. Elisabeth Verpoorte) has led to the introduction of a new "lab-on-a-chip" line of research focusing on the combination of state-of-the-art micro-technologies with biology and biochemistry. Micro- and nanotechnologies are poised to play an integral role in today’s science world, and ultimately, in the betterment of human life, as they offer unprecedented means to directly probe our molecular and cellular worlds. Research in the Pharmaceutical Analysis group is primarily devoted to better understanding micro- and nanofluidic systems and how they can be applied to chemical and cell biological problems. A cleanroom for rapid prototyping of microfluidic devices was opened in early 2006. Specific projects include a flow-based electrokinetic technique for the separation of polymer microspheres and biological particles (e.g. cells, DNA), integrated systems for continuous glucose monitoring, and a microflow system for drug metabolism studies using precision-cut tissue slices. The establishment of a group with microfluidics expertise in a pharmaceutical sciences environment is, to the best of our knowledge, unique in Europe.

The group Pharmacokinetics, Toxicology and Targeting (head: Prof. Dr. Geny Groothuis) explores fundamental aspects of membrane transport of drugs with relation to drug elimination and distribution, as well as to drug interactions and drug toxicity. Novel in vitro models based on human tissue are being developed to predict drug disposition, metabolism and toxicity, whereas pharmacokinetic modelling and simulation contribute to the in vivo prediction of pharmacokinetics and pharmacodynamics. In addition, innovative drug delivery tools for the cell-specific targeting of drugs and therapeutic proteins especially to the liver and tumor tissue are being investigated. Specific peptides and protein fragments are being studied as homing devices and tools for improving bioavailability. Several promising compounds entered phase 1 and phase 2 clinical studies. The mission of the sub-programme Pharmaceutical Technology and Biopharmacy (head: Prof. Dr. Henderik Frijlink) is to perform research in the field of dosage forms, their production and their interaction with the living organism. Fundamental research around the central theme "pharmaceutical powder technology" on the design and development of novel and improved drug delivery systems (among others for biopharmaceuticals) covers a range of activities from lab to bedside, aiming at optimal drug administration. Translational research is an important theme. Dosage forms/formulations based on the group's intellectual property have a high societal impact (e.g. stabilization of vaccines) and provide substantial royalties from products that have reached the market.

**Drugs in practice**

A major challenge lies in the proper monitoring and control of medication use by patients. This requires research on the dangers of polypharmacy, severe drug interactions, as well as unwanted or threatening side-effects. Physicians and pharmacists need to team up to cope with these dangers and to ensure effective, safe and affordable pharmacotherapy. The sub-programmes PharmacoEpidemiology and PharmacoEconomics (head: Prof. Dr. Lolkje de Jong-van den Berg) and Pharmaco-therapy and Pharmaceutical Care (head: Prof. Dr. Johan de Gier) contribute significantly to this directly patient-driven research field. The two sub-programmes focus on the different aspects of drug use by specific high-risk (vulnerable) patient groups, such as pregnant women, neonates, the frail elderly, and psychiatric patients. Both research lines benefit from the in-house available drug research database IADB.nl, comprising prescriptions and other person-linked data from fifty pharmacies dating back to 1995, and collaboration with the EUROCAT network of registries of birth defects on the development and optimisation of a birth defect case-control monitoring system in Europe. Furthermore, a unique database of a cohort of nursing-home patients that covers the three northern provinces of The Netherlands has been established. Over recent years, genetics has become a part of pharmacotherapy practice. Genetic polymorphisms in drug targets have been related to differences in patient outcome. The sub-programme addresses this topic with respect to the pharmacotherapy of psychiatric patients. The pharmacoconomics sub-line has a unique position in health-economic research and cost-effectiveness analyses in infectious disease control. Moreover, the group is one of the few expert centres in the world that do research on cost-effectiveness of vaccines based on mathematical, population-dynamical modeling. Both sub-programmes have close collaborations with related groups in the University Medical Center Groningen (UMCG) and are members of the research institute SHARE.
Table 2  Research subjects of the GRIP research groups in key words.

<table>
<thead>
<tr>
<th>Sub-programme (research groups)</th>
<th>Key words</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analytical Biochemistry (AB)</td>
<td>Biomarkers, Proteomics, Bioinformatics, Mass spectrometry, Chemical biology</td>
</tr>
<tr>
<td>Biomonitoring and Sensoring (BS)*</td>
<td>Microdialysis, Biosensors, Glucose sensor, Neuropharmacology, Centrally acting drugs</td>
</tr>
<tr>
<td>Molecular Pharmacology (MP)</td>
<td>Receptor pharmacology, Novel molecular signalling pathways, Pathophysiology of chronic inflammatory diseases, Drug action, Translational research</td>
</tr>
<tr>
<td>Pharmaceutical Analysis (PA)*</td>
<td>Lab-on-a-chip, Drug development, Cell/tissue microculture, Microparticle handling, Glucose monitoring</td>
</tr>
<tr>
<td>Pharmaceutical Biology (PB)</td>
<td>Natural products, Biodiversity, Biosynthesis, Enzyme engineering, Protein design</td>
</tr>
<tr>
<td>Pharmaceutical Gene Modulation (PGM)</td>
<td>Gene therapy, Transgene transmission, Drug discovery, Epigenetics, Enzyme inhibition</td>
</tr>
<tr>
<td>Pharmaceutical Technology and Biopharmacy (PTB)</td>
<td>Formulation &amp; engineering, Pulmonary drug administration, Oral drug administration, Sugar glass stabilization, Nanotechnology</td>
</tr>
<tr>
<td>PharmacoEpidemiology and PharmacoEconomics (PE2)</td>
<td>Drug safety in pregnancy and children, Drug utilization, Vaccines, Methodology</td>
</tr>
<tr>
<td>Pharmacokinetics, Toxicology and Targeting (PTT)</td>
<td>Peptide- and protein-based drug targeting, In vitro-in vivo prediction of metabolism, transport and toxicity, PKPD modeling, Fibrosis, Alternatives to animal experiments</td>
</tr>
<tr>
<td>Pharmacotherapy and Pharmaceutical Care (PPC)</td>
<td>Patient safety and psychotropic medicines, Pharmacogenetics, Pharmacovigilance, Medication safety in vulnerable patient groups, Typology of health care services</td>
</tr>
</tbody>
</table>

Research subjects of the GRIP research groups in key words. The sub-programmes Biomonitoring and Sensoring, and Pharmaceutical Analysis are not included in this evaluation (indicated with an *).
Section 3: The sub-programmes of GRIP

The sub-programmes of GRIP are embedded in two research schools. Eight sub-programmes (Analytical Biochemistry, Biomonitoring and Sensoring, Pharmaceutical Analysis, Pharmaceutical Biology, Molecular Pharmacology, Pharmaceutical Gene Modulation, Pharmaceutical Technology and Biopharmacy, Pharmacokinetics, Toxicology and Targeting) participate in the Graduate School for Drug Exploration (GUIDE). Two groups (PharmacoEpidemiology and PharmacoEconomics, Pharmacotherapy and Pharmaceutical Care) participate in the Graduate School for Health Research (SHARE); these groups are associate members of GUIDE.

The groups Pharmaceutical Biology, Pharmaceutical Gene Modulation, Pharmaceutical Technology and Biopharmacy, and Pharmacokinetics, Toxicology and Targeting comprise the programme Biopharmaceuticals: Design, Discovery and Delivery (BDDD). These groups are described in detail in the BDDD self evaluation (Chapter 8). The groups Analytical Biochemistry, Biomonitoring and Sensoring, Pharmaceutical Analysis, plus the future group Drug Design together form the programme Synthesis & Analysis (S&A). As outlined above (see Section 1 of the Addendum; Introduction) only the Analytical Biochemistry group will be reviewed and details of this group are provided in the S&A self evaluation (Chapter 9).

The group Molecular Pharmacology participates in the programme Groningen Research Institute of Asthma and COPD (GRIAC). A description of the Molecular Pharmacology group can be found in the GRIAC self evaluation. The groups PharmacoEpidemiology and PharmacoEconomics, and Pharmacotherapy and Pharmaceutical Care are integrated and described in the self evaluation of SHARE.

However, to provide the peer review committee with a comprehensive description of all eight sub-programmes of GRIP that are to be evaluated, we describe the sub-programmes Molecular Pharmacology, PharmacoEpidemiology and PharmacoEconomics, and Pharmacotherapy and Pharmaceutical Care in more detail below.

Sub-programme Molecular Pharmacology (MP)

Programme leaders: Prof. Dr. Herman Meurs and Prof. Dr. Martina Schmidt

Objectives
The research of the Molecular Pharmacology group is devoted to receptor pharmacology and cellular signalling pathways. Fundamental research is performed on the function, signalling and regulation of receptors in health and disease, to develop new pharmacological interventions for chronic diseases, in particular asthma, COPD, cardiovascular diseases - heart failure, arrhythmias - and Alzheimer’s dementia.

Research area
The research is focused on novel molecular signalling mechanisms governing specific cellular functions in the airways, heart and brain. There is a major emphasis on the mechanisms and pharmacological treatment of airway obstruction, airway hyperresponsiveness and airway remodelling in asthma and COPD. The research is performed at the molecular and cellular level and in isolated organs and intact organisms, using cells and tissues of both animal and human origin as well as advanced animal models, from guinea pigs to (genetically modified) mice. Within this research area, the following research questions are being addressed:

- Physiological and pathophysiological roles of the novel cAMP effector Epac.
- Pathological role of acetylcholine in asthma and COPD.
- Regulation of B2-adrenoceptor (dys)function in airway smooth muscle and lymphocytes.
- Airway smooth muscle phenotype plasticity in asthma and COPD.
- Role of Rho-kinase in the pathophysiology of allergic asthma.
- The Wnt-β-catenin- GSK-3 signalling pathway and airway remodelling.
- Role of nitric oxide (NO) and arginase in the pathophysiology of asthma and COPD.
- Histone acetyltransferases and deacetylases as a target for airway inflammation and glucocorticosteroid resistance.

Changes in the period 2003-2008
In 2004, Dr. Herman Meurs obtained as adjunct professor a chair in Immunopharmacology. In 2006, Prof. Johan Zaagsma retired and the chairmanship of the group was handed over to Prof. Herman Meurs. In 2005, Dr. Martina Schmidt joined the group as a Rosalind Franklin Fellow. She reinforced the molecular research of the group and obtained as adjunct professor a chair in Molecular Pharmacology in 2006. In 2009 the group added a tenure-track position in Translational Pharmacology (Dr. Reinoud Gosens).

2 An adjunct professor at our university is an associate professor with ius promovendi, who is on a track (career path) that may lead to a full professorship/chair.
As of January 2009 the Molecular Pharmacology group has given up its full membership of the Center for Behaviour and Neuroscience (CBN) to assume a full membership in the Groningen Research Institute of Pharmacy (GRIP), an associate membership of CBN has been retained. As a consequence the Molecular Pharmacology group is full member of GUIDE since January 2009. Previously, it was an associate member of GUIDE.

The group has intensified its collaboration with clinical groups within GRIAC, as is indicated by an increased number of joint projects and publications. In addition, the international profile has been strengthened by extended collaborations and increased participation in international boards and committees. With these achievements, the recommendations of the previous evaluation have been clearly met.

Funding and impact

Considerable financial support has been provided by grants from the Netherlands Asthma Foundation, the Netherlands Foundation for Scientific Research (NWO, Veni Award, Dr. Gosens), the European Community (Marie Curie International Outgoing Fellowship, Dr. Gosens), the German Foundation for Scientific Research (DFG), the International Graduate School on Vascular Medicine GRK880 (DFG-NWO) and pharmaceutical companies (Organon/Schering Plough for arginase inhibitor research, Boehringer Ingelheim for longacting muscarinic receptor antagonist research, Bayer Health Care for biomarker development, European Screening Port GmbH for PKB/Akt inhibitor screening). Scientific staff members participate on boards and committees of the Netherlands Asthma Foundation, the Dutch Pharmacological Society and the American Thoracic Society, as well as on editorial boards of scientific journals. Articles translating scientific research to clinical practice are published on a regular base, and there is significant interest in the group’s work in the public domain. Pharmaceutical companies occasionally request scientific consults. Research findings in the Molecular Pharmacology group have recently resulted in three (pending) patents.

Sixteen externally financed projects were running during the period 2003-2008, amounting to 2.9 M€.

The group has an annual output of 10-15 international publications in highly ranking journals in the field. There has been a clear trend towards increased numbers of publications in recent last years, and citations raised exponentially. In addition, 10 (chapters in) books were published. The group had 8 PhD defences.

Sub-programme PharmacoEpidemiology and PharmacoEconomics (PE2)

Programme leaders: Prof. Dr. Lolkje T.W. de Jong-van den Berg and Prof. Dr. Maarten J. Postma

Objectives

The objective of the PharmacoEpidemiology and PharmacoEconomics group is to support clinical practice, based on epidemiological studies, implementation research, and economic evaluations. Researchers of the group form expertise centres to support and improve methodologies and quality of clinical research in collaboration with the UMCG, and provide consulting and facilities to assist primary care settings to enhance scientific approaches in implementation.

Pharmacoepidemiology

The research line pharmacoepidemiology focuses on topics related to specific potentially high-risk groups, such as pregnant women, infants, children and the chronically ill (kidney and cardiovascular diseases). A primary focus is on drug use and pregnancy. When drugs are authorized to enter the market, information with respect to reproductive toxicity is only available from animal studies carried out to support the registration. We learn about teratogenic effects in humans only after the medicinal products have been used by pregnant women. Close collaboration has existed now for 5 years with the EUROCAT network of registries of birth defects, focussing on the development and optimisation of a birth defect case-control monitoring system in Europe This network is currently being used to assess the risks of specific birth defects in relation to anti-epileptic drugs and will be expanded to other chronic drug groups such as insulins (human and analogues), asthma medication, and psychotropics.

Pharmacoconomics

This research line is primarily directed to pharmacoeconomic evaluation of vaccinations within large-scale infant and adult programmes, and of screening programmes to identify and treat patients at risk for (complications of) infectious, kidney and cardiovascular diseases.

The three key areas for research are as follows:

1. cost-effectiveness analysis in infectious diseases control;
2. economic analyses in the area of nephrology/cardiology;
3. econometric approaches to the data registered in the IADB (see below).
With regard to cost-effectiveness analysis, some specific aspects are related to infectious disease control. In particular, the study of the impact of indirect effects on cost-effectiveness is challenging and presents a focus of our research, involving the linkage of complex mathematical models and economic information.

Pharmacoeconomic analysis is often pursued in co-operation with research groups in the UMCG, including the Departments of Nephrology, Cardiology and Epidemiology.

IADB.nl
Both the pharmacoepidemiologic and pharmacoeconomic research lines benefit greatly from the in-house drug research database IADB.nl, comprising prescriptions and other person-based data from 50 pharmacies since 1995. IADB.nl is updated (bi-) annually to support pharmacoepidemiologic and pharmacoeconomic research. To enhance valid studies it is very important to maintain and extend this collaboration with community and hospital pharmacists in the framework of the IADB.nl. In 2006 the database comprised prescription information for a total of approximately 500,000 patients in The Netherlands. For a subset of patient data, linkage with hospital admission data has been achieved (IADB-PREVEND database). IADB.nl is also part of the Mondriaan project of TI-Pharma, aiming at linking different databases in health (services).

Changes in the period 2003-2008
Based on the recommendations in the previous evaluation the group has implemented/carry out the following changes:

- The sub-programme has further focused on specific topics: drug use in pregnancy and birth defects, pediatric drug use, pharmacoeconomics, infectious diseases and nephrology/cardiology.
- The visibility in the international scientific community has increased, as can be deduced from many publications in high-ranking peer-reviewed journals, a number of invited lectures, reviewing tasks and invitations for relevant committees and boards.

In 2006, the sub-programme left GUIDE and joined the EBM (Evidence-Based Medicine) programme within SHARE.

Funding and impact
- Successful implementation of the project “Care for …. folic acid for those women considering pregnancy” in Dutch community pharmacies.
- Using the EUROCAT network of birth defect registries with improved drug exposure information in the data-set, a case-control study evaluating the risk of lamotrigin on orofacial clefts (this research also landmarked the start of EUROmediCAT) was successfully concluded.
- A dynamic approach was developed to assess cost-effectiveness of infectious disease control, with applications to chlamydia screening and pertussis vaccination.
- In cooperation with the UMCG, various PhD-theses have been prepared on the pharmacoepidemiologic and pharmacoeconomic data gathered in the local PREVEND screening study.
- Related to the project on enhancing clinical pharmacy in Vietnam, a NUFFIC grant was acquired to investigate the cost-effectiveness of hepatitis B vaccination (PhD study).
- Two post-docs could be appointed on two projects, externally financed by ZonMw.
- EU-project applications were awarded in the areas of pharmacoeconomics, pharmacogenetics and pharmacovigilance.

Sixteen externally financed projects were running during the period 2003-2008, amounting to 1.7 M€. Important financers were ZonMW, the Royal Dutch Association for the Advancement of Pharmacy (KNMP), the WHO, the Dutch Kidney Foundation, Sanofi and Glaxo Smith Kline (GSK).

The group is very productive, with an annual output of 30-40 international publications in top journals in the field. In addition, 9 (chapters in) books were published, as well as a series of professional publications (in Dutch). The latter is also important because of the high relevance of the work of the group for the national professional field. The group had 9 PhD defences.
Sub-programme Pharmacotherapeutics and Pharmaceutical care (PPC)

Programme leaders: Prof. Dr. Jacobus R.J.B. Brouwers, Prof. Dr. Johan J. de Gier and Prof. Dr. Katja Taxis

Objectives
Following the recommendations in the previous evaluation the Pharmacotherapy and Pharmaceutical Care group has focused its research projects on a main major research topic, namely patient and medication safety, with a particular emphasis on psychotropic medication).

Research area
The research projects focus on the safety of vulnerable patient groups such as neonates, psychiatric patients and the elderly. Complex pharmacotherapy and care processes make these patients very vulnerable for adverse events, especially in the case of psychotropic medication, which is associated with considerable morbidity and mortality, leading to (preventable) hospital admissions and reducing the quality of life of patients. A specific patient safety file exists for patients who are prescribed (psychotropic) medication which could impair the operation of a motor vehicle.

The overall aim of the research programme is to identify and quantify safety issues and to investigate possible interventions to improve medicine use. This has resulted in several studies involving vulnerable patient groups, such as neonates, psychiatric patients and frail elderly. To improve drug safety in the hospital setting, the focus is on the detection of undertreatment and peri-operative drug management. Furthermore, pharmacogenetics is being used as a tool to develop tailor-made pharmacotherapy in psychiatric diseases, rheumatology and coagulation disorders.

The safety of peri-operative drug management in the elderly as well as drug safety in nursing home patients have been investigated as well. To this end, a collaboration with the UMCG has been established to exploit a unique database comprising a cohort of nursing home patients. Ultimately, it aims to cover 5,000 individuals from the three northern provinces of the Netherlands over the next few years. Data will be used to perform drug utilization studies and observational studies on main and side effects, adverse effects and safety of medication. Thus, the safety of medication newly introduced onto the market will be investigated. This research is being performed in collaboration with the Dutch Pharmacovigilance Centre (LAREB). Furthermore, the sub-programme has been a partner in the EPHOR institute, the Dutch centre of experts on ‘Pharmacotherapy for Elderly’, since 2008.

Other research focuses on medication safety in psychiatric patients (PHAMOUS, IMPROVE-R) and medication review. A new project was started in 2008, investigating depressive co-morbidities in patients with psychotic disorders. In addition, there is international collaboration with researchers in Russia (Tomsk) to investigate practical pharmacogenetics and drug-related problems (DRPs) in psychiatry.

Patient and medication safety is a main topic of a European project entitled: ‘Driving under the influence of drugs, alcohol and medicines’ (DRUID), which started at the end of 2006 and runs until 2010. The project involves the study on relative risk estimates for traffic accident involvement for patients exposed to psychotropic medicines (based on linkage of medication records to accident data), for which a collaboration exists with the Pharmacoepidemiology and Pharmacoconomics group. A second research topic is on the establishment of criteria for a European categorization of drugs affecting driving performance. This is based on expert consensus, guidelines and professional standards for improving the prescription and dispensing of medicines that affect driving performance. It also comprises the evaluation and implementation of new ICT technologies to support prescribing and dispensing practices.

A third research focus is on patient and medication safety, for evaluating integrated pharmaceutical care. Using a web-based pharmaceutical care plan, pharmacists and physicians are better prepared to detect patients’ drug related problems, and to define care issues and process interventions for improving drug treatment outcomes. In this approach specific attention is given to develop approaches for designing and implementing new health care services, based on in depth investigation of the collaboration between health care providers and patients.

Methodological aspects of medication safety are investigated in collaboration with the Dutch Pharmacovigilance Centre (LAREB). Current projects investigate the participation of patients in pharmacovigilance, and the implementation of drug safety information to individual patients.

Medication safety issues in third world countries is a relatively new topic. As part of the grant obtained from NUFFIC on “Strengthening the Role of Clinical Pharmacy in Vietnam”, a project was started in 2008 on antituberculosis agents in that country.

The focus on Healthy Ageing, expressed by the UMCG, offers challenging opportunities for the sub-programme.
Changes in the period 2003-2008
Prof. Dr. Johan J. de Gier joined the group as a part-time professor in 2003. Dr. Katja Taxis was attracted as a tenure track assistant professor in 2004. She recently (November 2009) became an adjunct professor. Prof. Dr. Anton J.M. Loonen has been a visiting professor since 2004 occupying the extraordinary chair Pharmacotherapy of Psychiatric Patients (0.2 FTE). Prof. A.C. (Kees) van Grootheest, director of the Dutch Pharmacovigilance Centre (LAREB), has been visiting professor since 2008, occupying the extraordinary chair Pharmacovigilance (0.2 FTE).
Prof. Brouwers retired as per August 2009. Prof. de Gier is head of the department ad interim, until a new full professor has been appointed. The selection procedure is in progress at the time of writing this self-evaluation report.

Funding and impact
Four externally financed projects were running during the period 2003-2008, amounting to 1.2 M€. Financers were the EU (FP6 project DRUID), the Royal Dutch Association for the Advancement of Pharmacy (KNMP) and the MAG (Management Apothekers en Gezondheidszorg) Foundation.

The sub-programme is a partner in the EPHOR institute, the Dutch centre of experts on ‘Pharmacotherapy for Elderly’, since 2008. Prof Brouwers is the part-time managing director of EPHOR.

The group has an average of 20 international publications annually in good journals in the field. In addition, 19 (chapters in) books have been published, as well as a series of professional publications (in Dutch). The latter is also important because of the high relevance of the work of the group for the national professional field. The group had 8 PhD defences.
Section 4: Research staff

In Table 3 the total GRIP research staff is depicted in terms of full-time equivalents (FTE) contribution to research activities.

<table>
<thead>
<tr>
<th>Year</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>FTE</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
<tr>
<td>Tenured staff</td>
<td>10.24</td>
<td>9.84</td>
<td>10.32</td>
<td>8.82</td>
<td>8.46</td>
<td>8.76</td>
</tr>
<tr>
<td>(29)</td>
<td>(30)</td>
<td>(30)</td>
<td>(27)</td>
<td>(28)</td>
<td>(27)</td>
<td></td>
</tr>
<tr>
<td>Full professors*</td>
<td>4.14</td>
<td>4.94</td>
<td>5.02</td>
<td>5.02</td>
<td>5.66</td>
<td>5.76</td>
</tr>
<tr>
<td>(11+1)</td>
<td>(10+4)</td>
<td>(10+5)</td>
<td>(8+7)</td>
<td>(9+9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associate professors</td>
<td>2.50</td>
<td>1.40</td>
<td>1.80</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>(7)</td>
<td>(4)</td>
<td>(5)</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assistant professors</td>
<td>3.40</td>
<td>3.20</td>
<td>3.10</td>
<td>2.80</td>
<td>1.80</td>
<td>2.00</td>
</tr>
<tr>
<td>(9)</td>
<td>(10)</td>
<td>(8)</td>
<td>(6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other senior staff</td>
<td>0.20</td>
<td>0.30</td>
<td>0.40</td>
<td>0.40</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td>(1)</td>
<td>(2)</td>
<td>(2)</td>
<td>(2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-tenured staff</td>
<td>11.79</td>
<td>11.60</td>
<td>11.33</td>
<td>11.86</td>
<td>7.79</td>
<td>10.01</td>
</tr>
<tr>
<td>(19)</td>
<td>(20)</td>
<td>(18)</td>
<td>(18)</td>
<td>(15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhD-students</td>
<td>30.98</td>
<td>29.93</td>
<td>26.95</td>
<td>24.15</td>
<td>23.28</td>
<td>27.65</td>
</tr>
<tr>
<td>(57)</td>
<td>(56)</td>
<td>(62)</td>
<td>(66)</td>
<td>(67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>30.98</td>
<td>29.93</td>
<td>26.95</td>
<td>24.15</td>
<td>23.28</td>
<td>27.65</td>
</tr>
<tr>
<td>(49)</td>
<td>(47)</td>
<td>(46)</td>
<td>(44)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non employed</td>
<td>8/----</td>
<td>9/----</td>
<td>16/----</td>
<td>22/----</td>
<td>25/----</td>
<td>29/----</td>
</tr>
<tr>
<td>(14.04%)</td>
<td>(16.07%)</td>
<td>(25.81%)</td>
<td>(33.33%)</td>
<td>(37.31%)</td>
<td>(40.28%)</td>
<td></td>
</tr>
<tr>
<td>Total research staff</td>
<td>53.01</td>
<td>51.36</td>
<td>48.60</td>
<td>44.83</td>
<td>39.52</td>
<td>46.42</td>
</tr>
<tr>
<td>(105)</td>
<td>(106)</td>
<td>(110)</td>
<td>(111)</td>
<td>(110)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Explanation: Tenured staff members (full professor, associate professor, assistant professor and other senior staff) are expected to spend 40% of their time on research and 60% on education and/or management. Clinical researchers also have obligations for patient care. For the sake of simplicity, a normative approach has been taken to establish input figures. Accordingly, the research input in GUIDE of tenured researchers is set at 40% (0.4 FTE) for non-clinical researchers, 30% (0.3 FTE) for clinical researchers, 90% (0.9 FTE) for non-tenured staff members (e.g. postdoctoral fellows) and 70% (0.7 FTE) for PhD students with an employment contract. For PhD students with no employee status (student status), expression as FTE is not appropriate.

* In between brackets after the + symbol, the number of adjunct and extraordinary professors is given.

The most significant conclusion from Table 3 is that during the period 2003-2008 the tenured staff decreased from 10.2 to 8.8 FTE. Note that the table does not discriminate between the 1st, 2nd and 3rd money flow. For a more detailed analysis of the financial position of GRIP please refer to section 5 of the Addendum (Earning capacity).

The number of full professors increased over the years, at the cost of the number of associate and assistant professors. An important reason for this is promotion of existing personnel according to the human resource programme ‘Career Paths in Science’ introduced by the faculty FMNS in 2001. With this programme, a new and for The Netherlands revolutionary- tenure-track system was created. The system is a transition from a formation-driven policy to a career-driven human resources system. Young talent receives the opportunity to develop an independent research line, to eventually grow into the next generation leaders in science.

Table 4 shows the number of PhD students in GRIP over the period 2003-2008. The number increased over the years from 57 in 2003 to 72 in 2008. It is important to note that the faculty FMNS did not appoint directly funded new employed PhD students after 2005. Employed PhD students, appointed after 2005, are all financed from external sources. In November 2009, GRIP had 16 bursary PhD students financed by the faculty FMNS, 14 bursary PhD students financed from external sources, and 45 employed PhD students financed from external sources. This means that at present about 80% of the PhD students are funded from external sources.
<table>
<thead>
<tr>
<th>Number of PhD students</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>employed</td>
<td>57</td>
<td>56</td>
<td>62</td>
<td>66</td>
<td>67</td>
<td>72</td>
</tr>
<tr>
<td>non-employed</td>
<td>8</td>
<td>9</td>
<td>16</td>
<td>22</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>% non-employed</td>
<td>14.04%</td>
<td>16.07%</td>
<td>25.81%</td>
<td>33.33%</td>
<td>37.31%</td>
<td>40.28%</td>
</tr>
</tbody>
</table>
Section 5: Earning capacity

The contribution of direct funding (1st money flow), research grants (2nd money flow) and contract research (3rd money flow) to the total research funding of GRIP is presented in Table 5. Figures are given both in full-time equivalents (FTE) research staff and costs in k€.

Table 5  Overview of research funding at the level of GRIP

<table>
<thead>
<tr>
<th></th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FTE (%)</td>
<td>FTE (%)</td>
<td>FTE (%)</td>
<td>FTE (%)</td>
<td>FTE (%)</td>
<td>FTE (%)</td>
</tr>
<tr>
<td><strong>Funding:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct funding (1)</td>
<td>25.19(47.52)</td>
<td>24.64(47.98)</td>
<td>21.32(43.87)</td>
<td>17.05(38.02)</td>
<td>12.27(31.03)</td>
<td>12.92(27.84)</td>
</tr>
<tr>
<td>Research grants (2)</td>
<td>9.15(17.26)</td>
<td>7.20(14.02)</td>
<td>7.38(15.18)</td>
<td>5.58(12.44)</td>
<td>8.21(20.77)</td>
<td>12.61(27.17)</td>
</tr>
<tr>
<td>Contract research (3)</td>
<td>18.67(35.21)</td>
<td>19.52(38.01)</td>
<td>19.90(40.95)</td>
<td>22.21(49.54)</td>
<td>19.05(48.19)</td>
<td>20.89(45.00)</td>
</tr>
<tr>
<td><strong>Total funding</strong></td>
<td>53.01(100)</td>
<td>51.36(100)</td>
<td>48.60(100)</td>
<td>44.83(100)</td>
<td>39.52(100)</td>
<td>46.42(100)</td>
</tr>
<tr>
<td><strong>Expenditure:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personnel costs (k€)</td>
<td>2,575.3</td>
<td>2,685.1</td>
<td>2,758.6</td>
<td>2,551.1</td>
<td>2,345.1</td>
<td>2,772.5</td>
</tr>
<tr>
<td>Costs non-employed PhD students (k€)</td>
<td>127.6</td>
<td>147.2</td>
<td>237.7</td>
<td>289.6</td>
<td>324.2</td>
<td>484.4</td>
</tr>
<tr>
<td><strong>Total expenditure</strong></td>
<td>k€ 3,762.5</td>
<td>k€ 3,942.6</td>
<td>k€ 4,179.5</td>
<td>k€ 3,969.5</td>
<td>k€ 3,733.7</td>
<td>k€ 4,541.1</td>
</tr>
</tbody>
</table>

Explanation The expenses for research include both personnel and other costs. The personnel costs comprise not only the actual salaries of the personnel, but also social security charges, the contribution to the provision “wachtgelden” (i.e. the obligation to provide personnel a reduced pay in case of unemployment for a restricted period of time; not applicable for direct funding), the costs for temporary workers or agency staff and other costs like allowances for child care and commuting. Although non-employed PhD students do not represent research FTE, the costs of these PhD students have been included. Other costs include exploitation costs (consumables) and investment debits, and are calculated based on a long-term average of 27.7%.

1  Direct funding by the university;
2  Funding obtained in national and international scientific competition (e.g. grants from NWO and the European Research Council programs ‘Advanced Grant’ and ‘Starting Independent Researcher Grant’);
3  Funding for specific research projects obtained from external organizations, such as industry, governmental ministries, European Commission (Framework programs) and charity organizations.

Table 5 shows that the direct funding of the research programme decreased considerably (25.1 to 13.0 FTE). This is mainly caused by reduction in the number of employed PhD students. In 2005 the faculty FMNS changed its policy for funding of PhD students and now finances bursary PhD students only; however in this table these positions are not included in the “direct funding FTE’s”, are included under Expenditure in this table.

From Table 5, it can be concluded that the percentage of acquired funding (summation of research grants, royalties and contract research) increased from 52% to 72% during the evaluation period. However, this conclusion is not valid since direct funding shifted from employed PhD students to non-employed bursaries during the evaluation period. As about 50% of the GRIP bursaries are directly funded, it can be calculated that the contribution of external funding rose from 50% in 2003 to about 60% in 2008.

In Table 6, we give an overview of external partners that finance research at GRIP, research grants (2nd money stream) and contract research (3rd money stream).
Table 6  Overview of external partners that finance research at GRIP.

<table>
<thead>
<tr>
<th>2nd money stream (research grants)</th>
<th>3rd money stream (contract research)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NWO (Netherlands Organization for Scientific Research)</td>
<td>Solvay Pharmaceuticals</td>
</tr>
<tr>
<td>NWO Veni (Innovative Research Incentives Scheme)</td>
<td>Spark Holland</td>
</tr>
<tr>
<td>NWO Vidi (Innovative Research Incentives Scheme)</td>
<td>Tibotec (J&amp;J)</td>
</tr>
<tr>
<td>NWO Vici (Innovative Research Incentives Scheme)</td>
<td>Top Institute Pharma (TI Pharma; see Table 7)</td>
</tr>
<tr>
<td>NWO Biopartner</td>
<td>Top Institute Biomedical Materials (TI BMM)</td>
</tr>
<tr>
<td>STW (Netherlands Technology Foundation)</td>
<td>Top Institute Food &amp; Nutrition</td>
</tr>
<tr>
<td>STW Valorisation</td>
<td>Trans Tech Pharma</td>
</tr>
<tr>
<td>ZonMW (Netherlands Organization for Health Research and Development)</td>
<td>Wyeth</td>
</tr>
<tr>
<td>DFG (Deutsche Forschungs Gemeinschaft)</td>
<td>Charity funds (collectebusfondsen)</td>
</tr>
<tr>
<td>Industry</td>
<td></td>
</tr>
<tr>
<td>European Union (EU)</td>
<td>Astma Fonds (Netherlands Asthma Foundation)</td>
</tr>
<tr>
<td>EU FP6 (Framework Programme 6)</td>
<td>KWF Kankerbestrijding (Dutch Cancer Society)</td>
</tr>
<tr>
<td>EU Marie Curie</td>
<td>Nierstichting (Dutch Kidney Foundation)</td>
</tr>
<tr>
<td>EU EFRO/KOP</td>
<td>(Semi-)governmental organizations</td>
</tr>
</tbody>
</table>
| EU Interreg | Nuffic (Netherlands Organization for International Coopera-
| | tion in Higher Education) |
| | Ministry of VWS (Health, Welfare and Sport) |
| | Senter Novem (agency of the Dutch Ministry of Economic Affairs) |
| | TCNN (Technology Center North Netherland) |
| | Proinno Europe |
| Charitable funds | Other |
| Astma Fonds (Netherlands Asthma Foundation) | Accare (Child and Adolescent Psychiatry in North Netherland) |
| KWF Kankerbestrijding (Dutch Cancer Society) | DGV (Dutch Institute for Rational Use of Medicine) |
| Nierstichting (Dutch Kidney Foundation) | GGZ Drenthe (Netherlands Mental Health) |
| | Jan Kornelis de Cock Stichting |
| | KNMP (Royal Dutch Society for the Advancement of Pharmacy) |
| | Stichting de Proeftuin Groningen |
| | Stichting Dioraphte |
| | Stichting Mag |
| | Stichting Rots |
| | TCNN (Technology Centrum Noord Nederland) |
| | WHO (World Health Organization) |

Over the period 2006 – 2012, GRIP has participated / will participate in 12 TI Pharma projects. A total of 71.8 man years of GRIP personnel are employed in these projects, financed by the Dutch government and the pharmaceutical industry. Employed PhD students make up a substantial portion of this personnel. Besides research articles, there will be a substantial number (11) of PhD theses produced in the TI Pharma projects. Several of these TI Pharma projects constitute collaborations between GRIP sub-programmes and / or the University Medical Center Groningen (UMCG).
In Table 7, we give an overview of all the TI Pharma projects in which GRIP is involved.

<table>
<thead>
<tr>
<th>Title</th>
<th>Project period</th>
<th>Personnel at GRIP (man years)</th>
<th>GRIP research groups involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNF ligands in cancer</td>
<td>01 Mar 2006 – 01 Jul 2012</td>
<td>4 yr PhD student, 1.6 yr postdoc, 1 yr technician</td>
<td>PB (+UMCG)</td>
</tr>
<tr>
<td>The CSF proteome / metabolome as primary biomarker compartment for CNS disorders</td>
<td>01 Nov 2006 – 01 Nov 2011</td>
<td>4 yr PhD student, 0.3 yr technician</td>
<td>AB</td>
</tr>
<tr>
<td>&quot;Hot medicines&quot;: breaking the cold chain requirement for polypeptide-based priority medicines</td>
<td>01 Sep 2006 – 01 Sep 2011</td>
<td>4 yr PhD student</td>
<td>PTB</td>
</tr>
<tr>
<td>Design quality into products</td>
<td>01 Jul 2007 – 01 Jul 2011</td>
<td>8 yr PhD student</td>
<td>PTB</td>
</tr>
<tr>
<td>The neurophysiological role of the endocannabinoid system in support of smoking cessation, fighting addiction and treating cognitive decline</td>
<td>01 Jan 2007 – 01 Jul 2011</td>
<td>4 yr PhD student</td>
<td>BS</td>
</tr>
<tr>
<td>Nanoscience as a tool for improving bioavailability and BBB penetration of CNS drugs</td>
<td>01 Jan 2007 – 01 Jun 2012</td>
<td>4 yr PhD student, 4 yr postdoc, 2 yr technician</td>
<td>PTT / PTB (+UMCG)</td>
</tr>
<tr>
<td>Investigation of drug induced weight alterations to identify novel therapeutic strategies for the treatment of obesity, dyslipidemia and diabetes</td>
<td>01 Nov 2006 – 01 Apr 2012</td>
<td>4 yr postdoc</td>
<td>AB (+ Neuroendocrinology (CBN / UMCG))</td>
</tr>
<tr>
<td>Mechanism-based PK/PD modeling platform</td>
<td>01 Oct 2007 – 01 Oct 2012</td>
<td>8 yr PhD student, 4 yr postdoc</td>
<td>PTT</td>
</tr>
<tr>
<td>Acute and chronic inflammatory responses</td>
<td>01 Oct 2007 – 01 Oct 2012</td>
<td>4 yr PhD student, 1.2 yr technician</td>
<td>AB (+UMCG)</td>
</tr>
<tr>
<td>Towards novel translational safety biomarkers for adverse drug toxicity</td>
<td>01 Oct 2007 – 01 Sep 2012</td>
<td>4 yr PhD student, 1 yr technician</td>
<td>PTT</td>
</tr>
<tr>
<td>Efficient eradication of (multidrug) resistant bacteria</td>
<td>01 Feb 2008 – 01 Feb 2010</td>
<td>2 yr PhD</td>
<td>PTB</td>
</tr>
<tr>
<td>Mondriaan project, The Dutch healthcare landscape as a population laborator</td>
<td>01 Jun 2009 – 01 Jun 2012</td>
<td>2.7 yr ICT expert</td>
<td>PP (+UMCG)</td>
</tr>
</tbody>
</table>
Section 6: Embedding and academic reputation

GRIP has numerous collaborations, both national and international, with academia, (semi)governmental organisations and industry (see also Section 5 of the Addendum; ‘Earning capacity’). This is reflected in an increasing number of acquired research grants and contract research projects, all obtained in competition (see also the previous section, describing the earning capacity of GRIP, and the following section, describing the scientific output of GRIP). As a result, there are many joint publications in international peer-reviewed journals, and many PhD theses produced. To improve the interaction between the various sub-programmes of GRIP, monthly seminars are organised that focus on areas of common interest.

The academic reputation of GRIP’s staff members is well illustrated by an increased international visibility, by extended collaborations with leading groups in the field of pharmaceutical sciences, (co-)organization of various international meetings, representation in international scientific committees and editorial boards, and considerable numbers of invited lectures and visiting international scientists.

For details, we refer to the chapters of the programmes BDDD, S&A and GRIAC and to the self evaluation of SHARE.

Also, the national and international visibility of the GRIP researchers contributes to high societal relevance and valorisation of research (see also Section 8 of the Addendum; ‘Societal relevance and valorisation’).

International cooperation and contacts with colleagues abroad is also important for the exchange of students who perform research projects as part of their master programme. Currently, approximately 15 master students in pharmacy per year go abroad for a period of 5-6 months. Such projects are supervised by a staff member in Groningen (who bears the final responsibility) and a staff member of the host institute. Scientific publications originate from such projects on a regular basis. Students from abroad are also hosted in Groningen to pursue research projects.
Section 7: Scientific output

In Table 8 the scientific output of GRIP is shown.

<table>
<thead>
<tr>
<th>Table 8</th>
<th>Main categories of research output at the level of GRIP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003</td>
</tr>
<tr>
<td>Refereed articles</td>
<td>133</td>
</tr>
<tr>
<td>Books and Book chapters</td>
<td>5</td>
</tr>
<tr>
<td>PhD theses</td>
<td>8</td>
</tr>
<tr>
<td>Patents</td>
<td>9</td>
</tr>
<tr>
<td><strong>Total publications</strong></td>
<td><strong>155</strong></td>
</tr>
</tbody>
</table>

Despite the decrease in funded staff (Table 3), the scientific output of peer-reviewed articles is quite constant for GRIP, with an average of about 140 per year. There is also a steady stream of contributions to books from the research staff. If applicable, scientific findings are patented.

The number of defended PhD theses has fluctuated over the years. The average number will increase in coming years as a result of the increased number of PhD students now involved in research (see also Table 4 of the Addendum).

GRIP has a considerable number of so-called external PhD theses (about 20% of the total). Involved are persons from outside the University of Groningen (employed elsewhere), who pursue their PhD thesis under the supervision of a promoter from GRIP. The high number of such PhD theses illustrates the good ties of GRIP with the professional field.

Over the period 2003-2008, the success rate (number of PhD students that finished their thesis versus the number that started) of the GRIP PhD programme has been 82%.
Section 8: Societal relevance and valorisation

Societal relevance
In general, pharmaceutical research has high societal relevance. The overall aim is to design and develop new and improved drugs, to make existing therapies more effective and safe.

Examples from GRIP sub-programmes are given below.

- The first dry powder inhaler developed by the PTB group (Novolizer®) reached the market, and is being produced for several drugs. The Genuair® inhaler is currently in Phase III studies.
- The second-generation dry powder inhaler (the Twincer®) has passed the clinical Phases I and II and will enter Phase III studies in 2010. The indication will be cystic fibrosis, a typical orphan disease (PTB).
- The sugar-glass stabilization technology yielded tremendous results for influenza vaccine, and opened the possibility of improved vaccination strategies. Other stabilization strategies were useful for pandemic preparedness (oseltamivir), and in the development of a heat-stable formulation of oxytocin. This last example has the potential to save the life of 125,000 women each year in sub-Saharan Africa (PTB).
- Clinical studies investigating the therapeutic use of the enzyme, alkaline phosphatase, are now in phase IIA. These studies include patients with septic shock, ulcerative colitis, and acute kidney injury, patients with coronary artery bypass graft surgery, and patients with rheumatoid arthritis. Significant clinical improvement or reduced death has been reported (PTT).
- Rotigotine (N0437), an antiparkinson drug developed in the Medicinal Chemistry group in the nineties, is now successfully being marketed worldwide as Neupro®.
- An experimental antidepressant developed by the BS sub-programme in collaboration with Lundbeck was evaluated in a Phase 2 study. A significant clinical improvement has been reported.
- Successful implementation of the project “Care for … folic acid for those women considering pregnancy” in Dutch community pharmacies (PE2).
- Using the EUROCAT network of birth defect registries with improved drug exposure information in the dataset, a case-control study evaluating the risk of lamotrigin on orofacial clefts was successfully performed (PE2).
- Safety issues and possible interventions to improve medicinal use is a main research programme in the PPC sub-programme. This has resulted in several studies involving vulnerable patient groups such as neonates, psychiatric patients and frail elderly.
- Research projects with the elderly have investigated the safety of peri-operative drug management as well as drug safety for nursing-home patients. The latter has lead to the establishment, in collaboration with the UMCG, of a unique database on a cohort of nursing-home patients with the aim to include 5,000 persons from the three northern provinces of the Netherlands over the next few years (PPC).
- The NUFFIC project “Strengthening the Role of Clinical Pharmacy in Vietnam”, started in 2008 (4 years, 2.2 ME). The project aims to bring clinical pharmacy in Vietnam to a higher, more developed level in daily practice. This is being achieved by GRIP, through the introduction of a programme on clinical pharmacy in the pharmacy curriculum and by developing human resources, including PhD studies conducted by young Vietnamese staff at the University of Groningen. A good example is a project directed at the use of antituberculosis drugs in Vietnam.
- Research in the field of in vitro ADME-tox contributes strongly to the reduction of animal use, which is an increasingly important ethical issue, and to a better prediction of human ADME-Tox by developing in vitro technologies with human tissues (PTT).
- The computer programme MwPharm has been developed and is continuously updated, and is marketed by the spin-off company Mediware BV. MwPharm is recommended by the Dutch Association of Hospital Pharmacists (NVZA) and used in many hospitals in the Netherlands and several other countries for therapeutic management of individual patients in daily practice.
- A new target for the treatment of asthma based on innovative research by the Molecular Pharmacology group has been adopted for drug development by industry.
- Novel technology for designing proteins leads to more effective biopharmaceuticals. A receptor-specific variant of TRAIL was shown to be superior in an ovarian cancer animal model and a clinical development plan has now been drafted in collaboration with industry (PB).
- The research on Anthriscus as a source for podophyllotoxin contributes to a sustainable production system for the widely used chemotherapeutic agents Etoposide® and Teniposide® (PB).
- A number of biomarker candidates for cervical cancer have been discovered by tissue proteomics using laser microdissection. These marker candidates are presently being validated and an attempt is being made to translate them into serum diagnostic tests for the early detection of cervical cancer (AB).
- The development of data-processing algorithms has resulted in a number of software applications that are presently being implemented on the national life science computing network (LifeScience GRID, SARA computing facilities) to facilitate use by non-experts in the ‘omics’ community (AB).
Various studies were undertaken to underpin decisions on vaccination strategies from a cost-effectiveness perspective (for example, meningococcal C, pneumococcal, HPV and influenza) (PE2).


Valorisation

Extensive royalties are being generated by a novel, in-house developed inhalation technology (Novolizer®) (PBT).

Extensive royalties have been generated by the sugar-glass technology (PBT).

During the period 2003-2008, several spin-off companies were created by scientists from GRIP. These spin-off companies are located in or in the immediate vicinity of the GRIP research laboratories. As a result, there is excellent interaction between the University and these companies, exchange of expertise, infrastructure and researchers. This leads to an inspiring and improved research environment. PhD students are financed as well from the finances that are generated by these research activities.

Overview of spin-off companies

In 2003 the company Pharma-aware (now called AM-Pharma BV) was founded based on a patent of Prof. Dr. K. Poelstra. The total investment in this company has been approximately 25 million euro. Alkaline phosphatase was the lead compound, and this is currently being successfully tested in patients (phase Ila clinical trials).

In 2003 BiOrion Technologies BV was founded by Prof. Dr. K. Poelstra. The company is based on a patent describing new drug carriers for growth factor receptors. The total investment in this company was 750 k€. Clinical trials are in preparation.

The computer programme MwPharm, developed by Dr. J.H. Proost and continuously updated within the PTT sub-programme, is marketed by the spin-off company Mediware BV.

In 2004 Brains-on-line BV (www.brainsonline.org) was founded by Prof. Dr. B.H.C. Westerink. The company applies in vivo pharmacology methods (including brain microdialysis). About 30 FTE employees are currently involved. The company has a strong interaction with the BS group (funding and external PhD students).

Health Economics Consultancy & Technology Assessments (HECTA) is a spin-off company founded by Prof. Dr. M.J. Postma. The aims of HECTA are to perform health-economic and pharmacoeconomic analyses, and to enhance this type of research in the PharmacoEpidemiology and PharmacoEconomics group.

Triskel Therapeutics is a spin-off company founded by Prof. Dr. W.J. Quax. The company will develop experimental therapeutics based on TRAIL proteins.
Section 9: SWOT analysis

Strengths

- **Strong interface position.** GRIP has a strategic position between the basic disciplines of the Faculty of Mathematics and Natural Sciences (FMNS) and the (pre)clinical disciplines in the University Medical Center Groningen (UMCG). This intermediate position fosters translational research and opens possibilities for multidisciplinary strategies. GRIP participates in the Groningen Graduate School of Sciences (GGSS), but also contributes to the PhD educational programme of the Groningen Graduate School of Medical Sciences (GGSMS). GRIP’s PhD students profit from this position.
- **Embedment in the medical faculty.** The strong interaction of pharmaceutical sciences with medical sciences through participation in the GGSMS is unique and offers excellent opportunities for preclinical and clinical drug research. This embedment provides intensive interactions in a stimulating multidisciplinary pre-clinical and clinical research environment with highly reputable investigators.
- **Quality of research.** GRIP has a large number of peer-reviewed articles in top 30% journals in the respective fields.
- **Successful external research funding.** External funding has now become the major money flow supporting GRIP’s research programme.
- **High societal impact.** Several drugs or related products developed in-house are on the market or are in phase 1, 2 or 3 clinical trials. Results from studies on economic, and/or epidemiologic aspects of drug use including pharmaceutical care (e.g. vulnerable patients groups), have a high societal impact. Improved formulations (by unique stabilizations of essential drugs or vaccines) have a large societal and medical impact in developing countries.
- **Collaboration with industry.** The broad research programme offers many attractive topics for collaboration with pharmaceutical industry. Several collaborations with industrial partners provide a steady and substantial source of financing. An example is the participation of GRIP in several programmes of the funding programme, Top Institute Pharma.
- **Valorisation.** The intellectual property policy adopted by the Executive Board of the University has been very fruitful for GRIP. Initiation of several small innovative companies (spin-offs) and substantial royalties derived from licenses on intellectual property improve the financial situation of the sub-programmes involved. A strong portfolio of new patents has been generated over the past few years by various sub-programmes.
- **Infrastructure and expertise.** The available unique expertise combined with the highly advanced infrastructure fosters investigations from molecular biology to the intact organism and enables the translation of animal model findings to humans, starting at the level of the cell and tissue and ending in the whole patient.

Weaknesses

- **Teaching responsibilities.** Although teaching is considered as fundamental for the mission of GRIP, the excessively high teaching load has put research – including the writing of grant applications - under pressure. However, as the result of additional funding recently made available (based on a loan by the Executive Board of the University and facilitated by the Faculty of Mathematics and Natural Sciences) we expect improvement here.
- **Representation at the international level and visibility.** Although several GRIP staff members are represented in (inter)national forums and review committees (e.g. NWO and STW), these activities may be increased.

Opportunities

- **Career perspectives for staff members.** In 2002, the Faculty of Mathematics and Natural Sciences introduced a transparent career policy (tenure-track system) for junior staff members. It enables young, talented researchers to establish an independent research line.
- **Further commercialisation of intellectual property.** In the various sub-programmes, and the development of promising new drugs, innovative products and methods are underway. The staff members have gained extensive expertise in obtaining intellectual property rights and the commercialisation of their findings, as evidenced by several spin-off activities. This expertise will provide more opportunities in the future, as governments increasingly acknowledge the importance of knowledge valorisation and stimulate this with financial sources.
- **New investments.** The decision of the Executive Board of the University to make more financial resources available to GRIP in the form of a “loan” will stimulate research capacity and quality. New tenure-tracks will open new research lines, thereby reinforcing the research position of GRIP. Re-establishment of a new Drug Design group will create a unique opportunity to initiate chemical research within a medical and biological environment.
• **Quality of research output.** Although GRIP has the tradition to publish in high ranking peer reviewed journals, it remains a challenge to enhance the number of articles in top 30% journals in the respective fields.

• **Healthy Ageing.** The focus on Healthy Aging expressed by the UMCG offers challenging opportunities for several GRIP sub-programmes.

**Threats**

• **Financial restrictions.** We are approaching a situation in which all PhD students and post-docs will be financed through external funding. In general, there is a risk of a significant deterioration of the funding landscape due to the world-wide financial crisis (e.g. less public funding for research; less financial support from industry).

• **Vacancies.** Due to shortage of highly qualified candidates, filling vacancies for PhD students and scientific staff members with highly talented scientists is difficult. This is especially true for persons with a pharmaceutical education, who seem to be less interested in an academic career. However, now we have succeeded in attracting highly talented people up to.
Section 10: Policy and future strategy

Response to the comments of the Peer Review Committee 2003

- The PRC recommended to merge the programmes Biomonitoring & Sensing, Medicinal Chemistry, and Molecular Pharmacology on grounds of content and leadership. In this regard it is of importance to note the decision that the Biomonitoring & Sensing group will be discontinued in 2010. The new Medicinal Chemistry group (in preparation; name of the Chair is changed into Drug Design) is expected to be an active member of the Division Synthesis & Analysis. The Molecular Pharmacology group entered GRIP in January 2008 and is fully integrated in the Division GRIAC.

- The PRC recommended to merge the programmes Pharmacokinetics, Toxicology, and Targeting and Pharmaceutical Gene Modulation. Both programmes are now firmly integrated in the Division BDDD. More details of this collaboration is given in Chapter 8 (e.g. see Section 8.2; ‘Description of the research unit composition’).

- The PRC recommended to pay special attention to the adequacy of equipment necessary to realise the programme Analytical Biochemistry. Chapter 9 describes in detail that the infrastructure of the sub-programme has highly improved during this evaluation period (although mainly based on external funding). Investments done ion mass spectrometry and HPLC equipment amounted to approximately 2,700 k€. The group has also invested considerably in informatics infrastructure. For more details see Chapter 9.1; ‘Changes/modifications/policy’.

- The PRC recommended to strengthen the academic focus of the programme Pharmaceutical Technology and Biopharmacy. During the present evaluation period much attention was given to fulfill this recommendation. Chapter 8 (Section 8.1; ‘Changes/modifications/policy of the Pharmaceutical Technology and Biopharmacy group’) describes the measurements that have been undertaken to fulfill this recommendation.

- The PRC recommended to strengthen the academic focus of the programme PharmacoEpidemiology and PharmacoEconomics. During the present evaluation period much attention was given to fulfill this recommendation. In this Addendum (Section 3; ‘Sub-programme PharmacoEpidemiology and PharmacoEconomics’ heading ‘Changes in the period 2003-2008’) we describe the measurements that were undertaken to cope with this criticism.

Period 2003-2008 – an overview

In 2002, GRIP presented a strategic plan for the period 2002-2008, in which our vision of the future of GRIP was mapped out. Priorities were e.g. new chairs in Genomics-based Target Finding and Validation and Pharmaceutical Care (0.5 FTE). The plan implied expansion of the scientific staff of the institute. Unfortunately, execution of this plan was not possible due to the rapidly deteriorating financial position of the faculty FMNS.

In 2005 the FMNS faculty, fully responsible for the first money flow financing of GRIP, reported major financial problems. As a consequence, in 2006-2007 a faculty-wide reorganisation was initiated, in order to improve the financial situation. Although GRIP clearly had a different view on its financial position within the faculty, the institute was severely affected by these measures. As a result, the number of staff members of GRIP appointed on direct funding and available for research and teaching duties decreased. Table 3 in Section 5 of the Addendum is of significance in this respect. The permanent staff was reduced by 14%. In addition, temporary positions (non-tenured staff and employed PhD students paid with direct funding) decreased (compare the situation in 2007-2008 to that in 2003-2004), but were partly compensated by an increased number of bursaries, financed by the faculty FMNS. The number of supporting staff positions became reduced, mainly by not filling in vacancies (not shown in the tables). The most serious consequence of the reorganisation was the discontinuation of the sub-programme Medicinal Chemistry (consisting of one full professor, two associate professors and two technicians).

At the same time, starting in 2006, the number of new students strongly increased (from around 100 in 2003, 2004 and 2005 to almost 200 in 2006, 2007 and 2008). As a result, the teaching workload of the permanent staff members in the institute rose to an unacceptable level. For 2008 it was calculated that they would spend 80-90 % of their time with teaching duties, while still maintaining research activities at a high level.

Remarkably, the ‘output’ of GRIP, in terms of research papers and number of PhD students (Table 4), as well as the total financial sources acquired by the institute (Table 5) did not shrink during the period 2003-2008. External funding of research projects (second and third money flow), obtained from competitive grant applications, compensated for the reduction of the first money stream. External funding has now become the major money flow to support the research programme of GRIP. The contribution of external funding to total funding has increased from 50% in 2003 to 60% in 2008. Unlike 2003, the majority of the PhD students is now funded by external projects. This is particularly noteworthy when one considers how large the time investment required is to prepare a grant proposal.
Reflecting the period 2003-2009, we acknowledge that GRIP went through a very difficult time. The institute was able to overcome this, because of the full commitment and solidarity of its staff and co-workers.

**Major changes in staff during 2004-2009**

Apart from the discontinuation of the Medicinal Chemistry sub-programme, two associate professors, Dr. A.J.M. (Bert) Schoonen and Dr. Gerard K. Bolhuis, retired early but without succession. The desired successions of two heads of research units, Prof. Dr. Dirk K.F. Meijer (Pharmacokinetics and Drug Delivery; retirement in 2004) and Prof. Dr. Johan Zaagsma (head of Molecular Pharmacology, retirement in 2005) were blocked and finally filled in by internal promotions, initially from associate to adjunct professor and in 2009 to full professor. (In our university an adjunct professor is on a track (career path) for a full professorship/chair. He/she has ius promovendi.)

**New chairs**

The part-time chair Pharmaceutical Engineering (0.2 FTE) was established in 2005 and is occupied by Dr. Kees van der Voort Maarschalk.

The following chairs (full professors) were realised in 2009 by internal promotions:

- Drug Metabolism and Toxicology (Prof. Dr. Gemy M.M. Groothuis; currently head of the sub-programme Pharmacokinetics, Toxicology and Targeting and adjunct professor since 2004)
- Drug Targeting (Prof. Dr. Klaas Poelstra; sub-programme Pharmacokinetics, Toxicology and Targeting and adjunct professor since 2004)
- Immunopharmacology (Prof. Dr. Herman Meurs, currently head of the sub-programme Molecular Pharmacology and adjunct professor since 2004)

Regarding the strategic plan for the period 2002-2008 the (externally financed) chair in Pharmaceutical Care (0.5 FTE, occupied by Prof. Dr. Johan J. de Gier) was converted into a structural professorship (although external funding is still required, until 2010).

In addition, we succeeded to acquire two extraordinary chairs, Pharmacotherapy of Psychiatric Patients (0.2 FTE; Prof. Dr. Anton J.M. Loonen; 0.2 FTE; 2004) and Pharmacovigilance (Prof. Dr. A.C. (Kees) van Grootheest; 0.2 FTE; 2007), which are financed from sources outside the faculty.

Through internal promotions (Career Paths in Science policy) the following adjunct professors (on tenure track) have been appointed:

- The chair Pharmacoeconomics (Prof. Dr. Maarten J. Postma; 2007);
- The chair Biosynthesis of Natural Products (Prof. Dr. Oliver Kayser; 2007);
- The chair Pharmacotherapy and Clinical Pharmacy (Prof. Dr. Katja Taxis; 2009).

The Molecular Pharmacology group was strengthened in 2005 when Dr. Martina Schmidt was appointed as assistant professor on the chair Molecular Pharmacology (financed by the Roland Franklin programme). In 2006 she was appointed adjunct professor.

**Tenure-track positions**

Vacancies for tenure-track positions were initially blocked as of 2005. They originated after the departure of Dr. Jan Maarten van Dijl (PB) in 2003, Dr. Marianne G. Rots (PGM) in 2007 and Dr. M. Begonia Barroso Fernandez (AB) in 2005.

These three vacant positions could recently be filled by permission of the Faculty Board:

Dr. Frank J. Dekker (PGM) (in 2007)
Dr. Gerrit J. Poelarends (PB) (in 2006)
Dr. Peter L. Horvatovitch (AB) (in 2008)

**Future strategy**

**New investments**

To overcome the problems caused by the double influx of new students, the Executive Board of the University provided additional funding (a loan) to GRIP, that was facilitated by the Faculty Board. This funding amounts to approximately 18 FTE. In September 2008 GRIP presented how it would use the loan in a strategic plan for the period 2009-2013. This plan describes how GRIP will cope with the scientific, educational and managerial challenges for the coming five years (including an expected increase in teaching load and staff retirements), in the perspective of current developments in pharmaceutical sciences and professional pharmacy. The goal is to attain a level of human resources in the
The institute necessary for a healthy balance between research and teaching activities. The additional funding means that the staff will be enlarged. This will result in more time for grant applications and thus in more output and income. The number of PhD theses is expected to increase accordingly.

It was decided to spend the loan as follows:

- Start a new sub-programme in Drug Design.
- New tenure-track assistant professors will be employed, in the sub-programmes Pharmacokinetics, Toxicology and Targeting; PharmacoEpidemiology and PharmacoEconomics; Molecular Pharmacology; Pharmaceutical Technology and Biopharmacy; and Drug Design. These tenure tracks will contribute to the start-up of new research lines, strengthening the research position of GRIP.
- Appointment of a number of lecturers to take a major part in teaching thereby making more time available for the existing staff to concentrate more on research.
- Appointment of a number of post-doc positions, to perform highly innovative research and support the staff in the supervision of the PhD students.

A new chair in Drug Design

Although the chair in Medicinal Chemistry was discontinued in 2006, there was full consensus within GRIP that this area belongs to the core business of education for the professional curriculum as well as for the domain of pharmaceutical sciences, and has to be maintained. Thus, re-establishment of this chair was assigned the highest priority. A new chair, named Drug Design, was created to cover this field. The group to be established will consist of a full professor, a tenure track assistant professor, a post-doc researcher, a technician and several PhD students.

The new chair will require considerable investment in order to attract high-level candidates. A structural report for a full professor in Drug Design is now available and the selection procedure is ongoing. The candidate for this position needs to have a strong background in organic synthesis with applications in pharmacy and in systems biology. He/she must be able to translate questions emerging from the area of pharmacology (e.g. drug targets) into drug design (including molecular modelling) and synthesis, followed by the evaluation of biological activity in relevant in vitro and in vivo test models. Integration of the required disciplines and collaboration with existing groups in the institute should result in a healthy environment for research on new chemical entities.

Re-establishment of the S&A programme

Currently the S&A programme is rather weak. Discontinuation of the Medicinal Chemistry group in 2006, the planned discontinuation of the Biomonitoring and Sensoring group in 2010, and the limited size of the Pharmaceutical Analysis group jeopardize the viability of this programme (see also Chapter 9). In order to change this situation several measures will be taken:

- The establishment of a new Drug Design group will revive the design and synthesis activities in the programme.
- GRIP and the Pharmaceutical Analysis group will deliver a strategic plan, in order to become full member of GUIDE again and to fully contribute to the S&A programme.

More emphasis on Pharmacotherapy and Clinical Pharmacy in relation to the UMCG

With the retirement of Prof. Koos Brouwers in 2009, the chair in Pharmacotherapy and Clinical Pharmacy became vacant. As this domain is increasingly important for the professional education of pharmacists and related clinical pharmacy research, it was decided to increase the size of the chair from 0.5 to 1.0 FTE. Preferably a senior hospital pharmacist (full professor), with close ties to practical aspects of pharmacotherapy, should fill this vacancy. As GRIP attributes high value to structural collaboration with the UMCG in general and the Department of Pharmacy and Clinical Pharmacy in particular, it is proposed that 0.2 FTE of this chair is concomitantly spent at that department. In addition, and in close collaboration with the UMCG, a part-time chair in Hospital Pharmacy (0.2 FTE) will be established in GRIP.

Possible merger of GRIP with the UMCG

A transfer of GRIP to the UMCG could provide various advantages. As GRIP is housed in the facilities of the UMCG, the local management and organisation is expected to profit from such merger. The ease to share the existing infrastructure is expected to further stimulate the collaboration between GRIP and the UMCG. Recently, an informal process was started to investigate the feasibility of such transfer.
List of abbreviations
General List of Abbreviations

AGIKO  Assistant-Geneeskundige in opleiding tot Klinisch Onderzoeker  
(Assistant in training for clinical researcher)
AIO  Assistant in Opleiding (Assistant in training)
ARWU  Academic Ranking of World Universities
AZG  Academisch Ziekenhuis Groningen (University Hospital Groningen)
BCN  Institute for Behaviour and Cognitive Neurosciences
BDDD  Biopharmaceuticals, Discovery, Design & Delivery
BKO  Basis Kwalificatie Onderwijs (Basic Teaching Qualification)
Bsik  Besluit Subsidies Investeringen Kennisinfrastructuur  
(Decision concerning the governmental funding of investments in the Dutch infrastructure of science)
CLDS  Centrum voor Lever,- Darm- en Stofwisselingsziekten  
(Centre for Liver, Digestive and Metabolic Diseases)
CPP  Citations Per Paper
CTMM  Center for Translational and Molecular Medicine
CVb  College van Bestuur (Governing Board)
CVC  Cardiovascular Centre
CWTS  Centre for Science and Technology Studies
DFG  Deutsche Forschungs Gemeinschaft (German Organisation for Scientific Research)
EC  European Credits
ECTS  European Credits Transfer System
ERC  European Research Council
ERIBA  European Research Institute on the Biology of Ageing
ESF  European Science Foundation
ESMO  European Society of Medical Oncology
EU  European Union
EUROCAT  European Surveillance of Congenital Anomalies
FMNS  Faculty of Mathematics and Natural Sciences
FMS  Faculty of Medical Sciences
FP  (European) Framework Programme
FTE  Full Time Equivalent
GECKO  Groningen Expert Centre for Kids with Obesity
GGSS  Groningen Graduate School of Science
GIKD  Groningen Institute for Kidney Diseases
GLP/GCP  Good Laboratory Practice/Good Clinical Practice
GMP  Good Manufacturing Practice
GRIAC  Groningen Institute for Asthma and COPD
GRIP  Groningen Research Institute of Pharmacy
GRK  Graduierten Kolleg
GUIDE  Groningen Institute for Drug Exploration
HANNNN  Healthy Ageing Network Northern Netherlands
IOP  Innovation-directed research programme
ITP  International Training Programme (Japan)
JSM  Junior Scientific Master class
KNAW  Koninklijke Nederlandse Academie van Wetenschappen  
(Royal Netherlands Academy of Arts and Sciences)
KNMP  Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie  
(Royal Dutch Society for the Advancement of Pharmacy)
KOP  Kennis Ontwikkeling in Partnerschap (Valorisation of knowledge together with a private partner)
KWF  Koninging Wilhelmafonds (Dutch Cancer Foundation)
MD/PhD  Doctor of Medicine / Doctor of Philosophy (Medical student being a PhD-student at the same time)
MLDS  Maag-, Lever-, Darm-Stichting (Dutch Digestive Foundation)
MPDI  Medical Pharmaceutical Drug Innovation (Topmaster programme)
NethER  Netherlands House of Education and Research
NFU  Netherlands Federation of University Medical Centres
NNOC  Northern Netherlands Oncology Center
NSN  Nierstichting Nederland (Dutch Kidney Foundation)
NUFFIC  Netherlands Organization for International Cooperation in Higher Education
NWO Nederlandse Organisatie voor Wetenschappelijk Onderzoek
(Netherlands Organisation for Scientific Research)
PB Pharmaceutical Biology
PEDP Pharmaco-Epidemiology & Drug Policy
PGM Pharmaceutical Gene Modulation
PI Principal Investigator
PRC Peer Review Committee
PTB Pharmaceutical Technology and Biopharmacy
PTT Pharmacokinetics, Toxicology and Targeting
QANU Quality Assurance Netherlands Universities
RUG Rijksuniversiteit Groningen (University of Groningen)
S&A Synthesis & Analysis
SBGG Business Generator Foundation Groningen
SEP Standard Evaluation Protocol
SHARE Institute for Health Care Research
STW Stichting Technische Wetenschappen
(Technology foundation, a subsidiary of NWO and the Ministry of Economic Affairs)
SWOT Analysis Strengths, Weaknesses, Opportunities, Threats
THES Times Higher Education System
TIBMM Top Institute Biomedical Materials
TIFN Top Institute Food & Nutrition
TIP Top Institute Pharma
TLC Transfer & Liaison Group
TNO Nederlandse Organisatie voor toegepast-natuur wetenschappelijk onderzoek
(Netherlands organisation for applied scientific research)
TRIO Transplantatie, Immunologie en Ontsteking (Transplantation, Immunology & Inflammation)
TSP Training & Supervision Plan
UCO UMCG Centre for Geriatric Medicine
UCP University Centre of Pharmacy
UMCG University Medical Center Groningen
UNAM Universidad Nacional Autónoma de México
UNIFESP Universidade Federal de São Paulo
USP Universidade de São Paulo
VSNU Vereniging van Samenwerkende Nederlandse Universiteiten
(Association of Universities in the Netherlands)
RIVM Rijksinstituut voor de Volksgezondheid en het Milieu
(National Institute for Public Health and the Environment)
ICIN Interuniversity Cardiology Institute of the Netherlands
IP Intellectual Property
ZON-MW Zorgonderzoek Nederland – Medische Wetenschappen (Health Care Research, Medical Sciences)
### List of abbreviations - funding bodies programme TRIO

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALW</td>
<td>Aard- en Levenswetenschappen (Earth and Life Sciences)</td>
</tr>
<tr>
<td>CUNY</td>
<td>City University of New York</td>
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<td>DFN</td>
<td>Diabetes Fonds Nederland (Diabetes Fund Netherlands)</td>
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<tr>
<td>DIV</td>
<td>Diversen (various)</td>
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<td>EC</td>
<td>European Community</td>
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<td>EST</td>
<td>Esteve Loboaratorios</td>
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<td>FPF</td>
<td>Fuji Photo Film B.V.</td>
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<td>GEC</td>
<td>Genzyme Corporation</td>
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<td>ITN</td>
<td>EC People Initial Training Network</td>
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<td>JPR</td>
<td>R.W. Johnson Ph. Research Institute</td>
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<td>MED</td>
<td>Medtronic</td>
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<tr>
<td>MOW</td>
<td>Ministerie van Onderwijs, Cultuur &amp; Wetenschappen (Ministry of Education, Culture and Sciences)</td>
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<tr>
<td>NIH</td>
<td>National Institute of Health</td>
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<td>NKB</td>
<td>Nederlandse Kankerbestrijding (Dutch Cancer Society)</td>
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<td>NLD</td>
<td>Nederlandse Lever &amp; Darm Stichting (Dutch Liver and Gut Society)</td>
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<td>NRF</td>
<td>Nutricia Research Foundation</td>
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<td>NWO</td>
<td>Nederlandse Organisatie voor Wetenschappelijk Onderzoek. (Netherlands Organisation for Scientific Research)</td>
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<td>Uitvoeringsorganisatie Twinningfaciliteit Suriname - Nederland</td>
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