# Content

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTENT</td>
<td>2</td>
</tr>
<tr>
<td>MISSION STATEMENT</td>
<td>3</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>4</td>
</tr>
<tr>
<td>PERSPECTIVES</td>
<td>9</td>
</tr>
<tr>
<td>THE YEAR 2012 IN REVIEW</td>
<td>11</td>
</tr>
<tr>
<td>HIGHLIGHTS</td>
<td>11</td>
</tr>
<tr>
<td>PRIZES/AWARDS</td>
<td>11</td>
</tr>
<tr>
<td>VISITORS</td>
<td>12</td>
</tr>
<tr>
<td>SPECIAL TOPICS</td>
<td>13</td>
</tr>
<tr>
<td>SPECIAL TOPIC 1: A large lung gene expression study identifying fibulin-5 as a novel player in tissue repair in COPD</td>
<td>13</td>
</tr>
<tr>
<td>SPECIAL TOPIC 2: Characterization and regulation of protocadherin-1, a novel gene for asthma</td>
<td>16</td>
</tr>
<tr>
<td>SPECIAL TOPIC 3: Improving drug delivery to the lungs</td>
<td>19</td>
</tr>
<tr>
<td>SPECIAL TOPIC 4: GSK-3 as a novel drug target for tissue remodeling in COPD</td>
<td>21</td>
</tr>
<tr>
<td>MEMBERS GRIAC 2012</td>
<td>24</td>
</tr>
<tr>
<td>GRIAC INTERNATIONAL COLLABORATION 2012</td>
<td>29</td>
</tr>
<tr>
<td>GRIAC SEMINAR PROGRAM 2012</td>
<td>31</td>
</tr>
<tr>
<td>GRIAC RESEARCH MEETINGS 2012 - PRESENTATIONS</td>
<td>33</td>
</tr>
<tr>
<td>GRIAC BRAINSTORM SESSIONS 2012</td>
<td>36</td>
</tr>
<tr>
<td>RESEARCH PROJECTS IN 2012</td>
<td>37</td>
</tr>
<tr>
<td>PUBLICATIONS 2012</td>
<td>44</td>
</tr>
<tr>
<td>DISSERTATIONS</td>
<td>44</td>
</tr>
<tr>
<td>PUBLICATIONS SCI JOURNALS</td>
<td>45</td>
</tr>
<tr>
<td>PUBLICATIONS IN DUTCH</td>
<td>55</td>
</tr>
<tr>
<td>BOOKS / BOOK CHAPTERS</td>
<td>55</td>
</tr>
<tr>
<td>CONTRIBUTIONS TO OTHER RESEARCH INSTITUTES (NOT GRIAC)</td>
<td>57</td>
</tr>
</tbody>
</table>
Mission statement

The mission of GRIAC is the multidisciplinary translational study of obstructive airway and pulmonary diseases and healthy ageing

Program leaders:

Prof. dr. G.H. Koppelman

Prof. dr. H.M. Boezen

Visiting address:
University Medical Center Groningen
Hanzeplein 1
NL-9713 GZ Groningen

Secretariat:
Dept. of Epidemiology
University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone: 31-50-361 0739
Fax: 31-50-361 4493
Email: h.m.boezen@umcg.nl and g.h.koppelman@umcg.nl

Website: www.griac.nl
Webmaster: Prof. dr. W. Timens
Introduction

Research on obstructive and pulmonary diseases as currently done within the Groningen Research Institute for Asthma and COPD (GRIAC) is performed on the edge between clinical and fundamental research, arising from a clinical-scientific background. GRIAC fits within the research of the University Medical Center Groningen, which has a central focus on healthy ageing. GRIAC is part of the governmentally accredited organization GUIDE (Groningen University Institute for Drug Exploration) which is embedded in the Groningen School of Medical Sciences (GSMS). Most research is funded by external support as given by NWO, Dutch Lung Foundation, the European Community and industry. The research conducted in Groningen results from internal discussions within the scientific forum of researchers on asthma and COPD in Groningen and somewhat broader in the Netherlands. It is also stimulated by new developments internationally. Most of the members of the board of GRIAC have an acknowledged international reputation.

Participating departments
There is an intensive collaboration between the researchers of GRIAC, consisting of our members from different disciplines. The disciplines involved are allergology, lab allergology and pulmonary diseases, epidemiology, general practice, molecular pharmacology, pathology, paediatric pulmonology and paediatric allergology, pulmonology and respiratory insufficiency. Collaboration is based on freedom, equivalence and consensus. There exists extensive collaboration with Departments of Dermatology, Gastroenterology, Genetics, Haematology, Medical oncology and Transplantation. Furthermore, collaboration exists with the Department of Analytical Biochemistry (University Center for Pharmacy).

How we collaborate
Every two weeks GRIAC organises research meetings for the whole institute in which both internal and external speakers are invited to venture new ideas and to challenge the audience. This constitutes also the forum in which different types of research are being presented to all
members of GRIAC. Members of GRIAC participate in very different aspects of asthma and COPD research, ranging from epidemiology, clinical allergology, pulmonology, pharmacology, and general practice to basic 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 organises twice yearly a research retreat and monthly “brainstorm sessions” on a specific topic. These brainstorm sessions are used to stimulate novel ideas for multidisciplinary research, and to discuss publication ideas for high impact journals.

During the GRIAC retreat the members of the Board of directors, scientific staff and post-docs of GRIAC discuss new developments of research during these days and look into new collaborations within their research, based on international developments in the field. During and after the research meeting investigators can discuss their grant proposals with the staff members, who are expert in a particular field.

Every five years GRIAC organises an internationally well-received symposium aimed at understanding the differences and similarities between asthma and COPD. In 2009, the eighth symposium “Bronchitis VIII” was held in June with again an excellent international faculty. In 2014, we plan the next Bronchitis meeting, Bronchitis IX, from 23-25th of June to be held in Groningen.

At every occasion of the defence of a Ph.D. thesis care is taken to also invite a top-researcher of a particular research field. He or she is asked to judge the thesis and participate in the Ph.D. defence on site, and, in addition, to give a presentation. When these external visitors are present, workshops for exchange of ideas are organised for both senior and junior researchers.

Finally, there are weekly meetings for junior researchers and staff members. At these meetings there is ample time for discussion on the set-up of research protocols, analyses and interpretation of results of research, and for preparation and improvements in concepts of abstracts, and oral and poster presentations at international meetings. These weekly GRIAC meetings aim to teach the understanding of 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. PhD courses in Epidemiology, statistics and genetic data analyses are being organised for members of GRIAC and others interested as well.

**Organisation**

Two program leaders lead the Institute. They have the following tasks:

- Representatives in GSMS
- Contacts with the UMCG
- Contacts with the University of Groningen
- Policy preparation for KNAW, FMW, UMCG and University of Groningen
- Preparing propositions for research development

The coordinators are advised extensively by the Board of GRIAC, consisting of senior members of the participating departments, who all have their own specific expertise. This board advises in all aspects of research. The board meets once monthly to exchange ideas and prepare policies.

**Research Program**

Research projects have to fit within the research program, describing the projects in their mutual cohesion. The tuning of projects and development into a program is the responsibility of the program leaders of GRIAC, in exchange with the Scientific Board of the Institute.
Program description
Research is aimed to stretch from bench to bedside and back with feedback loops. Central to the research is the goal to translate fundamental findings into the clinical situation and vice versa, i.e. translational medicine (see figure below).

Clinical research is conducted in different patient groups in comparison with normal control volunteers in order to unravel underlying mechanisms of the diseases (genetics, aetiology, pathogenesis, pathophysiology). Furthermore responses to intervention (mediated by either medical therapy, behavioural counselling, rehabilitation or other treatment modalities) as well as parameters of progression of disease are being assessed in relation to the underlying mechanisms of the disease.

Questions that are generated, but unanswered by clinical research, are approached using \textit{in vitro} cellular systems and \textit{in vivo} animal models. The other way around, hypotheses generated from \textit{in vitro} or \textit{in vivo} research are translated to the (clinical) human situation.

To this aim GRIAC focuses on the following main topics related to obstructive airway and pulmonary disease:
- Identification of risk factors for development, progression and remission of disease
- Identification of disease related genes and their functionality
- Unravelling the pathophysiology of allergen-, environment- and smoke- induced disease, in both humans and animal models
- Unravelling the effects of disease related inflammation on lung function, hyperresponsiveness and remodelling of large and small airways
- Defining new targets for intervention and evaluation of intervention strategies
- Development of non- or minor invasive tools to assess severity of disease and (side) effects of treatment.
Research area

The focus of research is on asthma and COPD, which involves the sub-programmes:

1. Epidemiology: Epidemiological studies on endogenous, environmental and lifestyle risk factors, both in general and patient-based populations, from prenatal onwards to old age.
2. Genomics: Studies on genes, epigenetics, 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 (pharmacogenomics).
3. Pathophysiology and pathogenesis of allergen, smoking and other lifestyle factors, and environment-induced diseases: 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. Assessment, modulation and intervention in disease severity, progression and remission: 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.

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 (epi-)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 projects (allergy and asthma: MeDALL; COPD: COPACETIC) on genetics and epigenetics 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 Center and Pharmacy, including the development of knock out and transgenic mouse models. 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. 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 longterm 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.
Perspectives

Asthma and COPD research takes place in a lively and rapidly changing field. New developments will encompass the functional genomics (including proteomics) of asthma and COPD.

The population for genetic analyses in asthma and COPD has been greatly expanded, and will be expanded even further, allowing replication and association studies. A number of international genome-wide association studies on asthma and COPD, including analysis on gene-environment interactions are ongoing, as well as gene methylation studies. This might lead to identification of novel genes and environmental factors playing a role in disease onset and progression. We will incorporate integrative genomic approaches in follow up studies. Functional studies on gene variations in asthmatic and healthy individuals have started, both in cells and in animal studies. Integration of longitudinal epidemiological data 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 and this can be integrated into systems medicine. It is envisaged that comparative genomics in animals, cell culture and humans will be initiated.

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 remain a 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 (also during pregnancy) on allergy development, asthma progression and susceptibility to develop COPD 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, and genomic research. Additionally, the genetic make-up of these subjects will be studied using genome wide screens, and significant findings will be replicated in a large number of population-based cohorts. Unravelling the shared genetics underlying asthma and COPD is also part of our focus on the origins of chronic airway diseases.

Exacerbations are sometimes life-threatening occurrences in patients with asthma and COPD, which may affect activities of daily living, increase symptoms, reduce quality of life, and affect disease outcome. 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. Novel techniques like bronchoscopic lung volume reduction in severe COPD patients are explored and evaluated in relation to their effects on e.g. daily physical activity.

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 established food-challenge unit is carrying out double-blind placebo-controlled challenges,
and is engaging in a number of studies. Ongoing are studies on the genetics of food allergy and IgE heterogeneity.

Physical inactivity, obesity, and a low grade systemic inflammation are increasingly recognized as important risk factors for the induction and clinical expression of asthma and COPD. The determinants and consequences of physical inactivity in COPD are systematically investigated in relation with co-morbid disorders. A physical activity enhancement strategy has been developed in collaboration with the faculty of human movement sciences, which may be used in the primary, secondary and tertiary echelons of our health care system. 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 and chronic ventilatory support in COPD. As both improve exercise capacity in emphysema this might lead to a more effective rehabilitation.

Notwithstanding the fact that understanding of a disease is of prime importance, the management of the disease as it exists in current patients is of importance. Thus, it is of great interest that transmural management of asthma and COPD is becoming more mature. Collaborative efforts of lung function departments, general practitioners and pulmonologists in addition to nurse practitioners help to provide better health care for individuals with respiratory symptoms that affect their daily life. This ultimately may improve the quality of life of individuals with asthma and COPD.

Output, visibility and (external) funding
Productivity of GRIAC is at present overall very good. Results in internal medicine and basic science have been published in top peer reviewed journals and patents have also been filed. GRIAC members have been urged to further focus on publication strategy. Asthma and COPD are highly prevalent in the general population, and thus focussing on these two syndromes is appropriate and has a high societal relevance. At current the priority of the institute is ranging from cellular models to the underlying disease models to the clinic (translational research) with transdisciplinarity as a major feature.

The national and international academic reputation of the senior GRIAC members can be weighted at its merits judging the invitations to address international congresses and their prominent roles in various national and international research and professional societies and working groups in addition to their role in EU collaborations. Moreover, since several of these GRIAC members are relatively young and proven to develop their high potential in their specific research field (e.g. epidemiology, pediatric and adult pulmonology, and molecular pharmacology), GRIAC can face its future with confidence. We will continue to invest in the training of young scientists in the field of obstructive airways and pulmonary disease, with a focus on multidisciplinary translational research. Given the true interdisciplinary nature of the institute, we feel confident that ongoing close collaboration of GRIAC members who share their in-depth knowledge of specific research fields in asthma and COPD will keep the institute at the internationally acknowledged level of excellence in the future, and that they will be able to generate sufficient recourses to finance this research. We have shifted our focus from smaller (e.g. Dutch Lung Foundation, University Medical Centers) towards larger (inter)national and interdisciplinary research grants (NWO TOP grants, European funding) as well as personal grants (VENI, VIDI, VICI and ERC grants) given the increasingly limited national budget. Within the U4 collaboration of the Universities of Groningen, Ghent, Göttingen and Uppsala, international collaborations are being prepared for PhD students to stay at 2 or 3 of these universities for an international PhD project.
The year 2012 in review

All contributions to the scientific work in GRIAC are of importance and are appreciated. It cannot be stressed enough that all the scientific output and results obtained are only possible due to the contribution of every single person who works within our research institute. Nevertheless, without disrespect to the work of members who are not specifically mentioned, we like to highlight some topics that drew particular attention in 2012.

Highlights

Dr. R. Gosens obtained a prestigious VIDI grant from the Dutch Scientific Organisation.

Prof. dr. D.S. Postma received an honorary doctorate at the University of Sheffield (UK).

Three grants from the Dutch Lung Foundation were obtained for the following projects:

- The functional relevance of microRNAs in COPD; elucidating their role in regulating pulmonary fibroblast function in COPD development. Dr. C-A Brandsma, Prof.dr. W. Timens, Prof.dr. DS Postma.

- Follistatin-like 1, a crucial factor in lung development, as a novel regulator in COPD. Dr. H. Maarsingh, Dr. M. van den Hoff, Prof.dr. M. Schmidt.

- Laminin α4 and α5 as regulators of airway inflammation and remodelling in allergic asthma. Dr. B.G.J. Dekkers, Prof. L.M. Sorokin, Prof. H. Meurs.

Dr. R. Gosens was appointed Associate Editor of Respiratory Research.

Prof. dr. M. Schmidt was appointed member of the Editorial Board of The American Journal of Physiology - Cell Physiology.

Dr. M.N. Hylkema and Prof. dr. H. Meurs were appointed member of the Editorial Board of The American Journal of Physiology – Lung Cellular and Molecular Physiology.

Dr. B.N. Melgert organized a mini-symposium at the ERS entitled: ‘Sex related differences in pulmonary disease’ (Vienna, September 2012)

Prof. Dr. H.M. Boezen organized a Hot topic symposium at the ERS entitled: ‘Genetics and genomics in asthma and COPD: prediction and personalized medicine’ (Vienna, September 2012)

Prof. dr. D.S. Postma had a sabbatical of 3 months in Sydney at the Woolcock Institute and collaborated with many people, a.o. Judy Black, Janette Burgess, Gregg King, Christine Jenkins, Guy Marks, Cheryl Salome, Brian Oliver, and Helen Reddel, which gave a lot of new ideas for research as well as research collaboration.

Prof. dr. H. Meurs did a 4-months sabbatical at the Department of Pharmacology of the University of Melbourne, to investigate novel mechanisms of airway remodelling.

Prizes/Awards

K. Kumawat, MSc won the Stuart Hirst Abstract Excellence Award of the Respiratory Structure and Function Assembly of the ATS and won a poster prize at the NRS meeting.
A. Spanjer, MSc obtained a travel award from the ATS and won a poster prize at the FIGON meeting.

W. Poppema, MSc won a poster prize at the ERS meeting in Estoril.

**Visitors**

Prof. H. Reddel, Woolcock Institute of Medical Research and University of Sydney, Sydney Australia. “Improving the use of asthma medications”. January 17, 2012.

Prof. S.-S. Bolz, University of Toronto, Canada. “Two old dogs with new tricks: The emerging roles of TNFalpha and the cystic fibrosis transmembrane regulator (CFTR) as modulators of microvascular tone”. March 26, 2012.

Dr. C. Martin, Institute of Pharmacology and Toxicology, University of Aachen, Germany. “Precision-cut lung slices - revival of an old technique”. April 3, 2012.


Dr. M. Königshoff, Comprehensive Pneumology Center Helmholtz Zentrum München. “Wnt/beta catenin signaling in lung fibrosis: for good or for bad?” June 15, 2012.

Dr. R. Langen, Maastricht University. “GSK-3β in the control of skeletal muscle plasticity.” June 15, 2012.

Prof. P. Saldiva, Professor of Pathology at the Faculty of Medicine, University of São Paulo, Brazil. “Metrohealth: a proposal to study health effects of urban pollution using an autopsy based approach”. June 21, 2012.

Prof. G. Brusselle, University Hospital Ghent, Ghent, Belgium. “Pulmonary versus systemic inflammation in COPD”. September 10, 2012.

Dr. E. Mortaz, National Research Institute for Tuberculosis and Lung Diseases (NRITLD) Teheran, Iran. “Options for scientific collaborations between NRITLD and GRIAC”. September 18, 2012.

Prof. M. Peters-Golden, University of Michigan, US. “Complexities of cAMP signaling in the lung: from innate immunity to fibrosis”. September 25, 2012.

Dr. E. Ingenito, Brigham and Women’s Hospital, Boston, MA, USA and Chief Scientific and Medical Officer of Aeris therapeutics. “Physiologic Principles of Lung Volume Reduction Therapy; Lessons from Endoscopic Lung Volume Reduction”. October 9, 2012.

Prof. P. Horstijk, Molecular Cell Biology, Sanquin Institute Amsterdam. The Netherlands. “Novel mechanisms regulating the small GTPase Rac1, a key organiser of cell adhesion and migration”. October 16, 2012.
A large lung gene expression study identifying fibulin-5 as a novel player in tissue repair in COPD

C.A. Brandsma, M. van den Berge, D.S. Postma, L. Franke and W. Timens

COPD is a progressive, incurable lung disease characterized by abnormal tissue repair with emphysematous lung tissue destruction and small airways fibrosis. Since current therapy cannot modify this abnormal repair, it is crucial to unravel its underlying molecular mechanisms. Unbiased analysis of genome-wide gene-expression profiles in lung tissue provides a powerful way to further investigate these molecular mechanisms. However, thus far, studies using this approach have shown very limited overlap in their findings and have largely been hindered by small sample sizes due to the limited availability of lung tissue samples from patients with COPD and non-COPD controls. As part of the Lung eQTL Consortium [1] we have performed an unbiased analysis of genome-wide gene-expression profiles in lung tissue specimens derived from a large number of 581 well-characterized current- and ex-smokers with (n = 311) and without (n = 270) COPD. These lung tissue specimens were derived from three different patient cohorts i.e. Groningen, Vancouver and Quebec. Unlike previous studies we used a very conservative analytic approach correcting for several unknown and known confounders to increase the probability of identifying a COPD specific gene signature that is present in all three patient cohorts as assessed by a meta-analyses.

We found that a total of 112 genes (171 probesets) was upregulated in COPD patients compared to controls, whereas 61 genes (112 probesets) were downregulated (Figure 1).

**Figure 1. Heatmap of lung tissue gene expression.**
Differential gene expression comparing COPD and control subjects from three lung tissue cohorts from Groningen, Quebec and Vancouver. The most relevant genes for this proposal are highlighted in red. Blue represents lower and red higher relative gene expression.
The most significantly upregulated gene was fibulin-5 (*FBLN5*), which is essential for elastic fiber assembly and abundantly expressed during lung and vascular development [2]. Fibulin-5 knock out mice survive to adulthood but develop pronounced elastinopathy with human phenotypes that occur during aging like loose skin, vascular abnormalities, severe emphysema and genital prolapse [3,4].

Latent TGFβ-binding protein 2 (*LTBP2*), which was also one of the upregulated genes in COPD, binds fibulin-5 and stimulates elastic fiber assembly as well [5]. Interestingly, next to *FBLN5* and *LTBP2*, the expression of elastin (*ELN*) itself and microfibrillar associated protein 4 (*MFAP4*) that co-localizes with elastin in the lung [6], appeared to be upregulated in COPD as well. Together, we identified a set of at least 4 genes related to elastogenesis that were upregulated in COPD patients compared to controls.

These findings are intriguing and seem to be paradoxical as elastic fibers are destroyed with emphysema resulting in severely impaired lung elasticity in COPD. We propose that upregulation of these elastogenesis genes in COPD is the result of an attempt to repair the damaged lung, which is not effective.

Interestingly, a proteolytic cleaved form of fibulin-5 was found to be increased in the skin of aged mice and this cleavage was caused by serine proteases [7]. The latter is of particular interest as increased serine protease activity is present in COPD lungs and is thought to play an important role in emphysematous lung tissue destruction. Moreover, the cleaved form of fibulin-5 did not promote elastic fiber assembly in vitro, and thus seems to be non-functional. As COPD is regarded as an aging lung disease we propose that although fibulin-5 mRNA expression is increased in COPD as a repair response, cleavage of fibulin-5 protein is increased in COPD lungs due to high serine protease activity resulting in non-functional fibulin-5, which hampers elastic fiber assembly and tissue repair.

To validate our gene expression findings on the protein level, immunohistochemistry was performed to visualize the presence of FBLN5, MFAP4 and LTBP2 in lung tissue and demonstrate co-localization in elastic fibers (Figure 2). Western blot analysis was performed to analyse total and cleaved fibulin-5 protein levels in lung tissue comparing COPD patients and controls (Figure 3).

![Figure 2. FBLN5, LTBP2, MFAP4 and ELN staining in lung tissue. Presence of elastic fibers (black) is demonstrated with a Verhoef’s stain in the upper left panels. LTBP2 and MFAP4 staining (red) is shown in the right upper and lower panels, respectively. FBLN5 staining (brown) is shown in the left lower panels. Examples of co-localization with elastic fibers are indicated with black arrows in the matrix around the airways and white arrows in the vessel walls.](image-url)
A) Fibulin-5 protein levels in lung tissue.

B) Western blot staining showing total fibulin-5 and cleaved fibulin-5 protein levels in lung tissue of 3 COPD patients and 3 non-COPD controls.

In conclusion, using genome-wide gene expression analyses on a large dataset of lung specimens from COPD patients and non-COPD controls, we identified a clear gene signature for elastogenesis in COPD, with a central role for FBLN5.

We believe that our gene expression findings together with the currently available knowledge on the role of fibulin-5 in elastogenesis, the interaction with protease activity and its link with aging, provides a very strong basis for unravelling the role of fibulin-5 in elastogenesis and tissue repair in COPD.

As follow up for our gene expression analyses we also performed an eQTL analysis to identify SNPs that could be driving these gene expression changes. We are currently starting in vitro studies using pulmonary fibroblasts to determine functionality of these SNPs in tissue repair responses.

References
Asthma is a complex disease characterized by gene-gene and gene-environment interactions (1). Major advances in asthma genetics have resulted in the identification of many novel asthma susceptibility loci, one of these gene being Protocadherin-1 (PCDH1). Henk Koning defended his thesis November 21, 2013. This thesis describes the results of our investigations into the expression and regulation of Protocadherin-1 (PCDH1), a novel gene associated with bronchial hyperresponsiveness and asthma (2). Protocadherin-1 belongs to the protocadherin subfamily of the cadherin-superfamily of adhesion molecules. PCDH1 is characterized by seven extracellular cadherin repeats and the presence of three conserved motifs (CM1, -2 and 3) in the intracellular cytoplasmic tail (3). CM3 has been shown to bind to the catalytic subunit of protein phosphatase 1 alpha (4), a protein implicated in lung morphogenesis (5). The extracellular cadherin repeats of PCDH1 have been shown to display homotypic adhesion activity, but weaker than classical cadherins like E-cadherin (6;7). The function of PCDH1 is largely unknown, and hence its putative role in the pathogenesis of asthma.

Asthma and eczema have a common genetic background, but also disease specific genetic factors exist (9). We aimed to identify whether PCDH1 polymorphisms previously associated with asthma also associate with eczema. Therefore we investigated the association of PCDH1 polymorphisms with eczema in two Dutch birth cohorts. We report an association of one PCDH1 polymorphism Ala514Thr (rs38222357) with eczema in one birth cohort, whereas a second polymorphism, the insertion deletion polymorphism IVS3-116 associates with eczema in two independent birth cohorts (10). Eczema is a disease of the skin with a defective skin barrier. Protocadherin-1 is expressed in the epithelial barrier in the airway and skin, and is associated with both asthma and eczema. A defect in the skin and airway wall barriers may therefore be an underlying cause of both diseases.

We then performed an in-dept analysis of PCDH1 expression levels in cultured and ex vivo primary bronchial epithelial cells of asthma patients, and in differentiated bronchial epithelial cells of healthy subjects. We identified novel 3’ and 5’exons, and several alternative splice forms of PCDH1, especially regarding conserved domains, suggesting that PCDH1 may perform alternative signalling functions (8). Using immunohistochemistry, we observed an apical localization of Protocadherin-1 in ciliated bronchial epithelial cells. We also identified a clear association of PCDH1 mRNA and protein expression levels with epithelial differentiation of primary bronchial epithelial cells (8). Therefore, we conclude that PCDH1 is regulated during epithelial differentiation, but its exact function in differentiated epithelia needs further investigation.

One of the interesting outcomes of genetic studies was the identification of a stronger linkage of the PCDH1 gene region with asthma in subjects exposed to environmental tobacco smoke (ETS) (2). ETS is known as a risk factor for asthma. We thus investigated the influence of smoke exposure on Protocadherin-1 expression levels in vivo in mouse lung. We identified a direct effect of smoke exposure on Pcdh1 mRNA expression levels. Smoke exposure can adversely affect the epithelial barrier function by down-regulating adhesion molecules. We hypothesize that cigarette smoke downregulates Pcdh1 expression levels and thereby, together with lower levels of adhesion molecules, compromises the epithelial barrier function. To further investigate the function of PCDH1 in airway epithelium, we next investigated whether PCDH1 could act as a signalling molecule by identifying the subcellular localization of its protein isoforms, and by identifying potential interactors. We detected a novel extracellular soluble PCDH1 protein product (sPCDH1), and multiple intracellular protein products, that may play a role in signalling. Interestingly, we observed an interaction of PCDH1 isoforms with SMAD3, suggesting that PCDH1 can act as a signalling molecule. Interestingly, SMAD3 has been identified as an asthma gene by the genome-wide meta-analysis from the GABRIEL consortium.
SMAD3 is a key downstream molecule in the TGFβ-pathway, and is a critical factor for epithelial to mesenchymal transitions (EMT) and epithelial repair responses (12). Altogether, PCDH1 may perform signalling functions at three different levels; 1) by alternative splice-variants that express different signalling domains, 2) by intracellular protein products potentially generated by post-translational processing, and 3) by interacting with downstream signalling partners like SMAD3. The physical interaction between the proteins encoded by these asthma susceptibility genes implicates the existence of a novel pathway in asthma pathogenesis in which these two proteins play a central role.

How can we integrate our current knowledge on PCDH1 function into our understanding of asthma? Airway epithelial cells express PCDH1, which localizes to the apical site just below the brush border. Cigarette smoke (CS) exposure may down-regulate PCDH1 and junctional adhesion molecules, increasing vulnerability of the airway epithelial barrier. Due to a dysregulated interaction of PCDH1 with SMAD3 in asthmatic subjects with susceptible PCDH1-alleles, this may lead to airway epithelium with a continuous repair phenotype, and a subsequent weakened epithelial barrier. The weakened epithelial barrier may result in increased sensitization of the immune system. Together with increased cytokine and growth factor production by asthmatic epithelial cells this may lead to a chronic inflammatory response that is partly Th2-mediated (see Figure 1 for an overview).

Within GRIAC, we will further investigate the role of the PCDH1- SMAD3 pathway in asthma development using a.o. full and tissue specific knockout models, as well as transgenic mice overexpressing two different PCDH1 isoforms.

References


(9) van Beijsterveldt CE, Boomsma DI. Genetics of parentally reported asthma, eczema and rhinitis in 5-yr-old twins. Eur Respir J. 2007 Mar;29(3):516-21


Drug inhalation is the cornerstone in the treatment of pulmonary diseases like asthma and chronic obstructive pulmonary disease (COPD). Treating these diseases by specific targeting of the airways with bronchodilating and anti-inflammatory drugs has resulted in major improvements to control these diseases. Next to inhaled treatment of pulmonary diseases, inhaled therapy to provide systemic drug delivery via the lung may open the way for treatment of systemic disorders like diabetes mellitus with insulin, or delivering vaccines (e.g. influenza, measles).

However, inhaled therapy is not that simple. Drug deposition in the lung after inhalation therapy is highly variable and ranges from 1-50% of the label claim depending on a variety of factors such as the inhalation device, delivered drug mass, inhalation manoeuvre (technique, inspiratory flow rate and breath hold), adherence to treatment, disease related and environmental factors. All these factors are summarized in a mind map (see figure).

The primary aim is to improve treatment of respiratory and systemic diseases by improving inhalation treatment.

Three concepts
First, from trachea to alveoli, the airway surface area exponentially increases and therefore, even when peripheral airways are targeted, a 25 fold decrease in drug concentration towards the alveoli will be inevitable. Second, even when location of disease process and drug receptors may vary from drug to drug and from disease to disease, targeting the peripheral airways is important because of this concentration gradient. Then, drug deposition is not governed by particle size only; the inspiratory manoeuvre is equally important.
Small particles
For efficient deposition in the airways, the preferred aerodynamic particle size diameter is in the range of 1-3 µm with an appropriate slow inhalation and a breath hold after inhalation.2

For ICS-pressurized metered dose inhalers (pMDI’s), the most striking finding was a decrease in delivered dose during the life-span of fluticasone 125- and 250 µg/dose.3

For pMDI’s with spacers, we found that an increase in relative humidity from low (25-35%) to high (75-80%) can result in an up to two-fold increase in drug output from the spacer. From bench to bedside, the efficacy of the therapy might thus be improved by administrating the medication in a humid environment (e.g. a used bathroom). The particle size distribution does not change with increasing humidity, thus a higher output translates directly to a higher fine particle fraction.

For inhaled insulin, the use of a new device with the first available Insulin Dry Powder (Exubera®), by the use of innovative inhaler technology (Twincer ™) resulting in a desired increase in fine particle dose (1-3 µm) within one inhalation almost doubled the systemic availability of insulin.

When nebulizers that were used with Tobramicin for Inhalation Solution in a 6 month time frame, the elapsing time as well as the poor adherence of patients to cleaning instructions despite active communication, resulted in an undesired increase in particle size.4

Myths and mists
Many myths exist in inhalation technology.5 Examples that are discussed above are the emphasis on particle size without taking the inhalation manoeuvre into account, and that even with optimal technology a concentration gradient is inevitable. More importantly, when Dry Powders Inhalers are discussed in the literature, emphasis is placed on the importance of a flow independent fine particle dose.6 However, deposition shift to larger airways with increased flow, and therefore a device that compensates for this effect by releasing a higher fine particle dose is preferable.7

Communication is difficult and cultural issues can lead to additional confusion.8

All together, the studies show that many interactions have an impact on pulmonary drug delivery. Those insights can be used to improve devices, to make better use of environmental conditions and stress the importance of communication; the latter with patients and between scientists alike.

References
Special Topic 4:
GSK-3 as a novel drug target for tissue remodeling in COPD.
Author: R. Gosens. Study group: H.A. Baarsma (PhD student), R. Gosens (projectleader), H.A.M. Kerstjens (promotor), H. Meurs (promotor), W. Timens, D.S. Postma.

Introduction
Chronic obstructive pulmonary disease (COPD) is a major health problem world-wide and both its morbidity and mortality are rising. Significant ongoing research efforts have resulted in the identification of several processes that contribute to disease progression in COPD, which include the findings that both persistent airway inflammation, airway remodeling, emphysema and mucus hypersecretion contribute to symptoms and lung function decline in COPD. Nonetheless, the fundamental biological mechanisms that regulate these processes are poorly understood indicating that much research effort is needed to develop successful interventions.

In this project, we aimed to establish a fundamental mechanism that contributes centrally to these remodeling and emphysematous responses and hypothesized a key role for the transcriptional co-activator β-catenin and its negative regulator glycogen synthase kinase-3 (GSK-3) that induces intracellular β-catenin breakdown. We aimed to establish the functional role of β-catenin/GSK-3 signaling in airway remodeling and emphysema using in vitro studies of fibroblasts and smooth muscle cells, in vivo models and clinical samples.

Extracellular matrix production
Our first aim was to demonstrate the role of β-catenin/GSK-3 signaling in the production of extracellular matrix proteins. We have addressed this question using pulmonary fibroblasts and airway smooth muscle cells. In both cell types we observed that transforming growth factor-β (TGF-β), a key mediator of repair and remodeling, activates β-catenin signaling via inhibition of GSK-3, resulting in nuclear translocation and association with TCF/LEF transcription factors of β-catenin. As a result of β-catenin activation by TGF-β, gene expression of matrix proteins (collagen I, fibronectin, versican) was activated, which was established using siRNA directed against β-catenin and using pharmacological inhibitors of the β-catenin/TCF interaction. Furthermore, expression of a non-degradable constitutively active β-catenin mutant (S33Y-β-catenin) had the opposite effects, and promoted extracellular matrix protein deposition in the absence of extracellular stimuli (see also Figure 1). This indicates that β-catenin is required and sufficient for extracellular matrix protein expression by airway smooth muscle cells and fibroblasts, making it an attractive target for therapeutic intervention.

Figure 1. Extracellular matrix protein production by airway smooth muscle is β-catenin dependent. (A) TGF-β induces gene expression of collagen 1α1, fibronectin and versican, which is inhibited by β-catenin siRNA. (B) TGF-β induces active β-catenin and fibronectin protein, which is inhibited by β-catenin siRNA. (C) Expression of a constitutively active S33Y β-catenin mutant is sufficient for fibronectin production. Data from Baarsma et al., AJP Lung Cell Mol Physiol (2011) 301:L956-965.
promote fibroblast activation leading to extracellular matrix protein expression. Surprisingly, however, GSK-3 inhibitors were found to be highly potent and effective inhibitors of the fibrotic responses activated by TGF-β (Figure 2). We observed that the time- and dose-dependent activation of sm-α-actin, MMP-2 and fibronectin production by lung fibroblasts in response to TGF-β required GSK-3. This was established using three structurally distinct (SB216763, LiCl, CT99021) GSK-3 inhibitors and using targeted GSK-3 knockdown with siRNA. Interestingly, the capacity for GSK-3 inhibitors to reduce extracellular matrix protein expression was retained in lung fibroblasts obtained from COPD patients. The paradoxical role of GSK-3 inhibition in repressing fibroblast activation was explained by the activation of CREB signaling by these inhibitors, as GSK-3 is a highly compartmentalized kinase that phosphorylates multiple cellular substrates. GSK-3 inhibition was found to activate the phosphorylation of CREB, which in its activated form functions as a physiological antagonist of Smad signaling by competing with Smad for the common binding partner CBP. Indeed, we observed that that GSK-3 inhibition did not affect TGF-β induced ERK or Smad phosphorylation, but repressed Smad dependent gene expression (PAI-1, CTGF) and the Smad dependent SBE4-luciferase reporter. These findings indicate that GSK-3 inhibition represents another potential new approach to target extracellular matrix protein and MMP expression.

Figure 2: Effect of the selective GSK-3 inhibitor SB216763 on myofibroblast differentiation and extracellular matrix deposition in the lung. (A) Concentration dependent inhibition of myofibroblast differentiation by the GSK-3 inhibitor SB216763. (B) Stress fiber formation induced by TGF-β is inhibited by SB216763. (C) Histological staining and quantification of the extracellular matrix protein collagen in LPS-exposed guinea pigs treated with SB216763. Data from Baarsma et al., Br J Pharmacol (2013) 169: 590-603.
The role of β-catenin and GSK-3 in an animal model of COPD

In view of these results, we next investigated the role of the β-catenin/GSK-3 signaling pathway in an animal model of COPD. To this aim, we used a guinea pig model of COPD, in which guinea pigs receive intranasal instillations with lipopolysaccharide twice a week for twelve weeks. We hypothesized that repeated LPS instillations would activate the β-catenin signaling pathway leading to airway fibrosis and that GSK-3 inhibitors would have anti-fibrotic effects in view of the results described above. We therefore investigated the effect of the selective GSK-3 inhibitor SB216763 on pulmonary remodeling and extrapulmonary pathology in this guinea pig model of COPD. Repeated LPS exposure activated β-catenin signaling and induced tissue remodeling as indicated by increased pulmonary fibronectin expression and small airway collagen content. Inhibition of GSK-3 by SB216763 prevented the small airway remodeling (Figure 2) and, unexpectedly, inhibited the activation of β-catenin in vivo. Also, GSK-3 inhibition prevented the LPS-induced extrapulmonary pathological features, including right ventricle hypertrophy and the skeletal muscle atrophy, which was assessed in collaboration with Dr. Ramon Langen and Prof. dr. Annemie Schols from Maastricht University. In conclusion, these findings suggest that GSK-3 inhibition is beneficial in attenuating pulmonary remodeling as well as extrapulmonary pathology in a guinea pig model of COPD, and that locally reduced LPS-induced β-catenin activation appears in part to underlie this effect. Collectively, this indicates that GSK-3 may be a novel drug target for the treatment of COPD.
Members Griac 2012

Scientific Board
Boezen H.M., PhD, Prof
Dubois A.E.J., MD, PhD, Prof
Duiverman E.J., MD, PhD, Prof
Hacken ten N.H.T., MD, PhD
Hylkema M.N., PhD
Kerstjens H.A.M., MD, PhD, Prof
Koppelman G.H., MD, PhD, Prof
Meurs H., PhD, Prof
Molen van der T., MD, PhD, Prof
Monchy de J.G.R., MD, PhD, Prof
Oosterhout van A.J.M., PhD, Prof
Postma D.S., MD, PhD, Prof
Schmidt M.A., PhD, Prof
Timens W., MD, PhD, Prof
Vonk J.M., PhD
Wijkstra P.J., MD, PhD

Other scientific staff
Brakel T., MSc
Diamant Z., PhD, Prof.
Douma W.R., MD, PhD
Gerritsen, J., MD, PhD
Gosens, R., PhD
Heide van der S., PhD
Jong de C., MSc
Kerkhof M., MD, PhD
Kneyber M.C.J., MD, PhD
Melgert B.N, PhD
Oude Elberink J.N.G., MD, PhD
Rottier B.L., MD
Schouten J.P., MSc
Slebos D.J., MD, PhD
Vrijlandt E.J.L.E., MD, PhD
Wempe J.B, MD, PhD
Willemseni B.W., MD, PhD
Zaagsma J., PhD, Prof.

Post-docs
Brandsma C.A., PhD
Berge van den M., MD, PhD
Dekkers B.G.J., PhD
Flokstra-de Blok B.M.J., PhD
Heijink H.I., PhD
Kocks J.W.H., MD, PhD
Maarsingh E.J., PhD
Maarsingh H., PhD
Nawijn M.C., PhD
Riemersma R.A., MD, PhD
Schiphof L., PhD
Schokker S., PhD
Tsiliogian J., MD, PhD
Xu C., PhD

PhD students
Altenburg W.A., MSc
Baarsma H.A., MSc
Boorsma C.E., MSc
Budulac S., MD
Cao, J.J. MSc,
van Dijk E., MSc
Dijk F.N., MD
Dijkstra A.E., MSc
Fattahi F., MD
Faura Tellez G., MSc
Figarska S.M., MSc
Fijkstra I., MSc
Gemert van F.A., MD
Fatta G., MD
Faura Tellez G., MSc
Fijkstra I., MSc
Gemert van F.A., MD
Fatta G., MD

Kumawat K., MSc
Maazi H., MSc
Metting E.I., MSc
Meyer, K. Msc.
Nieuwenhuis M.A.E., MSc
Oenema T.A., Msc
Oldenburger A., MSc
Poppinga W., MSc
Post S., MSc
Pouwels S.D., MSc
Rajendran V., MSc
Robbe P., MSc
Rozeveld D., MSc
Saleh-Langenberg J., MD/PhD student
Sattarzadeh A., MSc
Savenije O., MD
Shirinibaik S., MSc
Smolonska A, MSc
Spanjer A.I.R., MSc
Struijk F.M., MSc
Telenga E., MD
van der Valk R., MSc
Hoonhorst S.J.M., MSc
Ierodiakonou D., MD
Jong de K., MSc
Jong de L., MSc
Kistemaker L.E.M., MSc
Koning H., MSc
Koopmans T., MSc

Velde van der J.L., MD
Vink N.M., MD.
de Vries G.E., MSc
de Vries M., MSc
Vroegop J.S., MD
van der Wiel E., M.D.
Zijlstra J., MD/PhD student

Other research staff
Ban van C.H.
Berg van den M.
Bijma T.
Brandenburg S.M
Beusekamp B.
Beverdam H.R.
Bladder G.
Boef den L.E.
Bos I. S.T
Boudewijn I.
Bouwman J.
Brouwer S.
Brouwer U.
Briuns Slot F.J.
Eems van der M.R.
Elzinga C.R.S.
Gras R.
Groot de G.
Heijst van E.C.M.
Heuving M.E.
Hiltermann-Tilanus R.G.A., MSc
Homan A.A.J.
Jonge de O.R.M.
Jonker M.R.
Kies P.M.
Klooster K.
Kooistra W.
Klok P.

Koops H.
Kukler J.
Laan van der-Boers A.
Leever M.
Leij van der J., PhD
Lodewijk M.
Menzen M.
Naald van der T.
Noordhoek J.
Oeseburg D.S.
Olivier M.
Oomkes-Pilon A.M.
Oosterom H.
Platteel M.
Poppinga-van Heel A.M.A.
Rakers J.A.
Reinders-Luinge M.
Slijm K.
Smidt-Huizinga H.D.M.
Smit M.
Staal R.
Star-Kroesen M.
Swierenga M.
Thijn H.
Toorn van der M., PhD
Wetterauw P.
Zonderland J.
Zuidhof A.B.
Members GRIAC 2012
Dept. General Practice
University of Groningen, Faculty of Medical Sciences
A. Deusinglaan 1
NL-9713 AV Groningen
Phone 31-50-363 2963
Fax 31-50-363 2964
Principal Investigator: Prof. Dr. T. van der Molen

Dept. Epidemiology
University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone 31-50-361 0739
Fax 31-50-361 4493
Principal Investigators: Prof. Dr. H.M. Boezen, Dr. M. Kerkhof, Dr. J.M. Vonk

Dept. Internal Medicine, div. Allergology
University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone 31-50-361 2976
Fax 31-50-3121576
Principal Investigators: Prof. Dr. J.G.R. de Monchy, Dr. J.N.G. Oude Elberink

Lab. Allergology and Pulmonary Diseases
University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone 31-50-361 8043
Fax 31-50-361 9911
Principal Investigators: Prof. Dr. A.J.M. van Oosterhout, Dr. H.I. Heijink

Dept. Pulmonary Diseases and Tuberculosis
University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone 31-50-361 3532
Fax 31-50-361 9320
Principal Investigators: Prof. Dr. D.S. Postma, Prof. Dr. H.A.M. Kerstjens, Dr. N.H.T. ten Hacken

Dept. Pathology and Medical Biology
University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone 31-50-361 4684
Fax 31-50-363 2510
Principal Investigators: Prof. Dr. W. Timens, Dr. M.N. Hylkema
**Dept. Pediatric Pulmonology and Pediatric Allergy**
Beatrix Children’s Hospital, University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone: 31-50-361 2748
Fax: 31-50-361 4235
Principal Investigators: Prof. Dr. G.H. Koppelman, Prof. Dr. E.J. Duiverman, Prof. Dr. A.E.J. Dubois

**Working group on Respiratory Insufficiency**
University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone: 31-50-361 3235
Fax: 31-50-361 9320
Principal Investigator: Dr. P.J. Wijkstra

**Dept. Molecular Pharmacology, University Centre for Pharmacy**
University of Groningen
A. Deusinglaan 1
NL-9713 AV Groningen
Phone 31-50-363 3197
Fax: 31-50-363 6908
Principal Investigators: Prof. Dr. M.A. Schmidt, Prof. Dr. H. Meurs, Dr. R. Gosens
**GRIAC International collaboration 2012**
(As far as related to joint projects and publications in 2012)

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>City, Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prof. J. Antó</td>
<td>IMIM, CREAL</td>
<td>Barcelona, Spain</td>
</tr>
<tr>
<td>Prof. E.R. Bleecker</td>
<td>Wake Forest School of Medicine</td>
<td>Winston Salem, USA</td>
</tr>
<tr>
<td>Dr. B. Bohle</td>
<td>Medical University of Vienna</td>
<td>Vienna, Austria</td>
</tr>
<tr>
<td>Dr. Y. Bosse</td>
<td>Université de Laval</td>
<td>Quebec, Canada</td>
</tr>
<tr>
<td>Prof. J. Bousquet</td>
<td>INSERM</td>
<td>Villejuif, France</td>
</tr>
<tr>
<td>Prof. G. Brusselle</td>
<td>University Hospital of Ghent</td>
<td>Ghent, Belgium</td>
</tr>
<tr>
<td>Prof. D. Davies</td>
<td>University of Southampton</td>
<td>Southampton, UK</td>
</tr>
<tr>
<td>Dr. M. Denburgh</td>
<td>Boston University School of Medicine</td>
<td>Boston, USA</td>
</tr>
<tr>
<td>Prof. R.S. Goldstein</td>
<td>University of Toronto</td>
<td>Toronto, Canada</td>
</tr>
<tr>
<td>Prof. S.A. Grando</td>
<td>University of California</td>
<td>Irvine, USA</td>
</tr>
<tr>
<td>Dr. T.L. Hackett</td>
<td>University of British Columbia</td>
<td>Vancouver, Canada</td>
</tr>
<tr>
<td>Prof. A.J. Halayko</td>
<td>University of Manitoba</td>
<td>Winnipeg, Canada</td>
</tr>
<tr>
<td>Prof. A.J. Henderson</td>
<td>University of Bristol</td>
<td>Bristol, UK</td>
</tr>
<tr>
<td>Prof. F. Herth</td>
<td>University of Heidelberg</td>
<td>Heidelberg, Germany</td>
</tr>
<tr>
<td>Prof. J.C. Hogg</td>
<td>University of British Columbia</td>
<td>Vancouver, Canada</td>
</tr>
<tr>
<td>Dr. J.W. Holloway</td>
<td>University of Southampton</td>
<td>Southampton, UK</td>
</tr>
<tr>
<td>Prof. D. Jarvis</td>
<td>Imperial College London</td>
<td>London, UK</td>
</tr>
<tr>
<td>Prof. G. Joos</td>
<td>University Hospital of Ghent</td>
<td>Ghent, Belgium</td>
</tr>
<tr>
<td>Dr. F. Kauffmann</td>
<td>Inserm Paris</td>
<td>Paris, France</td>
</tr>
<tr>
<td>Prof. K. Kawashima</td>
<td>Kitasato University</td>
<td>Tokyo, Japan</td>
</tr>
<tr>
<td>Prof. C.J. Kirkpatrick</td>
<td>Johannes Gutenberg University</td>
<td>Mainz, Germany</td>
</tr>
<tr>
<td>Dr. S. Kolahian</td>
<td>University of Tabriz</td>
<td>Tabriz, Iran</td>
</tr>
<tr>
<td>Prof. M. Königshof</td>
<td>Helmholtz Zentrum</td>
<td>München, Germany</td>
</tr>
<tr>
<td>Dr. R. Korstanje</td>
<td>The Jackson Laboratory</td>
<td>Bar Harbor, USA</td>
</tr>
<tr>
<td>Dr. S. Krauss-Etschmann</td>
<td>Helmholtz Center Munich</td>
<td>Munich, Germany</td>
</tr>
<tr>
<td>Prof. B.N. Lambrecht</td>
<td>University Hospital of Ghent</td>
<td>Ghent, Belgium</td>
</tr>
<tr>
<td>Dr. S. London</td>
<td>National Institute of Environmental Health Sciences (NIEHS)</td>
<td>North Carolina, USA</td>
</tr>
<tr>
<td>Prof. D.A. Meyers</td>
<td>Wake Forest School of Medicine</td>
<td>Winston Salem, USA</td>
</tr>
<tr>
<td>Prof. P.D. Pare</td>
<td>University of British Columbia</td>
<td>Vancouver, Canada</td>
</tr>
<tr>
<td>Prof. M. Peters-Golden</td>
<td>University of Michigan Medical School</td>
<td>Michigan, USA</td>
</tr>
<tr>
<td>Prof. D. Price</td>
<td>University of Aberdeen</td>
<td>Aberdeen, UK</td>
</tr>
<tr>
<td></td>
<td>Institute/University</td>
<td>Location</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>Prof. N. Probst-Hensch</td>
<td>Swiss Tropical and Public Health Institute</td>
<td>Basel, Switzerland</td>
</tr>
<tr>
<td>Dr. B.A. Raby</td>
<td>Harvard Medical School</td>
<td>Boston, USA</td>
</tr>
<tr>
<td>Prof. K. Racké</td>
<td>University of Bonn</td>
<td>Bonn, Germany</td>
</tr>
<tr>
<td>Prof. F. van Roy</td>
<td>Flemish Institute of Biotechnology</td>
<td>Ghent, Belgium</td>
</tr>
<tr>
<td>Dr. I. Sayers</td>
<td>University of Nottingham</td>
<td>Nottingham, UK</td>
</tr>
<tr>
<td>Dr. P. Shah</td>
<td>Royal Brompton Hospital</td>
<td>London, UK</td>
</tr>
<tr>
<td>Prof. E. Silverman</td>
<td>Harvard Medical School</td>
<td>Boston, USA</td>
</tr>
<tr>
<td>Prof. D.D. Sin</td>
<td>University of British Columbia</td>
<td>Vancouver, Canada</td>
</tr>
<tr>
<td>Prof. L. Sorokin</td>
<td>University of Münster</td>
<td>Münster, Germany</td>
</tr>
<tr>
<td>Dr. A. Spira</td>
<td>Boston University School of Medicine</td>
<td>Boston, USA</td>
</tr>
<tr>
<td>Prof. A.G. Stewart</td>
<td>University of Melbourne</td>
<td>Melbourne, Australia</td>
</tr>
<tr>
<td>Dr. K. Tantisira</td>
<td>Harvard Medical School</td>
<td>Boston, USA</td>
</tr>
<tr>
<td>Prof. M. Tobin</td>
<td>University of Leicester</td>
<td>Leicester, UK</td>
</tr>
<tr>
<td>Prof. S.T. Weiss</td>
<td>Harvard Medical School</td>
<td>Boston, USA</td>
</tr>
<tr>
<td>Prof. J. Wess</td>
<td>National Institute of Health</td>
<td>Bethesda, USA</td>
</tr>
<tr>
<td>Prof. I. Wessler</td>
<td>Johannes Gutenberg University</td>
<td>Mainz, Germany</td>
</tr>
</tbody>
</table>
## GRIAC Seminar program 2012

<table>
<thead>
<tr>
<th>Date</th>
<th>Speaker</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>17-01-2012</td>
<td>Prof. Dr. H. Reddel</td>
<td>Improving the use of asthma medications</td>
</tr>
<tr>
<td></td>
<td>Woolcock Institute of Medical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Research and University of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sydney, Sydney Australia</td>
<td></td>
</tr>
<tr>
<td>07-02-2012</td>
<td>Dr. S. Scholtens</td>
<td>Gene by (passive) smoking interactions in asthma</td>
</tr>
<tr>
<td></td>
<td>Epidemiology</td>
<td>development – the GABRIEL study</td>
</tr>
<tr>
<td></td>
<td>UMCG</td>
<td></td>
</tr>
<tr>
<td>21-02-2012</td>
<td>F. Fattahi, MD</td>
<td>Atopy is a risk factor for COPD: result of Euroscop</td>
</tr>
<tr>
<td></td>
<td>Pulmonology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UMCG</td>
<td></td>
</tr>
<tr>
<td>06-03-2012</td>
<td>Dr. J.C.A. Trappenburg</td>
<td>Early detection and self-management of</td>
</tr>
<tr>
<td></td>
<td>UMCU</td>
<td>exacerbations in patients with COPD</td>
</tr>
<tr>
<td></td>
<td>Utrecht</td>
<td></td>
</tr>
<tr>
<td>20-03-2012</td>
<td>S. Post, MSc</td>
<td>HDM interacts with the airway epithelium to cause immunological and</td>
</tr>
<tr>
<td></td>
<td>Pathology and Medical Biology</td>
<td>barrier dysfunction</td>
</tr>
<tr>
<td></td>
<td>UMCG</td>
<td></td>
</tr>
<tr>
<td>03-04-2012</td>
<td>Dr. C. Martin</td>
<td>Precision-cut lung slices - revival of an old technique.</td>
</tr>
<tr>
<td></td>
<td>Institute of Pharmacology and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toxicology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>University of Aachen</td>
<td></td>
</tr>
<tr>
<td>17-04-2012</td>
<td>S. Vroegop, MSc</td>
<td>Evaluatie van de longpatiënt met onbegrepen dyspneu</td>
</tr>
<tr>
<td></td>
<td>Martini Ziekenhuis Groningen</td>
<td></td>
</tr>
<tr>
<td>15-05-2012</td>
<td>Dr. D.J. Slebos</td>
<td>Lung volume reduction coil treatment for patients with severe</td>
</tr>
<tr>
<td></td>
<td>Pulmonology</td>
<td>emphysema</td>
</tr>
<tr>
<td></td>
<td>UMCG</td>
<td></td>
</tr>
<tr>
<td>05-06-2012</td>
<td>Prof. Dr. G.H.Koppelman</td>
<td>Integrative genomics of asthma</td>
</tr>
<tr>
<td></td>
<td>Pediatric Pulmonology and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pediatric Allergology Beatrix</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children’s Hospital</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UMCG</td>
<td></td>
</tr>
<tr>
<td>19-06-2012</td>
<td>Dr. M. Kerkhof</td>
<td>Childhood origins of COPD</td>
</tr>
<tr>
<td></td>
<td>Epidemiology</td>
<td></td>
</tr>
<tr>
<td></td>
<td>UMCG</td>
<td></td>
</tr>
<tr>
<td>21-06-2012</td>
<td>Prof. Dr. P. Saldiva</td>
<td>Metrohealth: A proposal to study health effects of urban pollution</td>
</tr>
<tr>
<td></td>
<td>Faculty of Medicine</td>
<td>using an autopsy based approach</td>
</tr>
<tr>
<td></td>
<td>University of São Paolo Brazil</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>Speaker</td>
<td>Title</td>
</tr>
<tr>
<td>------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>10-09-2012</td>
<td>Prof. Dr. G. Brusselle</td>
<td>Pulmonary versus systemic inflammation in COPD</td>
</tr>
<tr>
<td></td>
<td>Pulmonology</td>
<td>University Hospital Gent, Gent</td>
</tr>
<tr>
<td>18-09-2012</td>
<td>Dr. E. Mortaz</td>
<td>Options for scientific collaborations between NRITLD and GRIAC</td>
</tr>
<tr>
<td></td>
<td>National Research Institute for Tuberculosis and Lung Diseases (NRITLD)</td>
<td>Teheran, Iran</td>
</tr>
<tr>
<td>02-10-2012</td>
<td>C. de Jong, MSc</td>
<td>The IMI PROactive Study, Development of a questionnaire to measure experience of physical activity in patients with COPD</td>
</tr>
<tr>
<td></td>
<td>General Practice UMCG</td>
<td></td>
</tr>
<tr>
<td>09-10-2012</td>
<td>Dr. E. Ingenito MD</td>
<td>Physiologic Principles of Lung Volume Reduction Therapy;</td>
</tr>
<tr>
<td></td>
<td>Pulmonary &amp; Critical Care Medicine, Brigham and Women’s Hospital, Boston, MA, USA and Chief Scientific and Medical Officer of Aeris therapeutics</td>
<td>Lessons from Endoscopic Lung Volume Reduction</td>
</tr>
<tr>
<td>16-10-2012</td>
<td>Dr. C.A. Brandsma</td>
<td>Abnormal tissue repair in COPD</td>
</tr>
<tr>
<td></td>
<td>Pathology and Medical Biology UMCG</td>
<td></td>
</tr>
<tr>
<td>06-11-2012</td>
<td>A. Oldenburger, MSc</td>
<td>Multiple facets of cAMP signalling and physiological impact: cAMP compartmentalization in the lung</td>
</tr>
<tr>
<td></td>
<td>Molecular Pharmacology RUG</td>
<td></td>
</tr>
<tr>
<td>20-11-2012</td>
<td>Dr. I.M. de Kleer</td>
<td>House dust mite sensitization in immature lungs</td>
</tr>
<tr>
<td></td>
<td>VIB Ghent University</td>
<td></td>
</tr>
<tr>
<td>04-12-2012</td>
<td>A.E. Dijkstra, MSc</td>
<td>Genetics and Environment as source of Chronic Mucus Hypersecretion</td>
</tr>
<tr>
<td></td>
<td>Pulmonology UMCG</td>
<td></td>
</tr>
<tr>
<td>18-12-2012</td>
<td>Dr. J.M. Vonk</td>
<td>Genetics of asthma remission</td>
</tr>
<tr>
<td></td>
<td>Epidemiology UMCG</td>
<td></td>
</tr>
<tr>
<td>Date</td>
<td>Speaker</td>
<td>Title</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>03-01-2012</td>
<td>Dennie Rozeveld</td>
<td>Role of metalloproteases in allergen-induced release of CCL20 from airway epithelial cells</td>
</tr>
<tr>
<td>10-01-2012</td>
<td>Carian Boorsma</td>
<td>Interactions between macrophages and myofibroblasts in pulmonary fibrosis: a role for the RANK-RANKL-OPG axis?</td>
</tr>
<tr>
<td>17-01-2012</td>
<td>Grietje de Vries</td>
<td>Central sleep apnea syndrome in patients with heart failure</td>
</tr>
<tr>
<td>24-01-2012</td>
<td>Despo Ierodiakonou</td>
<td>Urokinase plasminogen activator receptor (uPAR) gene and airway remodelling in asthma.</td>
</tr>
<tr>
<td>31-01-2012</td>
<td>Nienke Vink</td>
<td>No association between basal or stress-induced cortisol and asthma development. The TRAILS study.</td>
</tr>
<tr>
<td>07-02-2012</td>
<td>Wytske Altenburg</td>
<td>COACH-study: Preliminary results.</td>
</tr>
<tr>
<td>21-02-2012</td>
<td>Susan Hoonhorst</td>
<td>The skin blanching test and susceptibility to COPD</td>
</tr>
<tr>
<td>28-02-2012</td>
<td>Jorine Hartman</td>
<td>Daily physical inactivity in COPD, a quantitative and qualitative analysis; Preliminary results</td>
</tr>
<tr>
<td>06-03-2012</td>
<td>Neomi Grotenboer</td>
<td>Functional consequences of genetic variation within the asthma susceptibility gene IL1RL1</td>
</tr>
<tr>
<td>20-03-2012</td>
<td>Sylwia Figarska</td>
<td>Genetic Risk Score for prediction of reduced lung function level in the general population</td>
</tr>
<tr>
<td>03-04-2012</td>
<td>Patricia Robbe</td>
<td>Effects of farm dust exposure on asthma development</td>
</tr>
<tr>
<td>17-04-2012</td>
<td>Tjitske Oenema</td>
<td>Crosstalk between muscarinic receptors and TGF-b1 in airway smooth muscle</td>
</tr>
<tr>
<td>24-04-2012</td>
<td>Eef Telenga</td>
<td>Indications of small airways dysfunction in healthy smokers</td>
</tr>
<tr>
<td>Date</td>
<td>Speaker</td>
<td>Title</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>01-05-2012</td>
<td>Maaike de Vries</td>
<td>Lab of Allergology and Pulmonary Diseases: The protective role for Pim kinases in maintaining airway epithelial integrity and barrier function</td>
</tr>
<tr>
<td>29-05-2012</td>
<td>Fatemeh Fattahi</td>
<td>Pathology: Atopy is a risk factor for COPD, results from EUROSCOP.</td>
</tr>
<tr>
<td>05-06-2012</td>
<td>Kim de Jong</td>
<td>Epidemiology: Occupational exposures and lung function in the LifeLines cohort</td>
</tr>
<tr>
<td>12-06-2012</td>
<td>Maartje Nieuwenhuis</td>
<td>Pulmonology: Severity of Bronchial Hyperresponsiveness: A Genome Wide Interaction Study</td>
</tr>
<tr>
<td>26-06-2012</td>
<td>Laura Hesse</td>
<td>Lab of Allergology and Pulmonary Diseases: Grass-pollen mouse model of allergic asthma and allergen immunotherapy</td>
</tr>
<tr>
<td>18-09-2012</td>
<td>Marike Boezen</td>
<td>Epidemiology: GRIAC-chair: What is GRIAC?</td>
</tr>
<tr>
<td>25-09-2012</td>
<td>Corry-Anke Brandsma</td>
<td>Pathology: Adaptive immune system in COPD: autoimmunity or bystander?</td>
</tr>
<tr>
<td>02-10-2012</td>
<td>Christina Draijer</td>
<td>Pharmacokinetics, Toxicology and Targeting: The role of different macrophage phenotypes in asthma</td>
</tr>
<tr>
<td>09-10-2012</td>
<td>Olga Savenije</td>
<td>Epidemiology: IL1RL1 pathway analyses: methods and first results</td>
</tr>
<tr>
<td>16-10-2012</td>
<td>Eef Telenga</td>
<td>Pulmonology: Airway wall thickness on HRCT-scans decreases with higher age and increases in smokers</td>
</tr>
<tr>
<td>23-10-2012</td>
<td>Anita Spanjer</td>
<td>Molecular Pharmacology: A role for the Frizzled-8 receptor in remodelling and inflammation in COPD</td>
</tr>
<tr>
<td>06-11-2012</td>
<td>Gerard Koppelman</td>
<td>Pediatric pulmonolgy: workshop Grant-writing</td>
</tr>
<tr>
<td>13-11-2012</td>
<td>Maaike de Vries</td>
<td>Lab of Allergology and Pulmonary Diseases: The protective role for Pim kinases in maintaining airway epithelial integrity and barrier function</td>
</tr>
<tr>
<td>20-11-2012</td>
<td>Daan Pouwels</td>
<td>Lab of Allergology and Pulmonary Diseases: The role of DAMPs in the genetic susceptibility towards COPD</td>
</tr>
<tr>
<td>27-11-2012</td>
<td>Fatemeh Fattahi</td>
<td>Pathology: An old dilemma: asthma with irreversible airway-obstruction or COPD? Preliminary results</td>
</tr>
<tr>
<td>Date</td>
<td>Speaker</td>
<td>Title</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------</td>
<td>---------------------------------------------------------</td>
</tr>
<tr>
<td>11-12-2012</td>
<td>Susan Hoonhorst</td>
<td>Systemic effects of acute smoking and COPD susceptibility</td>
</tr>
<tr>
<td></td>
<td>Pulmonology</td>
<td></td>
</tr>
<tr>
<td>18-12-2012</td>
<td>Erica van de Wiel</td>
<td>New tools to evaluate small airways disease in asthma; preliminary results</td>
</tr>
<tr>
<td></td>
<td>Pulmonology</td>
<td></td>
</tr>
</tbody>
</table>
### GRIAC Brainstorm sessions 2012

<table>
<thead>
<tr>
<th>Date</th>
<th>Initiator</th>
<th>Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>27-03-2012</td>
<td>Dr. M.N. Hylkema Pathology UMCG</td>
<td>Telomeres and (respiratory) aging (in collaboration with Prof. P.M. Lansdorp, European Research Institute on the Biology of Aging)</td>
</tr>
<tr>
<td>24-04-2012</td>
<td>Dr. M.N. Hylkema Pathology UMCG</td>
<td>Concepts of IPF and remodeling in relation to ageing (in collaboration with Prof. P.M. Lansdorp, European Research Institute on the Biology of Aging)</td>
</tr>
<tr>
<td>26-06-2012</td>
<td>Dr. M. van den Berge Pulmonolgy UMCG</td>
<td>Bronchitis symposium in 2014</td>
</tr>
<tr>
<td>27-11-2012</td>
<td>Prof. Dr. G.H. Koppelman Pediatric Pulmonology UMCG</td>
<td>LifeLines, second screening</td>
</tr>
</tbody>
</table>
Research projects in 2012

AstraZeneca: Differential effects of budesonide and fluticasone on gene expression in airway epithelial cells. Focusing on immune defense. 2011-2012. Dr. M. van den Berge, Dr. IH Heijink, Dr. N.H.T. ten Hacken, Prof W. Timens, Prof. A.J.M. van Oosterhout, Prof D.S. Postma.

AstraZeneca: The risk to develop pneumonia in COPD: Comparing the effects of fluticasone propionate and budesonide on airway epithelial barrier function. 2011-2012. Dr. I.H. Heijink, Dr. M. van den Berge, Dr. N.H.T. ten Hacken, Prof. W. Timens, Prof. A.J.M. van Oosterhout, Prof. D.S. Postma.


Boehringer Ingelheim International GmbH: Evaluation of the novel steroid “ICS”, alone and in concerted action with tiotropium bromide in a guinea pig model of chronic asthma. 2010-2013. Dr. R. Gosens, Prof.dr. H. Meurs, Dr. H. Maarsingh. Technician: M. Menzen.


Chiesi Netherlands: Is it possible to recognize asthmatic subjects with small airways involvement using small particle challenge test? 2011-2012. Dr. N.H.T. ten Hacken, Dr. M. van der Berge, Prof. Dr. D.S. Postma, Dr. A.H. de Boer. PhD student: E van der Wiel.

Chiesi: FAIR study: Role of small particle steroids and LABA in COPD. 2011-2013. Dr. M. van den Berge, Dr. N.H.T. ten Hacken, Prof. Dr. D.S. Postma. PhD student: E van der Wiel.
Chiesi: the role of small airways in asthma. 2011-2012. Prof. Dr. D.S. Postma, Dr. M. van den Berge, Dr. N.H.T. ten Hacken, Prof. T. van der Molen. Post doc: L. Schiphof, PhD student: E. van der Wiel

European Community (FP7): COPD Pathology; Addressing Critical gaps, Early Treatment & diagnosis and Innovative Concepts (COPACETIC). 2007-2012. Prof.dr. D.S. Postma, Prof.dr. H.M. Boezen, Prof.dr. C. Wijmenga. Prof.dr. H.G.M. Groen with University Medical Center Utrecht, the Netherlands; University Medical Center Groningen, the Netherlands; Hvidovre University Hospital, Denmark; Jagiellonian University School of Medicine, Poland; Deutsches Krebsforschungszentrum, Germany; AstraZeneca, Sweden. PhD Students: A.E. Dijkstra, A. Smolonska.

European Community (KP7, Innovative Medicines Initiative). PROactive. Physical Activity as a Crucial Patient Reported Outcome in COPD. 2009-2014. Prof.dr. M. Decramer, Prof.dr. T. Troosters, Prof.dr. W. MacNee, Prof.dr. C. Roussos, Prof.dr. M Polkey, Dr. P. de Boer, Prof.dr. T. van der Molen, Dr. N.H.T. ten Hacken, Dr. J.W.H. Kocks, Dr. S. Schokker, Drs. C. de Jong.

European Community (FP7); European Union MeDALL-mechanisms of the Development of Allergy. 2010-2014. Prof.dr. M. Decramer, Prof.dr. T. Troosters, Prof.dr. W. MacNee, Prof.dr. C. Roussos, Prof.dr. M Polkey, Dr. P. de Boer, Prof.dr. T. van der Molen, Dr. N.H.T. ten Hacken, Dr. J.W.H. Kocks, Dr. S. Schokker, Drs. C. de Jong.

European Community (FP7); European Union MeDALL-mechanisms of the Development of Allergy. 2010-2014. Prof.dr. van Oosterhout, Prof. Dr. G.H. Koppelman, Dr. M.C. Nawijn. Technician:U. Brouwer.


European Union/COST action (European Cooperation in the field of Scientific and Technical Research): Developmental Origins of Chronic Lung Disease. 2012-2016. Dr. M.N. Hylkema, Dr. R. Gosens, Prof.dr. D.S. Postma

Goedebuure / Air Liquide: Cost-effectiveness of obstRuctivE Sleep apnea Therapy (REST study); Comparison of MRA therapy versus CPAP therapy in moderate OSAS. 2011-2014. Dr. P.J. Wijkstra, Prof.dr. H.A.M. Kerstjens. PhD-student: G de Vries

Groningen Graduate School of Science (Ubbio Emmius Phd-position); Key role of A-kinase anchoring proteins in the pathophysiology of asthma. 2011-2015. Prof.dr. M. Schmidt, Dr. H. Maarsingh. PhD-student: B. Han.

GSK/IVAX/MSD/NAF (3.4.04.013) Stichting Astma Bestrijding; Predictive factors in children aged 1-5 years with recurrent respiratory symptoms for the development of asthma at the age of 6-10 years. 2005-2012. Prof.dr. E.J. Duiverman, Prof.dr. T. van der Molen. Post-doc: Dr. S. Schokker.


GUIDE: Genetics of the course of asthma. 2009-2013. Dr. J.M. Vonk, Prof.dr. D.S. Postma, Prof.dr. H.M. Boezen, Dr. J. Gerritsen, Prof.dr. G.H. Koppelman. PhD student: D. Ierodiakonou.


GUIDE/Joint project University of Southampton: Unravelling the protective role of Pim kinases in airways diseases. 2011-2014. Dr. M.C. Nawijn Prof.dr. D.E. Davies. PhD student: M. de Vries


GUIDE/ Shantou University Medical College, China (Abel Tasman bursaal). Effect of toxic exposures during pregnancy on fetal immune and lung development. 2012-2016. Dr. M.N. Hylkema, Prof.dr. X. Huo. PhD student: J.J. Cao


International Primary Care Respiratory Group. UNLOCK: Uncovering and Noting Long-term Outcomes in COPD to enhance Knowledge. 2010-2016. Dr. N. Chavannes, Dr. I. Tsiligianni, Prof.dr. D. Price, Prof.dr. T. van der Molen.

International Research Training Group GRK 880-3 Mannheim-Heidelberg-Groningen; Vascular medicine project – (Patho)physiological role of NO/cGMP-induced RhoGEF17 activation in the vasculature. 2008-2012. Prof.dr. M. Schmidt, Dr. S. Lutz. 2 PhD students: J. Rauch, vacancy

International Research Training Group: Diabetic microvascular complications (DIAMICON). Prof. dr. M. Schmidt. Project period 3 x 3 years. Vacancy


IPCRG: Fresh Air: prevalence and burden of COPD in a rural area of sub-Saharan Africa. 2010-2014. Prof.dr. T. van der Molen, Dr. N.H. Chavannes. PhD student: F.A. van Gemert


MD/PhD: Voedselallergie, een cross-cultureel vergelijk: kwaliteit van leven, socio-economische impact, kennisniveau van patiënten en huisartsen. 2010 - 2013. Prof.dr. A.E.J. Dubois, Prof.dr. EJ Duiverman, Prof.dr. T. van der Molen, Dr. B.M.J. Flokstra-de Blok. MD/PhD student: N.J. Goossens.

MD/PhD/ALK: Epinephrine auto-injector prescription, compliance and quality of life. 2011 – 2014. Prof.dr. A.E.J. Dubois, Dr. B.M. Flokstra-de Blok. MD/PhD student: J. Saleh-Langenberg
NAF 08.014: The role of acetylcholine in chronic inflammation and remodelling in asthma and COPD. 2009-2013. Dr. R. Gosens, Prof.dr. H.A.M. Kerstjens, Prof.dr. P.S. Hiemstra. PhD student: L.E.M. Kistemaker.

NAF 3.2.10.042. Wnt/FRZzled signalling in small airway remodelling in COPD. 2010-2014. Dr. R. Gosens, Dr. H.I. Heijink, Dr. W.M. Blankesteijn. PhD student: A.I.R. Spanjer.

NAF 03.2.07.019: Cutting down on E-cadherin; Evaluating E-cadherin as a key regulator of allergic asthma. 2008-2012. Dr. H.I. Heijink, Dr. M. Nawijn, Prof.dr. A.J.M. van Oosterhout. PhD student: S. Post.


NAF 3.2.09.055: Protocadherin-1 expression in airway epithelium: Investigations into a novel cause of bronchial hyperresponsiveness and asthma. 2009-2013. Dr. G.H. Koppelman, Dr. M.C. Nawijn, Prof.dr. D.S. Postma. Post doc: Dr. B.W. Willemse.


NAF 3.2.09.036: Th17 responses in asthma: Protection against atopy versus development of non-allergic asthma. 2010-2014. Dr. M.N.Hylkema, Dr. I. Wouters. PhD student: P. Robbe.


NAF 3.2.09.043. "The pediatric origins of COPD". 2009-2012. Dr. M. Kerkhof, Prof.dr. D.S. Postma.


NAF 3.2.11.024: Abnormal tissue repair and remodeling in COPD; from genomics to biological function. 2011-2013. Dr. C-A Brandsma, Dr. M. van den Berge, Prof.dr. W. Timens. Post-doc: C.A. Brandsma, technician: S. Brouwer

NAF 3.2.12.044: The functional relevance of microRNAs in COPD; elucidating their role in regulating pulmonary fibroblast function in COPD development. 2012-2016. Dr. C-A Brandsma, Prof.dr. W. Timens, Prof.dr. DS Postma. PhD-student: V. Rajendran

NAF 3.2.12.083: Follistatin-like 1, a crucial factor in lung development, as a novel regulator in COPD. 2012-2017. Dr. H. Maarsingh, Dr. M. van den Hoff, Prof.dr. M. Schmidt. PhD student: N.P. Tania

NAF 3.2.12.079: Laminin α4 and α5 as regulators of airway inflammation and remodelling in allergic asthma. 2012-2017. Dr. B.G.J. Dekkers, Prof. L.M. Sorokin, Prof. H. Meurs. Post-doc: vacancy

NAF 3.2.11.013: Prenatal programming by maternal smoking during pregnancy: susceptibility for development of COPD. 2012-2016. Dr. M.N. Hylkema, Prof.dr. L. Kobzik (Harvard School of Public Health). PhD student: K. Meyer


Nykomed; Development of the Clinical Short-form Inhaled Corticosteroid Questionnaire Scale. 2008-2012. Prof.dr. T. van der Molen, Prof.dr. R. Sanderman, Prof.dr. D.S. Postma. Post-doc: J.M. Foster.

Phadia; In vitro Diagnostiek en Eerstelijns Allergie Leidraad (IDEAL) 2009-2013. Prof.dr. A.E.J. Dubois, Prof.dr. T. van der Molen, Dr. B.M.J. Flokstra-de Blok, T. Brakel, MSc.


RESMED : SERVE-HF; The SERVE-HF trial is investigating the value of adaptive servo-ventilation (ASV) to improve morbidity and mortality rates in heart failure patients with predominant central sleep apnoea. 2012-2013. Dr. P.J. Wijkstra , Prof.dr. H.A.M. Kerstjens. PhD-student: G de Vries.

Rosetta Inpharmatics ; LKR57970: Identification of key mechanistic drivers of lung disease. 2009-2014. Prof.dr. W. Timens, Prof.dr. D.S. Postma. (Lung Cohort Study, together with University of British Columbia, Vancouver (P. Pare) and Hospital Laval, Quebec (Y. Bosse)).
Royal Academy of Arts and Sciences (KNAW). What is normal in inflammation? 2009-2013. Prof.dr. D.S. Postma, Dr. M. van den Berge. PhD-student E. Telenga.


SMF; Remission and progression of asthma: genetic and epigenetic regulation. 2012-2013. Prof.dr. D.S. Postma, Prof.dr. G.H. Koppelman, Dr. J.M. Vonk, O. Savenije, MSc, M.A.E. Nieuwenhuis, MSc.

Stichting Astma Bestrijding (SAB); Wat is de invloed van een dubbelblinde placebo gecontroleerde voedselprovocatie op kwaliteit van leven?; Responsiviteit en validiteit van de voedselallergie en kwaliteit van leven vragenlijsten voor voedselallergische patiënten. 2008-2012. Prof.dr. A.E.J. Dubois, Prof.dr. E.J. Duiverman, Dr. B.M.J. Flokstra-de Blok. PhD student: J.L. van der Velde.


STW Improvement of Diagnostic methods for Allergy assessment. Cashew allergy in children as a showcase (IDEAL/ORCA study). 2012-2016. Prof.dr. A.E.J. Dubois, Dr. B.M.J. Flokstra-de Blok. technician: A. Oomkes-Pilon


Top Instituut Pharma 1-201; Groningen, Maastricht, Utrecht; Transition of systemic inflammation into multiorgan pathology. 2008-2012. Prof.dr. A.M.W.J. Schols, Prof.dr. E.F.M. Wouters, Prof.dr. W. Buurman, Prof.dr. W. Lamers, Dr. E. Blaak, Dr. R. Langen, Dr. H. Gosker, Prof.dr. L. Koenderman, Prof.dr J.W.J. Lammers, Dr. L. Ulfman, Prof.dr. D.S. Postma. PhD student: R.F. Hoffmann, Technician: S.M. Brandenburg.

University of Groningen. The role of Wnt signaling in airway smooth muscle remodeling in asthma. 2010-2014. Dr. R. Gosens. PhD student: K. Kumawat


University Medical Center Groningen (Innovative research): “A structured life style intervention on enhancement of daily physical activity and physical fitness in COPD patients in the first, second, and third line. 2006-2012. Dr. N.H.T. ten Hacken, Dr. M.H. de Greef, Dr. J.B. Wempe. PhD-student: W. Altenburg.


ZonMW 80-82305-97-11018. A randomized controlled trial to evaluate the performance of bronchoscopic lungvolume reduction for patients with severe COPD using the best responder criteria (STELVIO trial), 2010-2013, Dr D.J. Slebos. Studycoordinator: K. Klooster


Also a substantial contribution for several projects has been obtained from the Stichting Astma Bestrijding (SAB).
Publications 2012

Dissertations

F. Talaei.
Modulation of endogenous H2S production. Its role in hibernation and pharmacological cell protection.
(January 30, 2012)
Promotores: Prof. RH Henning, Prof. M Schmidt.

B.J.A. Piavaux
Mapping of asthma susceptibility in recombinant congenic mouse strains.
(April 4, 2012).
Promotor: Prof. AJM van Oosterhout
Co-promotor: Dr. MC Nawijn

H. Maazi
Immune regulation by allergen immunotherapy, lessons learned from experimental approaches.
(April 11, 2012)
Promotor: Prof. AJM van Oosterhout
Co-promotor: Dr. MC Nawijn

S. Shirinbak
Immune regulation by allergen immunotherapy, lessons learned from experimental approaches.
(April 11, 2012)
Promotor: Prof. AJM van Oosterhout
Co-promotor: Dr. MC Nawijn

H.A. Baarsma
Glycogen synthase kinase-3 (GSK-3) and beta-catenin: potential novel therapeutic targets for COPD.
(June 15, 2012)
Promotores: Prof. H Meurs, Prof. HAM Kerstjens
Co-promotor: Dr. R Gosens

S.E. Budulac
Linking gene polymorphisms with COPD onset and pathology
(September 10, 2012)
Promotores: Prof. HM Boezen, Prof. DS Postma, Prof. W Timens

J.B. Snoeck-Stroband
Clinical phenotyping of COPD - Effects of inhaled corticosteroids in the GLUCOLD study
(September 12, 2012)
Promotores: Prof. PJ Sterk, Prof. PS Hiemstra, Prof. DS Postma

H. Koning
Characterization and regulation of Protocadherin-1, a novel gene for asthma
(November 21, 2012)
Promotores: Prof. GH Koppelman, Prof. AJM van Oosterhout, Prof. DS Postma
Co-promotor: Dr. MC Nawijn

B.L. Rottier
Improving drug delivery to the lungs. Towards better inhalation therapy.
(November 28, 2012)
Promotor: Prof. EJ Duiverman
Co-promotor: Dr. AH de Boer
M.H.J. Doff
Long term management of the obstructive sleep apnea hypopnea syndrome; continuous positive airway pressure versus oral appliance.
(November 28, 2012)
Promotores: Prof. LWG de Bont, Prof. Stegenga
Co-promoter: Dr PJ Wijksta

J.L. van de Velde
Quality of life of food allergic patients
(December 3, 2012)
Promotores: Prof. AEJ Dubois, Prof. EJ Duiverman
Co-promotor: Dr. BMJ Flokstra-de Blok

J. Prins
Reproductive Immunology: Modulation of immune responses in pregnancy and effects on pregnancy outcome
(December 5, 2012)
Promotores: Prof. JG Aarnoudse, Prof. AJM van Oosterhout, Prof. SA Robertson

Publications SCI journals


Berg van den ME, Flokstra-de Blok BM, Vlieg-Boerstra BJ, Kerkhof M, van der Heide S, Koppelman GH, Postma DS, Dubois AE. Parental eczema increases the risk of double-blind, placebo-controlled reactions to milk but not to egg, peanut or hazelnut. Int Arch Allergy Immunol 2012;158:77-83.


Budulac SE, Vonk JM, Postma DS, Siedlinski M, Timens W, Boezen MH. Nicotinic acetylcholine receptor variants are related to smoking habits, but not directly to COPD. PLoS One 2012;7:e33386.


Savenije OE, Kerkhof M, Koppelman GH, Postma DS. Predicting who will have asthma at school age among preschool children. J Allergy Clin Immunol 2012;130:325-331.


Telenga ED, Tideman SW, Kerstjens HA, Ten Hacken NH, Timens W, Postma DS, van den Berge M. Obesity in asthma: more neutrophilic inflammation as a possible explanation for a reduced treatment response. Allergy 2012;67:1060-1068.


Publications in Dutch


Kocks JWH. Hoe vaak moet de CCQ-/MRC-vragenlijst worden afgenomen? Spreekuur Huisartsgeneeskunde 2012(May).


Books / Book chapters


CONTRIBUTIONS TO OTHER RESEARCH INSTITUTES (NOT GRIAC)

Publications SCI journals


