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Mission statement

The mission of the GRIAC is the multidisciplinary study of all aspects of obstructive airway and pulmonary diseases by interaction between clinicians and basic scientists. The focus of research is on asthma and COPD, which involves:

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.

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

Ad 2) Studies on genes, gene expression and function, and the molecular mechanisms and the interplay of genetic and environmental factors in disease development, progression, remission, and severity, as well as disease intervention (pharmaco-genomics).

Ad 3) In vivo studies in man and in animal models using mice and unrestrained guinea pigs. Investigations include lung function techniques and studies in tissues or cells derived from airway or lung tissue. Furthermore, in vitro studies assess cellular activation and interaction as well as signaling 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 from lung tissue obtained by bronchoscopy, by surgical biopsy or autopsy.

Ad 4) Disease outcome assessment is being studied with techniques such as exhaled breath analyses and studies of small airway function. In addition, validated questionnaires on Quality of Life, drug side effects, hyperresponsiveness and symptoms are being developed for diagnostic purposes as well as outcome assessment. Interventions can be at the level of cell cultures, animal models, and clinical studies.

Coordinators:
Prof. dr. H.M. Boezen
Prof. dr. W. Timens (until June 1, 2011)
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**Introduction**

Research on asthma and COPD as currently performed within the Groningen Research Institute for Asthma and COPD (GRIAC) fits within the research of the University Medical Center Groningen. The institute is part of the governmentally accredited organization GUIDE (Groningen University Institute for Drug Exploration). Traditionally research on asthma and COPD in Groningen is performed on the edge between clinical and fundamental research, arising from a clinical-scientific background. Most research is funded by external support as given by NWO, Dutch Asthma 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).
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.

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 defense 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. defense 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 coordinators lead the Institute. They have the following tasks:

- Division coordinator in GUIDE
- 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 coordinators 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 *in vitro* cellular systems and *in vivo* animal models. The other way around, hypotheses generated from *in vitro* or *in vivo* research are translated to the clinical human situation.

To this aim GRIAC focuses on the following main topics related to asthma and COPD:
- 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.
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 and gene-treatment interactions are ongoing, as well as gene methylation studies. Together with the joint effort involving three prospective birth cohorts in the Netherlands (Universities of Utrecht, Rotterdam, Maastricht and Groningen) this might lead to identification of novel genes and environmental factors playing a role in disease onset and progression. We intend to 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.

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.
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. A study which will be starting in the near future will examine the effect of anti-IgE treatment in patients with peanut allergy.

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.

Top Institute Pharma has provided the opportunity to better understand the heterogeneity of COPD. This heterogeneity may encompass both the respiratory system and systemic inflammatory mechanisms as well as the existing co-morbidities of muscle wasting and fat changes. It can be foreseen that these collaborative effort can be expanded to a European level in the European KP7 within the IMI frame. This opens exciting foresights into the understanding of COPD.

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. Some of the results in internal medicine and basic science have been published in top peer reviewed journals and patents have also been filed. GRIAC members will be 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, several of these GRIAC members are relatively young (mid-thirty to early-forty years of age), and show high potential to excel even more prominently in their specific research field (e.g. epidemiology, pediatric and adult pulmonology, and molecular pharmacology) in the future. 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. A shift in focus from
smaller (e.g. Dutch Asthma Foundation) towards larger (inter)national and interdisciplinary research grants (NWO TOP grants, European funding) as well as personal grants (VENI, VIDI, VICI and ERC grants) is warranted given the increasingly limited national budget (e.g. from the Dutch Asthma Foundation, and the Universities and Medical Centers).
The year 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 2011.

Highlights

Prof. dr. W. Timens ended his coordinatorship of GRIAC after many years of dedication. He was succeeded by Prof. dr. G.H. Koppelman, who now joined Prof. dr. H.M. Boezen as coordinator. We thank Prof. Timens for his enthusiastic and highly appreciated leadership and wish Prof. Koppelman success in the coming years.

We are very happy with the appointments of Prof. dr. M. Schmidt as Full Professor of Molecular Pharmacology, Dr. G. Koppelman as Tenure Track Professor of Pediatrics, in particular Pediatric Pulmonology, and Dr. M.N. Hylkema as Associate Professor.

Dr. B.L. Rottier was elected secretary of the Pediatric Asthma and Allergy Group of the ERS.

Several international meetings were organized by GRIAC members:
- Dr. B.N. Melgert organized a minisymposium at the ERS entitled: ‘Macrophage heterogeneity in respiratory diseases’ (Amsterdam, September 24-28, 2011).
- Prof. dr. M. Schmidt organized the BPS focused meeting ‘Novel cAMP signaling paradigms: New insights into the development and progression of chronic inflammatory diseases’ of the British Pharmacological Society (London, July 7-8, 2011)
- Prof. dr. H. Meurs, Prof. dr. M. Schmidt, Dr. R. Gosens and Prof. dr. H.M.W. Boddeke organized the ‘3rd International Conference on Non-neuronal Acetylcholine’ in Groningen (August 24-26, 2011).

Prof. dr. W. Timens was a member of expert panel meetings on ‘Future Visions of Prevention, Diagnosis and Therapy for Asthma: priorities in asthma research’ (Utrecht) and of the ETOP (European Thoracic Oncology Platform, NKI Amsterdam, November 11, 2011).

In October 2011 a delegation of GRIAC investigators visited the Department of Pulmonology, University Medical Centre in Ghent, Belgium for a joint meeting. Each group presented their work and collaborations were discussed.
**Prizes/Awards**

Prof. dr. H.M. Boezen was awarded the prestigious COPD Research Award of the European Respiratory Society.

Dr. B.G.J. Dekkers was awarded the Thesis Award 2010 of the Dutch Society for Pharmaceutical Sciences, for the best PhD thesis in Pharmaceutical Sciences presented in 2010.

Dr. J.W.H. Kocks was awarded the Vasco da Gama Junior Research Champion Award 2011 of Wonca Europe.

**Visitors**

Prof. dr. Guy Brusselle, Dept of Pulmonology, University Medical Centre, Gent, Belgium: ‘New insights into the pathogenesis of COPD’, June 17, 2011

Prof. dr. Pieter S. Hiemstra, Leiden University Medical Centre, Leiden, The Netherlands: ‘Role of vitamin D in regulating airway epithelial cell function’, June 17, 2011

Dr. Paul Kirkham, National Heart & Lung Institute, Imperial College London, UK: ‘Carbonyl stress and autoimmunity in COPD’. September 13, 2011.

Introduction
Chronic obstructive pulmonary disease (COPD) is characterized by a progressive lung function decline that is associated with an inflammatory response of the airways to noxious particles or gases. Inhaled corticosteroids (ICS) are capable to suppress inflammation and are very effective in asthma treatment. Although some beneficial long-term effects of ICS in COPD have been reported in several studies, results have been conflicting. For this reason, the role of ICS in COPD has been the subject of much debate. Recently, the Groningen and Leiden Universities study of Corticosteroids in Obstructive Lung Disease (GLUCOLD) has been carried out. In this randomized placebo-controlled study, the long-term effects of fluticasone or fluticasone/salmeterol were investigated in patients with COPD.

The GLUCOLD study showed more positive effects than most earlier studies. As could be expected, COPD patients who were treated with placebo experienced a considerable decline in their forced expiratory volume in one second (FEV₁) of 87 ml/year between 6 and 30 months of follow-up. Importantly, treatment with fluticasone with or without added salmeterol significantly diminished the rate of FEV₁ decline, being close to zero for fluticasone and only 21 ml/year for fluticasone/salmeterol. The larger benefits by ICS observed in the GLUCOLD may suggest that long-term ICS treatment can have a beneficial effect, at least in a subgroup of COPD patients.

To better understand the underpinning molecular mechanisms of these long-term beneficial effects of corticosteroids, we performed genome-wide gene expression profiling in bronchial biopsies from COPD patients who participated in the GLUCOLD study both before and after 6 and 30 months of treatment with inhaled fluticasone with or without added salmeterol.

Methods
All COPD patients participating in the GLUCOLD study were included. The in- and exclusion criteria have been published earlier. COPD patients were randomly assigned to receive 1 of 4 double-blind treatments: fluticasone 500 μg b.i.d. for 30 months; fluticasone/salmeterol 500/50 μg b.i.d. for 30 months, placebo b.i.d. for 30 months, or fluticasone 500 μg b.i.d. for the first 6 months followed by placebo b.i.d. for the remaining 24 months of the study. During follow-up, spirometry was performed every three months. In addition, a bronchoscopy with endobronchial biopsies was performed at baseline and after 6 and 30 months of treatment. Biopsies were immediately snap-frozen and stored at -80 °C allowing to extract RNA for genome-wide gene expression profiling using the Affymetrix Gene ST version 1.0 microarray.

Results
A total of 89 out of 114 randomized COPD patients in GLUCOLD had two or more frozen biopsies available with RNA and microarray data of sufficient quality for analysis.

Linear mixed effects modeling revealed that the expression of 138 genes significantly decreased, whereas the expression of 140 genes increased after both 6 and 30 months of treatment (False Discovery Rate [FDR] < 0.25). Thus, a total of 278 genes were affected by ICS treatment (figure 1). Importantly, a relatively large number of 50 out of these 278 genes could be validated in the 4th GLUCOLD study arm.
Gene Set Enrichment Analysis (GSEA) showed that genes down-regulated after ICS treatment are involved in pathways related to cell cycle, oxidative phosphorylation, epithelial cell signaling, p53 signaling and T cell signaling. Genes up-regulated after ICS treatment are involved in pathways related to focal adhesion, gap junction and extracellular matrix deposition.

Finally, we applied GSEA to evaluate whether the treatment-related changes in airway gene-expression from GLUCOLD are associated with disease activity in an independent cohort that investigated airway epithelial gene expression in a large group of 87 patients with COPD compared to 151 non-COPD controls. Importantly, it was found that genes with a decrease in expression after ICS treatment are enriched for genes with a higher expression in COPD relative to non-COPD controls (GSEA FDR < 0.001, figure 3). Conversely, genes with increased expression after ICS treatment are significantly enriched for genes with a lower expression in COPD (GSEA FDR < 0.001).

Implications
Our study has identified 278 genes that change in expression after treatment with fluticasone ± salmeterol versus placebo in patients with moderate-to-severe COPD. We validated these treatment-associated changes in gene expression in 21 independent patients who were treated with fluticasone for 6 months followed by withdrawal of treatment during the remaining 24 months of the study. This finding suggests that many of the treatment-induced changes in gene expression are dependent on the continued administration of ICS. Importantly, we showed in an independent dataset that the ICS-induced gene expression changes are the converse of the ones associated with the presence of COPD, compatible with the observation that ICS-treatment improved COPD disease activity in GLUCOLD.

Our findings support the concept a molecular “field of injury” in the airways of smokers with COPD. They provide, for the first time, evidence that this field of injury is dynamic with COPD treatment and may potentially serve as an intermediate marker of therapeutic efficacy. The data provide insight into the biological pathways that potentially mediate treatment-induced clinical improvement in COPD.

Reference List


Figure 1 Heatmap showing the changes in expression of the 278 genes that are significantly affected after A) 0-6 and B) 0-30 months of treatment with fluticasone ± salmeterol compared to placebo.
Special Topic 2:

Linking gene polymorphisms with COPD onset and pathology

SE Budulac, DS Postma, W Timens, HM Boezen

Advances in knowledge about the biology and genetics of COPD have been accompanied by improved understanding of the factors leading to this disease. The main goal of performing genetic research in complex diseases like COPD is to investigate and question why some people develop the disease while others do not, independent of their smoking status. Another goal is to identify the best strategy to prevent the progression of the disease and minimize the detrimental effects of the genetic factors or take advantage of the beneficial effects some genes are displaying and incorporate this knowledge into the existing COPD treatment.

In the current PhD research project we have studied genetic aspects of COPD onset and pathology in COPD patients from the GLUCOLD study (n=114) who were previously studied with respect to anti-inflammatory and clinical effects of inhaled corticosteroids (ICS) with or without long-acting β-agonists (LABAs) [1].

One of the genes we have studied was Multidrug resistance-associated protein-1 (MRP1) that is involved in the cellular oxidative defence system and inflammation and may play a role in smoking related development of COPD and severity and progression of the disease. Our previous studies had shown that single nucleotide polymorphisms (SNPs) in MRP1 are associated with level and decline of lung function in the Vlagtwedde-Vlaardingen cohort [2]. Consequently, we investigated these SNPs in individuals with established COPD (GLUCOLD) [3]. We showed for the first time that MRP1 plays a role in COPD severity, given the association of the SNPs in MRP1 with airway wall inflammation, the level of lung function and moreover MRP1 protein levels (see table 1).

<table>
<thead>
<tr>
<th>FEV₁ level</th>
<th>Inflammatory cells</th>
<th>MRP1 protein level</th>
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<tbody>
<tr>
<td></td>
<td>Bronchial biopsies</td>
<td>Induced sputum</td>
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<tr>
<td>rs2120393</td>
<td>↑</td>
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<tr>
<td>rs4143382</td>
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<td>–</td>
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<tr>
<td>rs504348</td>
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<td>rs4781699</td>
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<td>↓</td>
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<td>rs36621</td>
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</tbody>
</table>

Table 1: Summary of MRP1 SNPs’ associations for COPD patients. FEV₁ = forced expiratory volume in one second; MRP1 = multidrug resistance-associated protein-1; ↑ = positive association; ↓ = negative association; – = no association.

We focused additionally on the associations of MRP1 SNPs and MRP1 protein expression in airway wall biopsies with the decline of lung function in the same population of COPD patients. We found a higher MRP1 protein expression to be associated with less FEV₁ decline in COPD patients using long-term therapy with inhaled corticosteroids (ICS) as well as with a faster FEV₁ decline after withdrawal of ICS, but observed no associations in patients using placebo or the combination of long-acting β-agonists (LABAs) and ICS. This suggests that MRP1 protein expression may reflect one of the COPD phenotypes that is sensitive to inhaled corticosteroid therapy.
Additionally, in search for genetic determinants that lead to COPD onset we used longitudinal data from the general population-based Vlagtwedde/Vlaardingen cohort study. We investigated whether genetic variation in the nicotinic receptor nAChR (previously identified as being associated with COPD in genome wide association studies) is associated with COPD independently or via smoking habits. We investigated 3 SNPs in the nAChR cluster (rs569207, rs1051730 and rs8034191) and observed that rs1051730 and rs569207 are associated with an increased respectively decreased ability to quit smoking, but have no significant effect on the annual FEV1 decline in smokers and ex-smokers separately (figure 1). This is the first longitudinal study from the general population suggesting that SNPs in the nAChR cluster potentially have a causal role in COPD, yet purely via smoking habits (Figure 2). Thus of great interest to the interpretation of other genetic studies in the field of COPD genetics, our study suggests that nAChR cluster variants are related to the onset of COPD via their association with smoking habits, and they are not independently associated with COPD [4].

Although genetic studies on COPD have some limitations and should be carefully interpreted, we believe they can greatly contribute to the progress in elucidating the pathogenesis of COPD. Future studies will bring us insight into mechanisms underlying various phenotypes of COPD including onset of and type of emphysema, pulmonary hypertension and mucus hypersecretion, leading to the development of a specific treatment for each part of the disease process.

---

**Figure 1:** SNPs in the nAChR cluster and OR (95%CI) for quitting smoking in subjects who smoke (upper graph), and OR (95%CI) for restarting to smoke in ex-smokers (lower graph). Nr. of pairs= number of paired observations in which the subject stopped respectively restarted smoking/ total number of paired observations included in the analysis; Circles represent the odd ratio (OR) and vertical bars represent 95% confidence interval (CI); Wild type was set to one as the reference category; Different total number of paired observations for the SNP genotypes are due to missing data on genotype or smoking habits. The analyses are adjusted for gender and the time between 2 successive surveys.
Figure 2: Summary of the observed associations in the current study. SNPs = single nucleotide polymorphisms; COPD = Chronic Obstructive Pulmonary Disease; nAChR = nicotinic acetylcholine receptor; + = association; - = no association.

Reference list
Special Topic 3:

GRIAC Hot Topic: Health status measurement in the treatment of COPD

JW Kocks

With the inclusion of health status measurement in the 2011 GOLD strategy[1], one of GRIAC primary care group’s goals has been achieved. The respiratory group within the department of general practice has been promoting the inclusion of symptoms and health status in the evaluation and management of COPD for the last decade. In 2011 Roland Riemersma and Janwillem Kocks, both practicing general practitioners, defended their PhD theses. Roland Riemersma described the development of the bronchial hyperresponsiveness scale and the development of an successful integrated care program for respiratory diseases in primary care[2] and Janwillem Kocks defended his thesis on health status guided care in COPD[3].

One of the tools to assess health status in routine clinical practice is the Clinical COPD Questionnaire (CCQ)[4]. The CCQ has been developed for both research and clinical use as a COPD specific health status measure according to the high standards of questionnaire development and validation and was first published in 2003. The CCQ has been translated into more than 70 languages and is used worldwide(www.ccq.nl). It has shown good measurement properties [4-6]. The CCQ consists of 10 questions rated on a seven point Likert scale. Higher scores represent worse health status. Questions are divided into three domains: symptoms (4 questions), functional status (4 questions), and mental state (two questions).

Why measure health status?
Health status measurement is a way of quantifying, in a standardised and objective manner, the impact of COPD on patients’ daily life, health, and wellbeing [7]. In clinical studies, patients have traditionally been categorised according to FEV₁ and effectiveness of therapy has routinely been assessed as change of lung function. The COPD research community and regulatory agencies have underlined it’s importance as an objective index of that measures both symptomatic relief and disease progression [8]. However, FEV₁ has a very poor correlation with most measures of COPD that matter to patients, such as exercise tolerance, symptoms, and also HRQOL.

Therefore, currently most researchers regard changes in patient centred outcomes, such as symptoms, exacerbations, functional status and health status, more important than changes in lung function [8], because these better reflect the complexity and the impact of the disease and several aspects of health status also predict clinical meaningful outcomes in COPD [9, 10]. Functional status as part of health status has been shown to predict exacerbations [11, 12], hospital admissions [11-15] and mortality [16, 17]. Mental status can be measured with different tools and usually at least partially reflect anxiety and depression which are predictors of worse outcome in COPD [18-22].

For clinical practice, health status gives the opportunity to quickly assess the impact of COPD, evaluate treatment and follow disease progression in a standardised way[23-25].

How to measure health status?
In routine clinical practice, health care professionals ask their patients how they are doing, the patient’s response informs the health care professional about parts of the patient’s health status. These answers might not completely reflect what is really important to the patient and health care professional. A thorough clinical history gives a better insight of a patient’s health status.
than (just) the question “how are you?”. But highly structured history taking and recording requires much more effort than using standardised patient completed questionnaires. Reviewing standardised questionnaires about the impact of the disease over longer periods takes less effort than reviewing notes in medical records and the information is more comprehensive [26].

Many instruments have been developed in the last decades to measure health status, first for the use in clinical trials, and later for the use in clinical practice as well. Carefully developed and validated questionnaires are precision measurement instruments that are able to capture patient’s health state in a reliable, reproducible way and are responsive to changes in a patient’s health state [27]. These instruments can roughly be divided in tools that measure general health status like the MOS 36-item short-form health survey SF-36 [28], or disease specific health status, for COPD for example the Saint Georges’ Respiratory Questionnaire [29], Chronic Respiratory Questionnaire [30], the GlaxoSmithKline’s COPD Assessment Test[31] or the Clinical COPD Questionnaire [4]. The advantage of general health status questionnaires is that the scores can be compared with other diseases, the greatest disadvantage is that these general questionnaires are less sensitive for changes in the impact of a specific disease like COPD [32]. Therefore, in COPD disease specific questionnaires are more often used to assess health status.

For clinical use, the International Primary Care Respiratory Group (IPCRG) issued a review of tools that measure ‘COPD wellness’ as a practical guide for healthcare professionals working in their everyday clinical practice [33].

Results of using health status in guiding COPD care and future perspective
The integrated asthma and COPD care service[2], which currently contains more than 12,000 patients in the northern parts of the Netherlands, uses health status questionnaires in algorithms to aid the lung physician in advising the general practitioner how to treat the patients. Both the feedback from the lung physicians and preliminary follow-up data show that guiding treatment that is partly guided by information on health status scales improve asthma control and health status in this real life setting.

The Lung Alliance Netherlands is developing a study and implementation protocol to include burden of disease measurement to guide treatment in COPD patients. This “burden of disease” measure is the results of an extensive literature research and will include the Clinical COPD Questionnaire, exacerbation and smoking history, and two questions about emotions. This study RCT will prospectively study the effects of real health status driven care on health outcomes in both primary and secondary care. The primary care group look forward to the results and will continue to improve respiratory care from a primary care perspective.
References

1. [http://www.goldcopd.org/]
Special Topic 4:

Tiotropium inhibits airway inflammation and remodelling in a guinea pig model of COPD

T Pera, AB. Zuidhof, J Valadas, M Smit, RG Schoemaker, R Gosens, H Maarsingh, J Zaagsma, H Meurs

Airway wall remodelling, including peribronchial fibrosis, mucous cell hyperplasia and microvascular changes, is a characteristic feature of chronic obstructive pulmonary disease (COPD), contributing to a progressive decline in lung function and airflow limitation in this disease. The mechanisms of airway remodelling in COPD are largely unclear, but likely involve chronic inflammation of the airways, characterized by infiltration of neutrophils, macrophages and lymphocytes [1].

Anticholinergics are indicated as bronchodilator therapy in COPD [2]. However, recent reports indicate that anticholinergics may have effects beyond bronchodilation as well. Thus, the recent UPLIFT study [3-6] has shown that the use of the long-acting anticholinergic tiotropium is associated with a reduction of the number of exacerbations, and of respiratory and cardiac morbidity and mortality of COPD patients [3,4]. In addition, prespecified subgroup analyses of that study have indicated protective effects of tiotropium on postbronchodilator FEV₁ decline in patients with GOLD stage II and in young patients with COPD [5,6]. Interestingly, recent findings from airway cells and animal models have indicated that in addition to its well-known role in airway constriction and mucus secretion, acetylcholine may be importantly involved in the regulation of other pathophysiological processes in the airways, including airway inflammation and remodelling [7,8]. The role of acetylcholine in the development and progression of COPD is currently unknown. Recently, we addressed this question, using a guinea pig model of lipopolysaccharide (LPS)-induced COPD [9].

To this aim, guinea pigs were instilled intranasally with LPS (1 mg/200 µl in saline) or saline (200 µl) twice weekly for 12 weeks and were pretreated by inhalation of the long-acting muscarinic receptor antagonist tiotropium (nebulizer concentration 100 µM in saline, 3 min) or saline (3 min), 30 min before each instillation. Twenty-four h after the last instillation, the guinea pigs were sacrificed by experimental concussion, followed by rapid exsanguination. Subsequently, lung tissue was collected to investigate indices of airway inflammation and remodelling, including infiltration of neutrophils, airway fibrosis, mucous cell hyperplasia and microvascular remodelling.

The results showed that repeated LPS instillation induced significant increases in the numbers of neutrophils in both cartilaginous (2.0-fold) and non-cartilaginous (1.9-fold) airways (Figure 1). Tiotropium treatment fully prevented the LPS-induced neutrophilia in these compartments, whereas neutrophil numbers in the airways of saline-challenged animals were unaffected.
Figure 1. Effects of repeated LPS challenge and tiotropium treatment on neutrophil numbers in cartilaginous and non-cartilaginous airways. Data represent means ± S.E.M. of 8-10 experiments. *P<0.05; **P<0.01.

To evaluate fibrotic changes, lungs were analysed for hydroxyproline as an estimate of collagen content. Repeated LPS instillation induced a significant 1.3-fold increase in total lung hydroxyproline, which was fully inhibited by tiotropium (not shown). To confirm the anti-fibrotic effect of tiotropium in the airways, sirius red staining was evaluated in the airway wall of non-cartilaginous airways. Figure 2A shows that LPS induced a 1.7-fold increase in airway wall collagen, which was similarly completely inhibited by tiotropium, whereas tiotropium had no effect in saline-challenged animals.

In order to investigate the effects of LPS and tiotropium on mucus-producing goblet cells, sections were stained with a MUC5AC antibody. Repeated LPS challenge induced a significant 3.1-fold increase in the number of MUC5AC-positive cells in the epithelium of cartilaginous airways of the guinea pigs (Figure 2B). Tiotropium treatment fully inhibited the LPS-induced increase, whereas MUC5AC-positive cells in saline-challenged animals were unaffected (Figure 2B).

Repeated LPS instillation also increased the number of muscularized (sm-MHC-positive) microvessels in the adventitia of cartilaginous airways (2.4-fold; Figure 2C). This increase was similarly prevented by tiotropium. No LPS-induced changes were observed for airway smooth muscle mass under the conditions used (not shown).
Figure 2. Effects of repeated LPS challenge and tiotropium treatment on A: collagen content in non-cartilaginous airways, B: MUC5AC-positive goblet cell number in cartilaginous airways and C: the number of muscularized microvessels in the adventitia of cartilaginous airways. Data represent means ± S.E.M. of 6-9 experiments. **P<0.01, ***P<0.001.

In conclusion, this study has demonstrated for the first time that tiotropium inhalation inhibits airway inflammation and remodelling in an animal model of COPD, indicating that endogenous acetylcholine may play a major role in the pathogenesis of this disease. These effects could underly the non-bronchodilating effects of tiotropium as recently observed in COPD patients.

This study was supported by Boeringer Ingelheim Pharma GmbH & Co. KG

References
Bronchoscopic Lung Volume Reduction for patients with severe COPD

D J Slebos

Patients with end-stage COPD suffer from severe dyspnea already at very mild exercise or even at rest, resulting in a poor quality of life. The current medical treatment options like stop smoking cigarettes, inhaled bronchodilators, inhaled- and oral anti-inflammatory agents, proper nutritious support, pulmonary rehabilitation, and the use of long term oxygen treatment give some relief. However, unfortunately no therapeutic options are widely available to significantly improve the health status of these patients. Only for a very small group of COPD patients (NL 2011 ± n=40), effective, but very invasive surgical procedures with significant mortality, like lung volume reduction surgery (LVRS) or lung transplantation can be performed.

Five years ago we started with a program in our hospital focused on the development and clinical implementation of minor-invasive treatments for patients with severe COPD. This program involves a wide range of non-surgical bronchoscopic treatment modalities for patients with severe COPD, called “bronchoscopic lung volume reduction” (BVR). These much less invasive procedures have the potential of being at least equal efficacious when compared to LVRS, and is suitable for a larger group of patients. In 2011 we were already able to perform 71 bronchoscopic lung volume reduction treatments [1].

The clinical improvements seen after surgical- or bronchoscopic lung volume reduction is mainly due to a series of changes in lung mechanics: a reduction in residual volume, change in diaphragm position, improving lung tissue elastic recoil, and a reduction in dynamic hyperinflation. Because of the enormous variety in COPD phenotypes visible on a chest CT (e.g. different emphysema types, different distribution patterns, concurrent airways disease) a wide array of bronchoscopic therapies for patients with severe COPD is under development.

Current interventions focus on either reduction of airtrapping by creating a transbronchial “Airway Bypass” to release the “trapped air”, or by reducing lung hyperinflation using intrabronchially placed devices like one-way valves or nitinol coils.

The use of the concept of “Airway Bypass” was evaluated in “The EASE Trial” (NCT00391612) [2], a global, randomised (2:1), double-blind study comparing Airway Bypass to sham control (SC), aiming to evaluate safety and efficacy of creating these transbronchial passages into the lung which are supported with paclitaxel coated stents (figure 1) in patients with severe homogenous emphysema. To maintain the double-blind design, investigators were divided into blinded Team-A, completing pre and post-procedure assessments, and unblinded Team-B, performing only bronchoscopies without further patient interaction. The 6-month co-primary efficacy endpoint required both ≥12% improvement in FVC and ≥1 point decrease in mMRC over baseline. The composite primary safety endpoint is a comparison of five severe adverse events. In total 315 patients at 38 centers with severe hyperinflation (RV/TLC≥0.65) were randomised to undergo either Airway Bypass (N=208) or sham control (N=107). For Airway Bypass, mean 4.7±1.4 stents per patient were placed in 107±29 minutes. The 6-Month co-primary endpoint was 14.4% for Airway Bypass vs 11.2% for sham control. By Bayesian analysis, the posterior probability that Airway Bypass was superior to sham control was below the success threshold of 0.965 indicating that the primary efficacy endpoint was not met, whereas, the composite safety rates (AB 14.4%, SC 11.2%) were non-inferior. On day 1, RV was significantly reduced associated with increased FEV₁ and FVC; however, these were not preserved at 6 months. CT showed lobar volume decreases after stent placement at day 1, but at 6 months RV increased with stent occlusion. At this moments efforts are underway to improve
stent patency, as well as creating a “transthoracic” airway bypass, thus resulting in a “Pneumostoma” to be able to release the trapped air, and also be able to keep the passage patent (ACTRN12610000190000) [3].

Bronchoscopic lung volume reduction by reducing lung hyperinflation involves careful examination of potential collateral ventilation between the target lobe and the ipsilateral lobe(s). In patients without collateral ventilation so called “one-way valves” (figure 2), a “blocking” technique is used. These valves are placed in one lung only and are designed to induce an atelectasis of the target lobe. Crucial for success is the absence of collateral flow that can be determined by careful 3D CT fissure analysis or by using a bronchoscopic technique of measuring collateral flow: the so called “Chartis” system. The use of this treatment approach was recently evaluated in the Chartis multicenter trial (NCT01101958) [3]. In this trial 80 patients underwent a pre-treatment Chartis assessment. Before and 30 days after implantation, high-resolution CT scans were taken to determine target lobe volume reduction (TLVR). A pre- to post-treatment reduction of ≥350 ml was defined as significant. In addition, clinical outcomes (FEV1, 6-minute walk test and SGRQ) were compared over the same time period. Of the 51 patients classified as having an absence of CV according to their Chartis reading, 36 showed a TLVR ≥350 ml. Twenty-nine patients were classified as having CV, and of these 24 did not meet this TLVR cut-off. Chartis showed an accuracy level of 75% in predicting whether or not the TLVR cut-off would be reached. Those predicted to respond showed significantly greater TLVR (p < 0.0001) and FEV1 improvement (p = 0.0013) than those predicted not to respond. This trial showed that Chartis is a safe and effective method of predicting response to EBV treatment. At this moment we are conducting a randomized controlled trial using a combined CT and Chartis patient selection approach to evaluate the efficacy of one-way valve treatment (NTR2876).

In patients who have presence of collateral flow, one-way endobronchial valves are not successful and a different “non-blocking” technique using nitinol coils (figure 3) has become available. In a first-in human pilot trial we showed the feasibility of this bronchoscopic lung volume reduction therapy by using segmentally inserted nitinol coils that contract the emphysematous lung tissue, therefore not being limited in efficacy by collateral flow (NCT01220908) [4]. In this prospective cohort pilot study patients were treated bronchoscopically with nitinol LVR-coils under fluoroscopic guidance in either one, or two sequential procedures. Follow-up tests included SGRQ, pulmonary function testing and 6MWT. A total of twenty-eight LVR-coil procedures were performed in 16 patients (baseline FEV1 28% (±7.6%) predicted). Four patients were treated in one, and 12 patients were treated in both lungs. Median 10 (5-12) coils in 36.5 (20-60) minutes were placed per lung. Adverse events rated as possibly related to either the device or the procedure <30 days after treatment were pneumothorax (n=1), pneumonia (n=2), COPD exacerbation (n=6), chest pain (n=4), or mild (<5mL) hemoptysis (n=21). From 30 days to 6 months these were: pneumonia (n=3), and COPD exacerbation (n=14). All events resolved with standard care. Six months after LVR-coil treatment there were significant improvements in SGRQ: -14.9 points (±12.1 points, with 11/16 patients improving >14 points), in FEV1 (+14.9% ±17.0%), FVC (+13.4% ±12.9%), RV (-11.4% ±9.0%), and 6MWT (+84.4m ±73.4m), all p<0.005. LVR-coil treatment is a promising technique for the treatment of patients with severe heterogeneous emphysema. The treatment is technically feasible and results in significant improvements in pulmonary function, exercise capacity and quality of life with an acceptable safety profile. At this moment we are conducting a multicenter follow-up multicenter trial (NCT01328899) and are exploring the use of coils in a broader range of emphysema phenotypes and are studying its mechanism of action (NCT01421082).
1. http://www.bronchoscopie.umcg.nl

Figure 1. “Exhale” Paclitaxel coated airway bypass stent

Figure 2. “Zephyr” One-way endobronchial valve

Figure 3. “RePneu” Nitinol Lung Volume Reduction Coil
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<td>Dr. A. de Boer</td>
<td>Mechanisms of lung deposition and influencing variables</td>
</tr>
<tr>
<td>07-06-2011</td>
<td>Dr. L. Franciosi</td>
<td>Analysis of human epithelial lining fluid for biomarker discovery in COPD: a proteomic approach</td>
</tr>
<tr>
<td>08-06-2011</td>
<td>Dr. M. Joerink</td>
<td>Maternal lifestyle and allergy, does it influence the intrauterine environment and the programming of allergic disease</td>
</tr>
<tr>
<td>21-06-2011</td>
<td>Dr. D. Caudri</td>
<td>Childhood asthma – perinatal risk factors and early detection</td>
</tr>
<tr>
<td>05-07-2011</td>
<td>Dr. J.W. Kocks</td>
<td>Changing current COPD care: towards health status guided care in COPD</td>
</tr>
<tr>
<td>06-09-2011</td>
<td>Dr. S. Budulac</td>
<td>Linking gene polymorphisms to pathophysiology of COPD</td>
</tr>
<tr>
<td>04-10-2011</td>
<td>Dr. B. Piavaux</td>
<td>Mapping of asthma susceptibility in recombinant congenic mouse strains</td>
</tr>
<tr>
<td>Date</td>
<td>Speaker</td>
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<tr>
<td>01-11-2010</td>
<td>Dr. N. Ten Hacken</td>
<td>Therapeutic implications of small airways in asthma</td>
</tr>
<tr>
<td></td>
<td>Dr. R. Rottier</td>
<td>(Ab)normal lung development in mouse and man</td>
</tr>
<tr>
<td>06-12-2011</td>
<td>Prof. Dr. H. Meurs</td>
<td>Anticholinergics in airway diseases: new tricks for an old dog</td>
</tr>
<tr>
<td>Date</td>
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<tr>
<td>04-01-2011</td>
<td>Anouk Oldenburger</td>
<td>The “old second messenger” cyclic AMP in cigarette smoke-induced inflammation and epithelial barrier function</td>
</tr>
<tr>
<td>11-01-2011</td>
<td>Tina van der Velde</td>
<td>The impact of food allergy on quality of life</td>
</tr>
<tr>
<td>18-01-2011</td>
<td>Fatemeh Fattahi</td>
<td>An old dilemma: asthma with irreversible airway-obstruction or COPD?</td>
</tr>
<tr>
<td>25-01-2011</td>
<td>Anda Hazenberg</td>
<td>EOLUS, initiation of chronic ventilatory support outside the hospital (the protocol and the lessons we learned)</td>
</tr>
<tr>
<td>01-02-2011</td>
<td>Henk Koning</td>
<td>Protocadherin-1 mRNA expression is regulated by house-dust mite and cigarette smoke exposure in mouse models</td>
</tr>
<tr>
<td>08-02-2011</td>
<td>Susan Hoonhorst</td>
<td>First results of skin blanching and AGE reader in the TIP study</td>
</tr>
<tr>
<td>15-02-2011</td>
<td>Eef Telenga</td>
<td>The effects of smoking on corticosteroid-induced changes in clinical and inflammatory variables in asthma</td>
</tr>
<tr>
<td>01-03-2011</td>
<td>Grietje de Vries</td>
<td>Conservative therapy in obstructive sleep apnea syndrome (OSAS)</td>
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<tr>
<td>08-03-2011</td>
<td>Despo Ierodiakonou</td>
<td>TGFβ1 gene polymorphisms and course of asthma</td>
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<tr>
<td>15-03-2011</td>
<td>Wytske Altenburg</td>
<td>The COACH study: A structured lifestyle physical activity counselling program, preliminary results</td>
</tr>
<tr>
<td>22-03-2011</td>
<td>Nienke Vink</td>
<td>NR3C1/NR3C2 gene polymorphisms and asthma development</td>
</tr>
<tr>
<td>29-03-2011</td>
<td>Tjitske Oenema</td>
<td>Crosstalk between muscarinic receptor and TGF-b1 in human airway smooth muscle cells</td>
</tr>
<tr>
<td>05-04-2011</td>
<td>Jorine Hartman</td>
<td>Sleep Quality and the association with Quality of life and physical activity in COPD</td>
</tr>
<tr>
<td>12-04-2011</td>
<td>Neomi Grotenboer</td>
<td>IL1RL1 re-sequencing in asthma patients</td>
</tr>
<tr>
<td>19-04-2011</td>
<td>Ines Schulten</td>
<td>A study on IgE heterogeneity in food allergy</td>
</tr>
<tr>
<td>Date</td>
<td>Author</td>
<td>Title (and Details)</td>
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<tr>
<td>26-04-2011</td>
<td>Kuldeep Kumawat</td>
<td>Molecular Pharmacology: Autocrine Wnt5a Signaling Regulates TGF-b1 induced Airway Smooth Muscle Remodeling</td>
</tr>
<tr>
<td>24-05-2011</td>
<td>Sylwia Figarska</td>
<td>Epidemiology: Long-term effects of dyspnea severity and changes in dyspnea status on mortality: 43 years of follow-up in the Vlagtwedde/Vlaardingen cohort study</td>
</tr>
<tr>
<td>31-05-2011</td>
<td>Loes Kistemaker</td>
<td>Molecular Pharmacology: The role of acetylcholine in cigarette smoke induced pulmonary inflammation</td>
</tr>
<tr>
<td>14-06-2011</td>
<td>Maartje Nieuwenhuis</td>
<td>Pulmonology: Is severity of bronchial hyperresponsiveness in asthma genetically determined?</td>
</tr>
<tr>
<td>21-06-2011</td>
<td>Christina Draijer</td>
<td>Molecular Pharmacology: Comparing three short models of HDM-induced asthma</td>
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<td></td>
<td>Patricia Robbe</td>
<td>Pathology: Effects of farm dust exposure on asthma development in mice</td>
</tr>
<tr>
<td>28-06-2011</td>
<td>Kim de Jong</td>
<td>Epidemiology: Gene environment interactions and COPD in the lifelines cohort</td>
</tr>
<tr>
<td>01-11-2011</td>
<td>Hoeke Baarsma</td>
<td>Molecular Pharmacology: Glycogen synthase kinase-3 (GSK-3) regulates TGF-beta1 induced myofibroblast differentiation by suppression of CREB signaling</td>
</tr>
<tr>
<td>08-11-2011</td>
<td>Akkelies Dijkstra</td>
<td>Pulmonology: Genetic susceptibility to chronic mucus hypersecretion in heavy smokers, in the common population and in COPD-patients</td>
</tr>
<tr>
<td>15-11-2011</td>
<td>Roland Hoffman</td>
<td>Experimental Allergy &amp; Lung Diseases (Medical Biology): Glucocorticoid resistance in COPD</td>
</tr>
<tr>
<td>22-11-2011</td>
<td>Joanna Smolonska</td>
<td>Genetics: 1 simple analysis of 2 complex disorders reveals 3 shared loci</td>
</tr>
<tr>
<td>29-11-2011</td>
<td>Erica van de Wiel</td>
<td>Pulmonology: Small airway disease in asthma; The association with inflammation</td>
</tr>
<tr>
<td>06-12-2011</td>
<td>Sijranke Post</td>
<td>Experimental Allergy &amp; Lung Diseases: House dust mite-induced ATP release plays a role in the innate immunological response and barrier dysfunction of airway epithelium</td>
</tr>
<tr>
<td>20-12-2011</td>
<td>Fransien Struij</td>
<td>Pulmonology: A Cochrane review update; work in progress.</td>
</tr>
<tr>
<td>Date</td>
<td>Initiator</td>
<td>Topic</td>
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<td>25-01-2011</td>
<td>Prof. Dr. H.A.M. Kerstjens</td>
<td>Dutch COPD Severe Exacerbations network (DuCoSEx):</td>
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<tr>
<td></td>
<td>Pulmonology UMCG</td>
<td>Towards a better understanding, treatment, and intervention of hospital exacerbations</td>
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<tr>
<td>26-04-2011</td>
<td>Dr. N.H.T. ten Hacken</td>
<td>Asthma remission vs asthma progression.</td>
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<td>Pulmonology UMCG</td>
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<tr>
<td>24-05-2011</td>
<td>Dr. M.C. Nawijn</td>
<td>Sub-acute cigarette smoke exposure in the mouse models:</td>
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<tr>
<td></td>
<td>Pathology &amp; Medical Biology UMCG</td>
<td>from genetics to functional studies</td>
</tr>
<tr>
<td>28-06-2011</td>
<td>Dr. N.H.T. ten Hacken</td>
<td>Small airways disease in asthma. How to define it, clinical</td>
</tr>
<tr>
<td></td>
<td>Pulmonology UMCG</td>
<td>implications and how to find patients with small airways disease in a population of asthma patients</td>
</tr>
<tr>
<td>25-10-2011</td>
<td>Dr. T. Brakel</td>
<td>The Ideal project how to improve the allergy diagnose in primary care</td>
</tr>
<tr>
<td></td>
<td>General Practice UMCG</td>
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</table>
Research projects in 2011

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: Role of muscarinic receptors in increased extracellular matrix deposition by fibroblasts in COPD. Prof.dr. H. Meurs, Dr. R. Gosens, Prof.dr. J. Zaagsma, Prof.dr. W. Timens, Prof.dr. D.S. Postma. 2009-2011. Res. Fellow: B.G.J. Dekkers.

Boehringer Ingelheim International GmbH: Evaluation of the novel \( \beta_2 \)-agonist olodaterol, alone and in concerted action with tiotropium bromide in animal models of acute asthma and COPD. Prof.dr. H. Meurs, Dr. R. Gosens, Dr. H. Maarsingh, Prof.dr. J. Zaagsma. 2010-2011. Technician: M. Smit.

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. Dr. R. Gosens, Prof.dr. H. Meurs, Dr. H. Maarsingh. 2010-2013. Technician: M. Menzen.

Boehringer Ingelheim International GmbH: A Phase III randomised, double-blind, placebo-controlled, parallelgroup trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (5 \( \mu \)g/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma. Prof.dr. H.A.M. Kerstjens. 2009-2011. Technicians A. van der Laan-Boers, M.R. van der Eems.


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 studie: 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 students E. van der Wiel

European Community (FP6), GABRIEL and University Medical Center Groningen: PhD Studentship, Protocadherin-1: Regulation and pathway analysis of a novel gene for bronchial hyperresponsiveness. Dr. G.H. Koppelman, Prof.dr. D.S. Postma, Prof.dr. A.J.M. van Oosterhout, Dr. M.N. Hylkema, 2007-2011; PhD student: H. Koning.

European Community (FP7); COPD Pathology: Addressing Critical gaps, Early Treatment & diagnosis and Innovative Concepts (COPACETIC). 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. 2007-2011. PhD Students: A.E. Dijkstra, A. Smolonska.

European Community (KP7, Innovative Medicines Initiative). PROactive. Physical Activity as a Crucial Patient Reported Outcome in COPD. 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. 2009-2014.

European Community (FP7); European Union MeDALL-mechanisms of the Development of Allergy. Prof.dr. D.S. Postma, Prof.dr. G.H. Koppelman, Prof. Dr. C. Wijmenga. 2010-2014. Postdoc: Dr. M. Kerkhof, PhD student M. Marutha Muthu, Technician U. Brouwer.

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


Groningen Graduate School of Science (Ubbo Emmius PhD-position); Key role of A-kinase anchoring proteins in the pathophysiology of asthma. Prof.dr. M. Schmidt, Dr. H. Maarsingh. 2011-2015. 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. Prof.dr. E.J. Duiverman, Prof.dr. T. van der Molen. 2005-2011. Post-doc: Dr. S. Schokker.


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

GUIDE: Genetics of healthy ageing. Prof. Dr. H.M. Boezen, Dr. J.M. Vonk. 2009-2013. PhD Student: S.M. Figarska.

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

GUIDE/Joint project University of Southampton: Functional characterisation of PCDH1, a novel gene for asthma and bronchial hyperresponsiveness. Prof dr G.H. Koppelman, Prof dr J Holloway. 2011-2015. PhD student: G Faura Tellez

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


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

MD/PhD/ALK: Epinephrine auto-injector prescription, compliance and quality of life. Prof.dr. A.E.J. Dubois, Dr. B.M. Fokstra-de Blok. 2011 – 2014. MD/PhD student: J. Saleh-Langenberg

MSD; Effects of specific arginase inhibitors on airway function, inflammation and remodelling in asthma and COPD. Prof.dr. H. Meurs, Dr. H. Maarsingh, Prof.dr. J. Zaagsma. 2008-2011. Post doc: Dr. H. Maarsingh.

NAF 3.2.08.28: Abnormal lung tissue repair of airways and parenchyma both contribute to COPD development. Prof.dr. W. Timens, Prof.dr. J.C. Hogg, Prof.dr. D.S. Postma. 2009-2011. Post-doc: C.A. Brandsma; technician: M.R. Jonker.


NAF 08.014: The role of stress in the etiology of asthma: a multidisciplinary approach. Prof.dr. H.M. Boezen, Dr. J.G.M. Rosmalen, Prof.dr. D.S. Postma. 2008-2012. PhD Student: N.M. Vink.


NAF, special grant for translational research in Pediatric Pulmonology: Asthma phenotypes. Prof.dr. G.H. Koppelman and Prof.dr. J.C. de Jongste. 2009-2015. 2 PhD students. N.S. Grotenboer, R. van der Valk


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


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


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

Nycomed; Development of the Clinical Short-form Inhaled Corticosteroid Questionnaire Scale. Prof.dr. T. van der Molen, Prof.dr. R. Sanderman, Prof.dr. D.S. Postma. 2008-2011. Post-doc: J.M. Foster.

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


PulmonX. A Study of the Use of Chartis™ System to Optimize Subject Selection for Endobronchial Lung Volume Reduction (ELVR) in Subjects with Heterogeneous Emphysema, PulmonX USA, Dr. D.J. Slebos. 2010-2011, Studycoordinator: K.Klooster.
Rosetta Inpharmatics; LKR57970: Identification of key mechanistic drivers of lung disease. 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)). 2009-2012.

Royal Academy of Arts and Sciences. What is normal in inflammation? Prof.dr. D.S. Postma, Dr. M. van den Berge. 2009-2013. PhD-student E. Telenga.

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. Prof.dr. A.E.J. Dubois, Prof.dr. E.J. Duiverman, Dr. B.M.J. Flokstra-de Blok. 2008-2011. PhD student: J.L. van der Velde.


Top Instituut Pharma 1-108; Groningen, Utrecht; Acute and chronic inflammatory responses induced by smoking in individuals susceptible and non-susceptible for development of COPD: from complex disease phenotype toward novel tailor-made therapy. Prof.dr. D.S. Postma, Prof.dr. L. Koenderman, Prof.dr. J.W.J. Lammers, Dr. N.H.T. ten Hacken, Dr. P. Zanen, Dr. R. Schweizer, Prof. Dr. R.P.H. Bischoff. 2008-2012. technician: J. van der Leij. PhD student: S.J.M. Hoonhorst, L. Franciosi. Research nurse. R.G.A. Hiltermann-Tilanus.

Top Instituut Pharma 1-201; Groningen, Maastricht, Utrecht; Transition of systemic inflammation into multiorgan pathology. 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. 2008-2012. PhD student: R.F. Hoffmann, Technician: S.M. Brandenburg.

University of Groningen. The role of Wnt signaling in airway smooth muscle remodeling in asthma. Dr. R. Gosens. 2010-2014; 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. Dr. N.H.T. ten Hacken, Dr. M.H. de Greef, Dr. J.B. Wempe. 2006-2011. PhD-student: W. Altenburg.

UMCG/GUIDE/ Tianjin Medical University, China (Abel Tasman bursaal). Epigenetic regulation of IL-4 signalling in allergic and non-allergic asthma. Dr. M.N. Hylkema, Prof. dr. M. Rots and Prof. dr. J. Yang. 2011-2015 PhD student: X. Fu

ZonMW 016.086.036; The role of beta-catenin in airway smooth muscle remodelling in asthma. Veni-award. Dr. R. Gosens. 2008-2011.

ZonMW 80-82305-97-11018. Bronchoscopic lungvolume reduction for patients with severe COPD. Dr D.J. Slebos. 2010-2012,


Also a substantial contribution for several projects has been obtained from the Stichting Astma Bestrijding (SAB).
PUBLICATIONS 2011

DISSERTATIONS

R.A. Riemersma
New Developments in the treatment diagnosing and management of asthma in general practice
(January 24, 2011)
Promotores: Prof. T van der Molen, Prof. DS Postma

J.W.H. Kocks
Towards Health Status Guided Care in COPD
(June 1, 2011)
Promotores: Prof. T van der Molen, Prof. HAM Kerstjens

T. Pera
Inflammation and remodelling in experimental models of COPD
(June 17, 2011)
Promotores: Prof. H Meurs, Prof. J Zaagsma

PUBLICATIONS SCI JOURNALS


Van den Berg ME, Flokstra-de Blok BMJ, Vlieg-Boerstra BJ, Kerkhof M, van der Heide S, Koppelman GH, Postma DS, Dubois AEJ. Parental eczema increases the risk of double blind, placebo-controlled reactions to milk, but not to egg, peanut or hazelnut. Int Arch Allergy Immunol 2011 Dec 29;158(1):77-83


Koppelman GH, Nawijn MC. Recent advances in the epigenetics and genomics of asthma. Curr Opin Allergy Clin Immunol 2011;11:414-419.


Postma DS, O'Byrne PM, Pedersen S. Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control. Chest. 2011; 139:311-8


Roscioni SS, Dekkers BG, Prins AG, Menzen MH, Meurs H, Schmidt M, Maarsingh H. cAMP inhibits modulation of airway smooth muscle phenotype via the exchange protein activated by cAMP (Epac) and protein kinase A. Br J Pharmacol 2011;162:193-209.


**Publications in Dutch (National (Refereed) Journals)**


**Contributions to Other Research Institutes (Not GRIAC)**


Han X, Yu R, Zhen D, Tao S, Schmidt M, Han L. beta-1,3-Glucan-Induced Host Phospholipase D Activation Is Involved in Aspergillus fumigatus Internalization into Type II Human Pneumocyte A549 Cells. Plos One 2011;6:e21468.


