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Mission statement

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

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**Introduction**

The Groningen Research Institute for Asthma and COPD (GRIAC) is dedicated to research on obstructive and pulmonary diseases on the edge of clinical and fundamental research. The main theme of GRIAC is unravelling the underlying mechanisms of the development, progression and remission of airway obstruction, allergy and airway hyperresponsiveness, their mutual interactions, and their relevance to treatment. These phenomena are important risk factors for the development of asthma and COPD and crucial characteristics in their clinical pictures.

GRIAC operates within the research framework of the University Medical Center Groningen, which has a central focus on healthy ageing and the Faculty of Science of the University of Groningen, which has a focus on molecular life and health. GRIAC is part of GUIDE (Groningen University Institute for Drug Exploration) which is embedded in the Groningen School of Medical Sciences (GSMS).

**Participating departments**

The multidisciplinary and translational research of GRIAC is the result of an intensive collaboration between the researchers of GRIAC, consisting of our members from different disciplines. The disciplines involved are allergology, experimental pulmonology and inflammation research, epidemiology, general practice, pharmacology, pathology, pediatric pulmonology and pediatric allergology, pulmonology and respiratory insufficiency. GRIAC recently added new members from the department of Clinical Pharmacy and from ERIBA, the European Research Institute for the Biology of Aging. Collaboration is based on freedom, equivalence and consensus. Extensive collaboration exists with Departments of Genetics, several research groups within the Groningen Research Institute for Pharmacy, and the Groningen Transplantation Center.
Research program

GRIAC defines ‘obstructive airway and pulmonary disease’ in relation to healthy ageing, as its main topic, which is reflected in our mission statement. Research projects have to fit within this research topic, 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. GRIAC operates within the University Medical Center Groningen (UMCG) and its overarching research theme “Healthy Ageing”, and partially within the Groningen Research Institute of Pharmacy (GRIP), with a focus on Molecular Life and Health. Research within GRIAC focuses on the main challenges of obstructive airway and pulmonary disease, as well as pulmonary fibrosis:

- Identifying risk factors for the development, progression and remission of disease
- Identifying disease-related genes, gene pathways, gene functionality and gene regulation and their relation to specific phenotypes of obstructive airways disease and pulmonary fibrosis
- Unravelling the pathophysiology of allergen-, environmental- and smoke- induced disease, in humans, animal models, and in vitro cell systems
- Unravelling the effects of disease-related inflammation on lung function, hyperresponsive- ness and remodeling of large and small airways
- Defining new targets for personalized (drug and device) intervention and evaluation of intervention strategies, which includes the development of novel approaches in preventive medicine
- Development of noninvasive or less invasive tools to assess severity of disease and effects (and side effects) of treatment.

Scope of research

These challenges are investigated particularly in asthma and COPD, resulting in integrated subprograms on:

1. Epidemiology and genomics
3. Clinical Medicine: Assessment, modulation of and intervention in disease severity, progression and remission

Epidemiology and genomics

The longstanding expertise in identifying risk factors and the availability of large, prospective, long-term follow up of patient-based and population-based cohorts (such as LifeLines) and the collaboration with the Department of Genetics enables extensive sub-programs, including exposomics, (epi)genome-wide association, genome-wide interactions and transcriptome sequencing studies. This has resulted in identification of numerous novel genetic loci related to asthma and COPD onset and progression. Proteomic and lipidomic research has led to identification of disease susceptibility and progression markers, relevant to prevention of disease. GRIAC has a longstanding collaboration with the proteomics facility, and recently incorporated its first member from the European Research Institute on the Biology of Ageing (ERIBA), strengthening its focus on bioinformatic analyses of integrated genomic datasets.

Molecular medicine

GRIAC is actively engaged in studies linking clinical outcomes to mechanisms of disease, also on a molecular basis. Often based on outcomes from and also involving omics studies, the functionality of genes and proteins in disease is studied using molecular approaches in cells and tissues from patients, in cell lines and in animal models. In vivo and in vitro silencing and overexpression of genes are now established techniques that are operational at the UMCG and GRIP, including the development of knock out and transgenic mouse
models, and the use of RNA interference and pharmacological modulation of cells and tissue slices. Fundamental to this line of research is the exploration of intracellular and intercellular pathways and interactions relevant for tissue repair, disease development, progression and remission, as well as for the exploration of novel drug targets.

Clinical medicine
Patient-centered research is at the heart of GRIAC focusing on innovative therapies. Our translational research approach includes large-scale clinical management in primary care, clinical and intervention studies in allergy, food allergy, asthma and COPD. Because it is moving towards precision medicine (predictive, preventative, personalized, and participatory) in obstructive and pulmonary disease, GRIAC is in an excellent position to incorporate genomic markers in intervention studies. GRIAC is actively engaged in the development of clinical questionnaires for disease diagnosis and monitoring of disease control. Pulmonary rehabilitation and novel, personalized bronchoscopic intervention techniques are evaluated for the treatment of COPD.

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, immunology, 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 members of the Board of directors, scientific staff and post-docs of GRIAC discuss future perspectives and new developments in research and explore potential 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.

Finally, there are weekly meetings for junior researchers and staff members. At these meetings there is ample time for discussion on choosing the appropriate study design, 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. Introductory lectures are provided in lung function measurements, laboratory techniques, genetic research and so on. We aim to make our PhD students familiar with these research techniques. 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 and 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.
Perspectives

Asthma and COPD research takes place in a lively and rapidly changing field. New developments will encompass the functional genomics (including exposomics, lipidomics and proteomics) of asthma and COPD. We envisage that integration of the – omics techniques will provide novel insight into the disease networks that lead to these obstructive airway diseases.

Within each sub-program, specific research goals are complemented with an overarching emphasis on healthy ageing, (personalized) drug development, societal impact and the relevance of infrastructure. As listed below, this GRIAC approach has resulted in important achievements in past years and in new targets to work on for the future.

The strategic sub-programs

• Epidemiology and genomics: Study approaches integrating epidemiological and genomic techniques are customary at GRIAC. Epidemiological studies encompassing endogenous, environmental and lifestyle risk factors, in general and patient-based population and from the prenatal phase to mature age. Genomic studies are performed at the level of genetics, 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), and these are integrated with proteomic approaches.

• Molecular Medicine: The focus here is on role of allergens, smoking and other lifestyle factors in pathophysiology and pathogenesis of environment-induced diseases including asthma, COPD, and pulmonary fibrosis. In vivo studies in humans and animal models (including transgenerational models) using mice and unrestrained guinea pigs are used to identify disease mechanisms and drug targets. 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, adhesion and interactions with other cell types and with their environment, including the extracellular matrix. Signaling pathways and the function of susceptibility genes that were identified in the epidemiology and genomics subprogram are studied in cells and tissue explants (e.g. lymphocyte subsets, epithelial cells, fibroblasts, intact airway and smooth muscle preparations). Interactions between different cell types are studied by using cells obtained from sputum induction and nasal brushings as well as airway wall and lung tissue obtained by bronchoscopy, surgical biopsy or surgical resection.

• Clinical Medicine: Assessment, modulation and intervention in disease severity, progression and remission: Disease outcome assessment is being studied with techniques such as exhaled breath analyses, nasal epithelial gene expression, and small airway dysfunction. 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.

Output, visibility and (external) funding

Productivity of GRIAC is at present overall very good and the number of PhD-students that obtain their PhD is steadily rising. Results in medicine and basic science have been published in top peer reviewed journals. GRIAC members have been urged to focus on publication strategy and brainstorm sessions have been organized to even further improve the impact of scientific output. 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. GRIAC members actively collaborate within the National Program for Lung Research from the Netherlands Respiratory Society to generate novel ideas in asthma and lung disease prevention as well as personalized medicine in lung research.

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, COPD, and pulmonary fibrosis will keep the institute at the internationally acknowledged level of excellence in the future, and that they will be able to generate sufficient resources to finance this research. We have shifted our focus from smaller (University Medical Centers) towards larger (inter)national and interdisciplinary research grants (Lung foundation consortium grants, NWO TOP grants, European funding) as well as personal grants (VENI, VIDI, VICI and ERC grants). Within the U4 collaboration of the Universities of Groningen, Ghent, Göttingen and Uppsala, international collaborations are ongoing for PhD students to stay at 2 or 3 of these universities for an international PhD project. To further stimulate our national and international interactions, we will host a new Bronchitis conference, Bronchitis X, in Groningen, on June 17-19, 2019. Please reserve this in your agenda, and we look forward to meeting you in Groningen.
The year 2017 in review

All contributions to the scientific work in GRIAC are important and highly 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 2017.

Highlights

Prof.dr. R. Gosens had his inaugural lecture entitled ‘De behandeling van longziekten: een pleidooi voor de regeneratieve farmacologie’ (English: “The treatment of chronic lung diseases: towards regenerative pharmacology”) on February 21st.

Prof.dr. H.I. Heijink, Dr. J.K. Burgess, and Dr. A. Faiz organized a major symposium entitled ‘Repair of the emphysematous lung: mesenchymal stromal cell and matrix interactions’ at the annual meeting of the European Respiratory Society in Milan.

Prof.dr. D.S. Postma was awarded with the Sadoul lecture at the annual meeting of the European Respiratory Society. The title of the lecture was: ‘Airway hyperresponsiveness: the riddle of asthma and COPD’.

Prof.dr. W. Timens and Prof.dr. T. van der Molen were awarded as Fellow of the European Respiratory Society

Dr. S.D. Pouwels got his PhD-degree with the distinction ‘cum laude’.

The team of the Bronchoscopic Intervention Center (Dr. D.J. Slebos, Dr. N.H.T. ten Hacken) were followed during a television-program on severe COPD.

In relation to the thesis defences of Dr. M.A.E. Nieuwenhuis, Dr. N.P. Tania, and Dr. E. Osei scientific workshops/lectures were organized. Speakers at these scientific workshops/lectures were national and international leading researchers.

At the annual consortia grant round of the Longfonds, 2 projects for which a GRIAC-researcher is coordinator were granted:

Dr. D.J. Slebos will, in collaboration with CIRO in Horn and with the Radboud MC in Nijmegen, embark on a project entitled “A prospective randomized controlled trial on the Systemic effects of bronchoscopic Lung Volume reduction in patients with severe Emphysema – The SoLVE study”.

Prof.dr. R. Gosens will, in collaboration with the MUMC+, the University of Colorado at Denver and the University of Vermont work on the project entitled “Targeting the COPD lung microenvironment for lung repair: mechanisms and novel therapeutic opportunities”.
**Prizes/Awards**

S. van der Leest, MD, won the Avril McDonald Prize, a prize for the best PhD-proposal of excellent female students at the University of Groningen.

H. Baarsma won the Young Investigator Award in Translational Pharmacology from the Federation of European Pharmacological Societies (EPHAR) and the European Association for Clinical Pharmacology and Therapeutics (EACPT).

Dr. S.D. Pouwels won an abstract award from the American Thoracic Society.

Dr. J.E. Hartman, Dr. J.-P. Ng-Blichfeldt and H. Zuo MSc won an International Trainee Travel Award from the American Thoracic Society.

H. Tasena, D. van der Plaat, and C. Cox won an Young Scientist Sponsorship from the European Respiratory Society.

C.D. van Ginkel won the best presentation prize of European Academy of Allergy and Clinical Immunology (EAACI).

Dr. S.D. Pouwels won the Van Bekkum Best Thesis Award from the Dutch Society for Immunology.

Prof.dr. W. Timens and Prof.dr. T. van der Molen were awarded as Fellow of the European Respiratory Society.

**Visitors**

Dr. A. Slok, Maastricht University, Maastricht. May 2, 2017

Dr. S. Kolahian, University of Tübingen, Germany, May 11, 2017

Prof.dr. K.C. Lodrup Carlsen, Oslo University Hospital, Norway. May 15, 2017

Prof.dr. R. Bowler, National Jewish Health Denver, USA. July 25, 2017

Prof.dr. T.L. Hackett, University of British Columbia, Canada. September 6, 2017

Prof.dr. K. Bracke, Ghent University, Belgium. September 6, 2017

Prof.dr. C. Bingle, University of Sheffield, UK. October 6, 2017

Dr. J. McDonough, Catholic University of Leuven, Belgium. October 17, 2017
COPD is a severe and progressive lung disease characterized by chronic inflammation in the lung, leading to chronic bronchitis as well as emphysema. In The Netherlands alone every year 7,000 people die from the consequences of COPD. COPD is caused by the chronic inhalation of toxic gases, of which cigarette smoke is the main risk factor in the western world. Furthermore, genetic predisposition contributes to the risk of developing COPD. Current treatment is largely focused on reducing symptoms. However, no curative treatments are available to date, illustrating the urgent need for novel treatment options. The underlying molecular and cellular mechanisms of COPD are still largely unknown and more insight is required in order to develop novel treatment strategies.

We proposed a new concept for the initiation of the inflammatory response in COPD, in which we hypothesized that endogenous danger signals, called damage associated molecular patterns (DAMPs) play a crucial role (Figure 1).

**Figure 1: The DAMP hypothesis in COPD.** Exposure of airway epithelial cells of genetically susceptible individuals to toxic gases, like cigarette smoke induces immunogenic cell death followed by the release of DAMPs which contribute airway inflammation in COPD via the activation of pattern recognition receptors (PRRs) on neighboring epithelial cells. Intervention in this process may be a promising therapeutic strategy for COPD patients, e.g. by inhibition of immunogenic cell death (necroptosis inhibitor), inhibition of DAMPs (Galectin-3) or the inhibition of DAMP receptors (RAGE).
Here, the inhalation of toxic gases is thought to induce immunogenic cell death, which is a form of uncontrolled cell death that is accompanied by damage and the release of DAMPs, acting on pattern recognition receptors (e.g. toll-like receptors; TLRs, purinergic receptors; P2XR/P2YR, receptor for advanced glycation end-products; RAGE) to contribute to airway inflammation in COPD patients (Figure 2).

Figure 2: Ligation of pattern recognition receptors (PRRs) by damage-associated molecular patterns (DAMPs), relevant for chronic obstructive pulmonary disease (COPD), initiates the release of proinflammatory cytokines by multiple pathways. Ref: Pouwels et al. Mucosal Immunol. 2014;7:215-26.

We propose that individuals who are genetically susceptible for COPD are more prone to the release of DAMPs by the airway epithelium, leading to the initiation of pro-inflammatory responses and the pathogenesis of COPD. During my PhD studies, we collected evidence for this DAMP theory in COPD. We used both in vitro models with airway epithelial cells isolated from COPD patients and controls as well as in vivo mouse models to show that airway epithelial cells release a variety of DAMPs upon cigarette smoke exposure, including dsDNA, HSP70, HMGB1, Galectin-3 and S100A8/A9, and that these DAMPs have pro-inflammatory properties. We were able to inhibit cigarette smoke-induced DAMP release and subsequent airway inflammation with the inhibitor for regulated necrosis, necrostatin-1, using in vitro models as well as in vivo mouse models. This indicates that cigarette smoke induces immunogenic cell death and airway inflammation largely via regulated necrosis, making this process a promising novel therapeutic target for COPD. Furthermore, in a mouse model using 30 different mouse strains, we have shown that genetic susceptibility for DAMP release exists, especially for dsDNA, and is associated with neutrophilic airway inflammation. We identified several novel susceptibility genes for cigarette smoke-induced airway inflammation and DAMP release using murine genome-wide association studies. Moreover, we showed that there is also genetic susceptibility for the cigarette smoke-induced release of specific DAMPs in humans. In epithelial cells derived from COPD patients compared to those from non-COPD controls, we observed that cigarette smoke extract induced a stronger release of Galectin-3. Moreover, stimulation of airway epithelial cells with Galectin-3 induced a pro-inflammatory response, which could only be blocked by TLR2/4 inhibition in control-
derived cells but not in COPD-derived cells, indicating that Galectin-3 acts on different receptors on airway epithelial cells from COPD patients. In line with these findings, functional gene-set enrichment analysis showed that cigarette smoke significantly increases airway epithelial gene expression of Galectin-3 in COPD patients. Another novel therapeutic target for COPD and more specifically emphysema is the DAMP receptor RAGE. Of interest, we observed that acute exacerbations of COPD are associated with increased levels of the well-known RAGE ligands HMGB1, LL-37 and S100A9. RAGE is a pleiotrophic multi-ligand receptor, which upon activation may not only induce a pro-inflammatory response but also contribute to the development of emphysema. Currently, we are performing several studies unraveling the role of RAGE in the pathophysiology of COPD and identifying the therapeutic potential of RAGE inhibition on lung tissue regeneration.

Taken together, our results indicate that DAMPs play an important role in the pathophysiology of COPD. Furthermore, we showed that specific DAMPs and/or their receptors are a novel possible target for future therapies of COPD patients. Our ongoing studies should illuminate the therapeutic potential for COPD of RAGE inhibition and other inhibitors of the immunogenic cell death-DAMP release-DAMP receptor activation axis.
Within GRIAC, the contribution from patients to improve study designs and help in prioritizing research areas is highly valued. The GRIAC advisory board of patients with asthma and COPD meet 4 times per year to review studies at an early stage of project development through to hearing final reports of completed studies. The patients’ input helps with ensuring the research is relevant and the outcomes are clearly communicated to the end users. Last year, nine new projects were presented (see table) and one projected was presented that has been completed.

Patients also received a guided tour of the Pathology department. One of the lung pathologists - dr Nils ‘t Hart – explained the logistics when patient material is being send to the Pathology department for diagnostic evaluation. This tour was very well received by the patients.

Our patient advisory board also received attention from academic centers outside of Groningen who were interested in setting up an advisory board and welcomed our guidance and suggestions. Besides, two articles were published last year in Pulmoscript (sept. 2017) and Medidact (dec. 2017) which was dedicated to the setup and achievements of our board.

For 2018 we plan to organize more small lab events to get our patients even more acquainted to the research interests of GRIAC scientists.

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Special topic 3

RECONSIDER

Treatment of chronic REspiratory failure in COPD patients with Non-invasive ventilation: Starting at home and selecting the Right Patient

How a patient’s need promotes successful recruitment

Marieke Duiverman
Department of Pulmonary Diseases and Tuberculosis, working group on Respiratory Insufficiency

Rationale
Increasingly more patients with chronic obstructive pulmonary disease (COPD) have chronic hypercapnic respiratory failure (CHRF) for which there are limited treatment options. Application of long-term non-invasive ventilation (NIV) in stable COPD patients has long been controversial, but has recently been shown to improve survival and quality of life when applied with sufficiently high inspiratory pressures and higher ventilator backup breathing frequencies. Initiation of high-intensity NIV was believed to be only feasible once patients are getting used to and titrated on this mode of NIV during a hospitalisation of 5-10 days. However, due to patients’ feedback we realised that this hospitalisation is a very unattractive option for our target group of very disabled dyspnoeic patients who more than everything else need rest and trust to get used to their ventilator. Therefore the aim of the RECONSIDER study is to investigate whether initiation at home of chronic NIV in stable COPD patients with CHRF with the use of telemonitoring is not inferior to in-hospital initiation.

Study progress
The study started on the 16\textsuperscript{th} of June 2016. We finalised inclusion March 2018, after the last 2 patients for whom the first visit was postponed because of an exacerbation, were also included. Patients were very willing to participate, actually only 6\% of the screened patients did not want to be initiated at home. Actually, 66 patients are being randomised, and 46 patients finished the study. We calculated that we would need 2 groups of 23 patients to test our hypothesis that initiation at home is not less successful as compared to initiation in the hospital. Some more patients were included as we had a large number of patients who were very willing to participate during the same period of time. Nine patients still have to complete the study, with the last patient expected to have completed the study by the end of September 2018.

We were also happily surprised that inclusion was so successful; studies in patients with severe COPD are frequently hampered by difficult inclusion as participating in a study might be very demanding for those patients. However, we experienced during RECONSIDER that the willingness to participate was very high, and in most cases that could be included, logistical problems were the reason. RECONSIDER is a good example of a patient’s wish that is translated into research!
Asthma can go into remission later in life in approximately 35% of all patients [1]. Asthma remission is associated with childhood onset of asthma [2,3], male sex, smoking cessation, initially less severe airway obstruction and, notably, more severe bronchial hyperresponsiveness (BHR) [4,5]. Unfortunately, subjects with asthma remission may show relapse later in life [7]. This could be due to e.g. specific exposures, gaining weight and hormonal changes [8]. Studies investigating childhood factors that predict clinical asthma remission in adulthood are sparse, and even fewer studies on complete asthma remission [6] or the persistence of asthma remission throughout the lifespan exist.

In 2017, we assessed whether asthma remission persisted during 39 years of follow-up and determined which childhood factors were associated with asthma remission [7]. The study included children diagnosed with asthma who were investigated 3 times over a period of 39 years: 1972–1976 (visit 1), 1987–1989 (visit 2), and 2013–2014 (visit 3). At visit 1, 406 children diagnosed with asthma were referred to the University Medical Center Groningen, and characterised by extensive standardised questionnaires, peripheral blood measurements, bronchial provocation, lung function and skin prick tests. At visit 2, 285 children (209 children with positive BHR at visit 1) were re-examined in young adulthood. At visit 3, 102 subjects with BHR at visit 1 were re-examined.

In our study we defined asthma remission based on our previous work [6]. Clinical asthma remission (ClinR) was defined as the absence of symptoms and no use of asthma medication but persisting BHR and/or an impaired lung function and complete asthma remission (ComR) was defined as the absence of symptoms, no use of asthma medication, no BHR and normal lung function). The flowchart is presented in figure 1.

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**Figure 1:** definitions of asthma remission, adapted from Carpaij et al. 2017
Being breastfed for more than six months was positively associated with asthma remission in adulthood, as was having a positive family history of leukaemia. Negatively associated factors were having a history of pneumonia and having an atopic mother. Of the 63 initial asthmatic children who successfully completed all three visits, only seven subjects remained in ClinR or ComR at both 25 (visit 2) and 49 years (visit 3). Notably, using the strict definition of remission, 75% of the subjects with ComR at visit 2 had no relapse of asthma at visit 3.

**Figure 2:** course of asthma over three visits. Legend: dark-grey represents asthmatics (PersA), light-gray represents ClinR and white-dotted represents ComR. At visit 1, all 63 children were asthmatic with a proven bronchial hyperresponsiveness.

This research fits into a long-standing research line within GRIAC in which we investigate the differences between subjects with persistent asthma, clinical remission, and complete remission. Identifying the underlying mechanisms and molecular events involved in the inception and remission of asthma may teach us how asthma can be stopped and thus may provide novel avenues for the treatment of asthma.

In one of our earlier studies we obtained bronchial biopsies from 165 (former) asthmatics. Using the ComR and ClinR definitions as in figure 1, we found that subjects with ClinR retained eosinophils, mast cells and remodelling in the airways. In contrast, individuals with ComR showed less airway inflammation, but still had basement membrane thickening [9]. This suggests that ComR is associated with less airway inflammation than ClinR and persistent asthma, but still retains a degree of tissue remodelling. To assess if the development of remission is under genetic control, we are currently using these same bronchial biopsies to investigate whether asthma remission is associated with a different DNA-methylation and/or gene expression profile (RNAseq) compared to persistent asthma. In addition, we also identified a few genes associated with ComR and ClinR in a genome wide association study which will be published in the Journal of Clinical and Experimental Allergy in 2018.
Another remission-study that is currently running is the Asthma ReMission Study (ARMS) (METc 2015/169). In this study, we have already enrolled more than 50 subjects i.e. asthmatics, healthy controls and subjects with either clinical or complete asthma remission. During four visits, a broad range of diagnostic tests is performed including a High Resolution CT (HRCT) thorax, a nasal brush and a bronchoscopy to obtain endobronchial biopsies and brushes. We use innovative techniques (i.e. FACS sorting of cell types (i.e. CD4+ T-cells, epithelial cells, eosinophils) and subsequently performing single cell RNA-sequencing) to identify cell-type specific transcriptomic profile changes within these four subject groups. Taking this altogether, we hope to find a biological pathway that triggers asthma remission, which can be used to identify a new treatment.

References
The regulation and functional role FKBP5 in corticosteroid resistance

Alen Faiz
Department of Pulmonary Medicine and Tuberculosis

Chronic inflammatory obstructive airway diseases remain one of the leading causes of death worldwide. Corticosteroids, known for their broad anti-inflammatory effects have been the mainstay in the treatment of these diseases. However, a subset of patients including severe asthma and chronic obstructive pulmonary disease (COPD) patients which share common pathophysiologic traits such as airflow obstruction remain corticosteroid insensitivity. The glucocorticoid receptor (GR) is a transcription factor crucial for the anti-inflammatory function of glucocorticoids. The GR plays a dual role 1) as a transcription factor binding the GR element (GRE) to promote gene expression, and 2) as a regulator of other transcription factors, most notably NF-kB. Overall the function of the GR is to reduce (pro-)inflammatory responses.

We aimed to investigate genes upregulated by corticosteroid treatment and to determine their functional role in corticosteroid resistance.

A meta-analysis of 4 studies (Healthy (GSE83233 n=11), Asthma (MAST n=12, SAGE n=20), COPD (GLUCOLD n=26)) was conducted on bronchial biopsies matched for pre-and post-corticosteroid treatment. From this analysis, the top candidate gene FKBP5 was chosen to be knocked out in the lung epithelial cell line A549 using CRISPR-Cas9. To identify the functional role of FKBP5, glucocorticoid receptor (GR) and NF-kB reporter assay and ELISA for the pro-inflammatory cytokine CXCL8 were performed on FKBP5 knockout A549 cells treated with Fluticasone Propionate (FP) 10-8 M (n=6).

The meta-analysis identified 93 genes increased and 170 genes decreased by corticosteroids (meta Bonferroni adjusted p<0.05, Figure 1).
FKBP5, identified as the most significantly increased gene, was knocked out in A549 cells using CRISPR-Cas9. In the absence of FKBP5, GR reporter activity increased ~6 times further upon FP treatment (p<0.05, Figure 2A). Additionally, the effectiveness of FP to suppress CXCL8 release upon TNFα stimulation was enhanced in the FKBP5 knockout compared to control A549 cells (p<0.05, Figure 2B). Interestingly, the baseline expression and induction of CXCL8 was suppressed in the KO cell line indicating a possible role in FKBP5 in NFκB signaling. To investigate this further we used a NF-κB activity assay and found that in the absence of FKBP5, NFκB signaling was suppressed (p<0.05, n=6, Figure 2C).

Based on our findings we propose that the expression of FKBP5 not only acts to suppress corticosteroid function by removing the GR receptor but also aids in the activation of the NF-κB signalling cascade leading to enhanced inflammation. This dual function of FKBP5 indicates that it plays an important role in regulating the function of corticosteroids as well as inflammatory response during high corticosteroid levels (figure 3).
In conclusion, FKBP5 provides a novel therapeutic target to improve corticosteroid sensitivity and suppress inflammation.
**Special topic 6**

**Granted projects in 2017**

**Unravelling the role of the epigenome in the development of COPD** - Dr. Maaike de Vries (UMCG)

 Granted by Lung Foundation Netherlands, junior investigator grant

Chronic Obstructive Pulmonary Disease (COPD) is a progressive inflammatory disease and the third leading cause of death worldwide. Today, the etiology of COPD is still not fully understood and there is an urgent need to get more insight in the mechanisms underlying this disease.

The development of COPD is influenced by both genetic and environmental factors. The epigenome is recognized as an important link between these factors and one well-defined epigenetic mechanism is DNA methylation. DNA methylation is tissue-specific and affected by exposure to cigarette smoke, air pollution and job-related exposures. Of interest, we previously found differences in DNA methylation at so-called CpG-sites that are associated with these exposures in whole blood. However, the functional relevance of these changes in DNA methylation in COPD is currently unknown. In this project, I will further investigate the functional relevance of changes in DNA methylation upon exposure to environmental factors in the development of COPD.

First, I will confirm the CpG-sites I have previously identified in whole blood in bronchial biopsies using the existing NORM database. With the airway epithelium as first defence to noxious environmental factors, I will secondly validate the confirmed CpG-sites in bronchial biopsies in airway epithelial cells (AECs) from bronchial epithelial brushes using pyrosequencing. Thirdly, I will assess the functional relevance of the differences in DNA methylation in AECs. To this end, I will mimic the exposures to environmental factors in vitro and test if changes in gene expression upon differential DNA methylation induces abnormalities as observed in AECs from COPD patients. Finally, I will reveal if interfering with DNA methylation using the CRISPR/(d)Cas9-system can restore the abnormalities in COPD-derived AECs.

Overall, this research project will result in a better understanding of the etiology of COPD, leading to novel approaches to better treat or prevent COPD in the future.

**Targeting the COPD lung microenvironment for lung repair: mechanisms and novel therapeutic opportunities** - Prof. Dr. Reinoud Gosens (RuG), Prof. Dr. Niki Reynaert (MUMC+), Prof. Dr. Melanie Königshoff (UCD), Prof. Dr. Yvonne Janssen-Heininger (UVM)

 Granted by Lung Foundation Netherlands, consortium grant

Chronic obstructive pulmonary disease (COPD) is characterized by a progressive loss of lung function with airflow obstruction that is not fully reversible. The key problem underlying COPD is defective airway and alveolar repair in response to inflammation and oxidative
stress, causing bronchitis, small airways remodeling and emphysema. As current therapies do not modify the course of the disease in COPD, new therapies need to be developed.

Epithelial progenitor cells of the distal lung interact with structural cells such as fibroblasts to contribute to lung repair, which is driven by canonical WNT/β-catenin signaling. This mechanism is impaired in COPD, in part because chronic inflammation and oxidative stress provide a hostile local microenvironment in the COPD lung, not only causing damage, but also hampering repair responses. We now demonstrate that inflammation and oxidative stress directly and indirectly affect canonical WNT/β-catenin signaling (responsible for repair) and that reversal of this process using targeted pharmacological inhibition is possible. We hypothesize that the distortion of regenerative signaling is driven by a canonical to non-canonical WNT signaling switch, skewing signaling towards JNK, p38 and Rho-kinase, which lead to halted repair. These pathways provide rational drug targets for alveolar repair and we propose that it is possible to restore lung repair by targeting these pathways.

A team of pharmacologists, pathologists, (stem) cell biologists and pulmonologists will form a consortium to investigate this hypothesis in detail. We propose experiments to investigate i) how inflammation and oxidative stress promote a canonical to non-canonical WNT signalling switch; ii) whether this pathway cross-talk contributes to impaired lung repair in COPD; and iii) whether these pathways can be targeted pharmacologically in order to restore endogenous and progenitor cell mediated repair.

A prospective randomized controlled trial on the Systemic effects of bronchoscopic Lung Volume reduction in patients with severe Emphysema – The SoLVE study - Dr. D.J. Slebos (UMCG), Dr. E. van Rikxoort (Radboud UMC), Dr. L. Vanfleteren (MUMC+)

Granted by Lung Foundation Netherlands, consortium grant

Bronchoscopic lung volume reduction (BLVR) using one-way endobronchial valves is an innovative, minor invasive bronchoscopic therapeutic strategy for severe COPD patients characterized by emphysema. With precise disease phenotyping being necessary to achieve results, this unique treatment is the perfect example of personalized medicine. In severe emphysema patients who, despite maximal current available treatment options, suffer from dyspnea, this treatment can improve pulmonary function, exercise capacity, quality of life, and physical activity. Because of recent published results, this therapy has been for the first time adopted as treatment option in the GOLD-COPD2017-guidelines. However, additional data are needed to define the optimal patient population to receive this therapy and to compare long-term durability of improvements in functional and physiological performance.

All clinical trials performed to date showed the challenges of this treatment as well as striking outcomes in a patient population deemed to have no therapeutic options anymore. With the current consortium we want to further develop and optimize this innovative and personalized therapy, and to gain knowledge on the impact of modifying the severe emphysema disease state for the individual patient. This all with specific focus on patient selection, exact positioning of pulmonary rehabilitation around BLVR, and impact on efficacy outcomes. BLVR will reduce the ventilatory limitation and consequently reveal cardiac, muscle or psychological limitations, leading to improvements in quality of life and physical activity, thus in fact whole body functioning. This will potentially further allow improved ability to increase
physical activity. The consortium leading this application is the perfect combination of world leading experts and centers on thoracic quantitative imaging, rehabilitation, COPD metabolism, and bronchoscopic lung volume reduction. All centers have an established working program around this topic, a high patient flow, significant experience in clinical trials, and a high scientific output on this topic, making the proposal very feasible.

“Proteomics-based Pharmacological Biochemistry (P2B2)” - A strategy to identify protein species and signaling pathways regulating inflammatory responses of pulmonary macrophages in NFκB-mediated inflammation and COPD. - M.D. Kwiatkowski (UMCG), Prof. Dr. B.N. Meigt (UMCG)

Granted by RESPIRE3 ERS/EU fellowship

NFκB-driven inflammation by macrophages contributes to many respiratory diseases and especially to the pulmonary inflammation found in COPD. The only way to dampen this inflammation is through corticosteroid treatment, but many patients are not benefiting from this treatment and it causes many side effects. Therefore, there is an urgent need to identify novel molecular mechanisms regulating inflammation in COPD that can be exploited for the development of diagnostics and therapeutics. Our recent results indicate that pharmacological inhibition of lysine deacetylases (KDACs) provides promising anti-inflammatory effects in different model systems for NFκB-mediated inflammation. KDAC inhibitor treatment resulted in significantly lower expression of pro-inflammatory IL-6 and IL-1β as well as significantly higher expression of anti-inflammatory IL-10 in vitro in macrophages, but not in bronchial epithelial cells and airway smooth muscle cells. Importantly, these in vitro results were also observed ex vivo in mouse precision cut lung slices and in vivo in cigarette smoke-exposed mice. KDAC inhibitor treatment resulted in lower IL-6 and IL-1β levels, lower numbers of neutrophils and higher numbers of IL-10+ macrophages. This highlights the promising KDAC inhibitor-induced switch from a pro- to an anti-inflammatory behavior of macrophages via novel molecular mechanisms related to KDAC inhibition and thus changes within the acetylome.

The aim of this research project is to investigate the role of the acetylome, namely acetylated and deacetylated protein species, in the regulation of NFκB-driven macrophage responses during inflammation. With a novel strategy denoted “proteomic based pharmacological biochemistry (P2B2)”, which combines differential proteomics, computational modeling and molecular biology, the proposed research will identify for the first time protein species and corresponding signaling pathways associated with NFκB-mediated pro-inflammatory responses in macrophages and with anti-inflammatory responses induced by lysine deacetylase (KDAC) inhibitors. This research project will make a significant contribution to understand the regulation of NFκB-mediated inflammatory responses of macrophages at the protein species level in respiratory diseases like COPD, thus having an important impact on future diagnosis and drug-development.
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### Post-docs

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<td>Baarsma H.A., PhD</td>
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<td>Kistemaker L.E.M., PhD</td>
<td>de Vries M., PhD</td>
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<td>Klooster K., PhD</td>
<td>Xu C., PhD</td>
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### PhD students

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<tr>
<td>Alma H.J., MSc, MD/PhD student</td>
<td>Klijnsma M., MD</td>
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<tr>
<td>Anrooij van B., MD/PhD student</td>
<td>Koopmans T., MSc</td>
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<td>Dijk F.N., MD</td>
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<td>Diltz B., MD</td>
<td>van der Plaat D.A., MSc</td>
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### International collaboration 2017
(As far as related to joint projects and publications in 2017)

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Prof. H. Maarsingh  Palm Beach Atlantic University  West Palm Beach, USA
Dr. T. Maes  University Hospital of Ghent  Ghent, Belgium
Dr. K. Malakauskas  Lithuanian University of Health Sciences  Kaunas, Lithuania
Dr. F.O. Martinez  Surrey University  Guildford, UK
Dr. T. Mauad  Sao Paolo University  Sao Paolo, Brasil
Dr. E. Melén  Karolinska Institute  Stockholm, Sweden
Dr. S. Meiners  Helmholtz Center Munich  Munich, Germany
Prof M. Mineshita  St Mariana University Kawasaki/Tokyo  Japan
Dr. M. Miravitlles  Hospital Universitari Vall d’Hebron  Barcelona, Spain
Prof. B. Oliver  Technical University Sydney  Sydney, Australia
Prof. P. Paggiaro  University of Pisa  Pisa, Italy
Prof. P.D. Paré  University of British Columbia  Vancouver, Canada
Prof. M. Peters-Golden  University of Michigan Medical School  Michigan, USA
Dr. H. Pinnock  University of Edinburgh  Edinburgh, UK
Dr. Y.S. Prakash  Mayo Clinic  Rochester, USA
Prof. D. Price  University of Aberdeen  Aberdeen, UK
Prof. N. Probst-Hensch  Swiss Tropical and Public Health Institute  Basel, Switzerland
Dr. B.A. Raby  Harvard Medical School  Boston, USA
Dr. H.K. Reddel  Woolcock Institute of Medical Research  Sydney, Australia
Dr. M. Rojas  University of Pittsburgh  Pittsburgh, USA
Prof M. Roth  University Hospital  Basel, Switzerland
Prof. F. van Roy  Flemish Institute of Biotechnology  Ghent, Belgium
Prof. L. Rumora  University of Zagreb  Zagreb, Croatia
Prof. I. Sabroe  University of Sheffield  Sheffield, UK
Prof. I. Sayers  University of Nottingham  Nottingham, UK
Dr. M. Schuler  University of Wuerzburg  Wuerzburg, Germany
Dr. K. Schultz  Klinik Bad Reichenhall  Bad Reichenhall, Germany
Dr. J. Schwarze  University of Edinburgh  Edinburgh, UK
Prof F. Sciurba  University of Pittsburgh Medical Center  Pittsburgh, PA, USA
Prof P.L. Shah  Royal Brompton Hospital  London, UK
Prof. S. Siddiqui  University of Leicester  Leicester, UK
Prof. T. Sigsgaard  Aarhus University  Aarhus, Denmark
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<td>Prof W. Windisch</td>
<td>Lungenklinik Merheim, Kliniken der Stadt Köln, Universität Witten/Herdecke</td>
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# GRIAC Seminar program 2017

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<tr>
<th>Date</th>
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<tbody>
<tr>
<td>17-01-2017</td>
<td>Dr. J. Burgess Pathology &amp; Medical Biology UMCG</td>
<td>The role of fibulin 1 in the development of fibrosis in the lung</td>
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<tr>
<td>07-02-2017</td>
<td>D. van der Plaat Epidemiology UMCG</td>
<td>Genetics, exposures and DNA methylation underlying COPD in never smokers</td>
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<tr>
<td>07-03-2017</td>
<td>Prof. Dr. P. Wijkstra Pulmonology UMCG</td>
<td>Chronic ventiler support in COPD: State of the art and future perspectives</td>
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<tr>
<td>21-03-2017</td>
<td>Dr. J.W.A. Rossen Medical Molecular Microbiology UMCG</td>
<td>Personalised diagnostics for outbreak management and prevention of antimicrobial resistance</td>
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<tr>
<td>04-04-2017</td>
<td>Prof. Dr. B. Toebes Faculty of Law University of Groningen</td>
<td>Tobacco control: the power of law and policy</td>
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<tr>
<td>18-04-2017</td>
<td>N. Dijk Pediatric Pulmonology UMCG</td>
<td>IL1RL1 gene in asthma: what do we know and what can we expect in the future</td>
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<tr>
<td>02-05-2017</td>
<td>Dr. A. Slok Research institute CAPHRI Maastricht University</td>
<td>Assessment of burden of disease: using the ABC tool; from development to nationwide RCT to implementation in COPD care</td>
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<td>16-05-2017</td>
<td>Dr. J.N.G. Oude Elberink &amp; H. Nienhuis Allergology UMCG</td>
<td>A different house dust mite allergy</td>
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<tr>
<td>06-06-2017</td>
<td>Dr. C. Vermeulen Pulmonology UMCG</td>
<td>A better understanding of asthma remission: an integrative genomic approach for biomarker development</td>
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<tr>
<td>20-06-2017</td>
<td>Dr. M. Nawijn Pathology &amp; Medical Biology UMCG</td>
<td>Single-cell RNA sequencing in translational genetics of chronic respiratory disease</td>
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<tr>
<td>25-07-2017</td>
<td>Prof. Dr. R. Bowler National Jewish Health Denver, USA</td>
<td>Reverse translation in COPD: understanding how human extracellular superoxide dismutase variants protect against lung disease</td>
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<td>05-09-2017</td>
<td>Dr. T.-L. Hackett University of British Columbia Vancouver, Canada</td>
<td>Small airways disease is an early feature of airflow obstruction in mild to moderate COPD</td>
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<tr>
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<td>06-09-2017</td>
<td>Prof. Dr. K. Bracke Ghent University Ghent, Belgium</td>
<td>Identification and functional characterization of microRNAs in the pathogenesis of COPD</td>
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<td>19-09-2017</td>
<td>Dr. V. Gurjev ERIBA UMCG</td>
<td>Hunting for disease genes: large cohorts vs personalised approach</td>
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<td>17-10-2017</td>
<td>Dr. J. McDonough Catholic University Leuven Belgium</td>
<td>The progression and regulation of IPF</td>
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<td>07-11-2017</td>
<td>E. Petterson Pediatric Pulmonology and Allergology UMCG</td>
<td>The severity of systemic allergic reactions</td>
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<td>21-11-2017</td>
<td>I. Boudewijn &amp; Dr. A. Faiz Pulmonology UMCG</td>
<td>Bronchial and nasal gene and miRNA expression in asthma and asthma remission</td>
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### GRIAC research meetings 2017 - presentations

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<tr>
<td>10-01-2017</td>
<td>Marieke Duiverman</td>
<td>Introduction to lung function measurements</td>
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<td>17-01-2017</td>
<td>Dorien van Ginkel</td>
<td>Genetics of food allergy</td>
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<td>Pediatric Pulmonology and Allergology</td>
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<td>24-01-2017</td>
<td>All</td>
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<td>31-01-2017</td>
<td>Loes Kistemaker</td>
<td>Neuronal remodeling: a novel perspective on airway hyperresponsiveness in asthma</td>
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<td>07-02-2017</td>
<td>Pavan Prabhala</td>
<td>Potential role for an imbalance between airway smooth muscle laminin α4 and α5 expression in asthma</td>
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<td>28-02-2017</td>
<td>Orestes Carpaij</td>
<td>Childhood factors associated with complete and clinical asthma remission</td>
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<td>14-03-2017</td>
<td>Anienke van de Veen</td>
<td>Does high baseline oxidative stress attenuate macrophage function during exacerbations of COPD and asthma?</td>
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<td>Pharmacokinetics, Toxicology and Targeting</td>
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<td>21-03-2017</td>
<td>Zhijun Zeng</td>
<td>The effect of smoke exposure on alveolar epithelial cell repair</td>
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<td>28-03-2017</td>
<td>Maarten van den Berge</td>
<td>Current treatments of COPD</td>
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<td>Virinchi Kuchibhotla</td>
<td>The role of beta-catenin in the development of asthmatic epithelial phenotype</td>
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<td>Dennis Kruk</td>
<td>Mesenchymal stromal cells in emphysema: finding the right niche for alveolar repair</td>
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<td>25-04-2017</td>
<td>Maaike de Vries</td>
<td>How to use Illustrator</td>
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<td>Mariska van den Berg</td>
<td>Targeting mast cell expressed arginase in allergic asthma</td>
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<td>30-05-2017</td>
<td>Ilse Boudewijn</td>
<td>MicroRNAs in asthma remission</td>
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<td>06-06-2017</td>
<td>Hendrik Jan Baretta</td>
<td>Quality of spirometry in primary care; a focus on clinical use of spirometry (FOCUS)</td>
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<td>13-06-2017</td>
<td>Huib Kerstjens</td>
<td>How to organize your data-base and track your statistics</td>
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<td>20-06-2017</td>
<td>Koshbayar Lkhagvadorj</td>
<td>Maternal smoking during pregnancy inhibits ciliated cell differentiation in association with Amphiregulin upregulation</td>
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<td>Marlies Ketelaar</td>
<td>Unraveling the role of IL-33 in asthma using a primary human bronchial epithelial cell model</td>
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<td>Emmanuel Osei</td>
<td>The role of interleukin-1 in driving inflammation and remodeling in the asthmatic EMTU</td>
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<td>Laura Florez-Sampredo</td>
<td>Elucidating the role of MIF in PF and COPD</td>
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<td>26-09-2017</td>
<td>Roy Woldhuis</td>
<td>Ageing phenotypes of lung fibroblasts of COPD patients</td>
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<td>03-10-2017</td>
<td>Orestes Carpaij</td>
<td>Is serum periostin useable as a biomarker for COPD?</td>
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<td>Tristan de Jong</td>
<td>Molecular, metabolic, and age-related factors modulating robustness of gene expression</td>
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<td>17-10-2017</td>
<td>Jennie Ong</td>
<td>Small RNA-seq in lung fibroblasts; differentially expressed miRNAs in relation to COPD, TGF-β treatment and smoking status</td>
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<td>Haoxiao Zuo</td>
<td>Cigarette smoke changes airway cAMP by upregulation of PDE3 and PDE4</td>
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<td>21-11-2017</td>
<td>Hataitip Tasena</td>
<td>Influence of Fibroblast-Epithelial Cell Crosstalk on Chronic Mucus Hypersecretion in COPD</td>
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<td>28-11-2017</td>
<td>Huib Kerstjens</td>
<td>Special session: Discussion of clinical case/clinical rounds</td>
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<td>05-12-2017</td>
<td>Alen Faiz</td>
<td>The role of FKBP5 in corticosteroid function and how this mechanism can be used to understand corticosteroid resistance.</td>
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<td>12-12-2017</td>
<td>Dennis Kruk</td>
<td>Differential gene expression of repair factors in mesenchymal stromal cells from different sources in emphysema</td>
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<td>The role of beta–catenin in the development of asthmatic epithelial phenotype</td>
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<td>Subject</td>
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<td>28-03-2017</td>
<td>Dr. M.C. Nawijn Pathology and Medical Biology UMCG</td>
<td>Improving visibility and graduate program of GRIAC by coordinating undergraduate education</td>
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<tr>
<td>27-06-2017</td>
<td>Dr. J.W. Kocks General Practice UMCG</td>
<td>How can we make the best use of the CERTE asthma/COPD database? Blood eosinophils as biomarker for cross-sectional and longitudinal outcome of asthma and COPD as an example?</td>
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<td>28-11-2017</td>
<td>Dr. P. Horvatovich Analytical biochemistry RUG</td>
<td>Imaging of drug deposition in the lung</td>
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</table>
**Research projects 2017**


AstraZeneca: 3D-bioprinted airways: A new breath to replace animal models for lung disease research. 2017-2018. Dr. M.N. Hylkema, Prof.dr. J.K. Burgess, Dr. M. van den Berge.

AstraZeneca; CARAT; identifying cutoff values. 2014-2018. Prof.dr. T. van der Molen, Dr. B.M.J. Flokstra – de Blok, Dr. C. de Jong.


AstraZeneca/Mundipharma/Boehringer Ingelheim: Inhaler Research Workgroup (IRW) study. 2016-2019. Prof.dr. T. van der Molen, Dr. J.W.H. Kocks, Dr. E.I. Metting, Dr. S. Schokker, Dr. I Tsiligianni, PhD student: M. Román-Rodríguez


Boehringer Ingelheim International GmbH: The role of TRPA1 in neurogenic inflammation and airway hyperreactivity in asthma. 2016-2017. Dr. L.E.M. Kistemaker, Prof.dr. R. Gosens, Dr. M. van den Berge. Technician: S. Nijboer-Brinksma.


Boehringer Ingelheim: Towards restoration of bronchial airways in COPD using epigenetic reprogramming of endogenous lung stem cells. 2017-2018. Dr. M.N. Hylkema, Dr. M. van den Berge, Prof.dr. M.G. Rots.


CAPES/NUFFIC (Edital 68/2013): Activation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) & antioxidant response element (ARE) as therapeutic target for tissue repair in chronic degenerative lung disease. 2013-2017. Prof.dr. S. dos Santos; Prof.dr. L.C. de Moraes Sobrino Porto; Prof.dr. M. Schmidt


Chiesi: Towards restoration of bronchial airways in COPD using epigenetic reprogramming of endogenous lung stem cells. 2017-2018. Dr. M.N. Hylkema, Dr. M. van den Berge, Prof.dr. M.G. Rots.


European Union (Horizon 2020): FRESH AIR: prevalence and burden of COPD in Uganda, Kyrgyz Republic, Vietnam and Greece. 2015-2018. Prof.dr. T. van der Molen, Prof.dr. N.H. Chavannes, Dr. J.F.M. van Boven, Dr. F.A. van Gemert.


European Union (Horizon 2020): Advancing Care Coordination and TeleHealth Deployment (ACT@Scale II). 2016-2018. Prof.dr. T. van der Molen, Dr. J.W.H. Kocks, E.I. Metting, Dr. M.M.H. Lahr.

Genentech: Molecular Phenotyping of COPD Patients by Inhaled Corticosteroids (ICS) Response. 2015-2017. Dr. C.A. Brandsma, Prof.dr. W.Timens, Prof.dr. D.S. Postma, Dr. M. van den Berge.
GlaxoSmithKline: A better understanding of asthma remission: An integrative genomic approach for biomarker development. 2014-2017. Dr. M. van den Berge, Dr. N.H.T. ten Hacken, Prof.dr. W. Timens, Prof.dr. I.H. Heijink, Dr. C. Xu, Prof.dr. G.H. Koppelman, Dr. J.M. Vonk, Prof.dr. D.S. Postma. Post-doc: Dr. C. Vermeulen.

GlaxoSmithKline: Single cell sequencing of CD4+ lymphocytes to better understand the molecular mechanisms leading to asthma and its remission. 2015-2017. Dr. M.C. Nawijn, Prof.dr. D.S. Postma, Prof.dr. G.H. Koppelman, Dr. J.M. Vonk, Prof.dr. W. Timens, Prof.dr. I.H. Heijink, Dr. M. van den Berge.


Groningen Research Institute for Pharmacy (MPDI fellowship): Role of MIF in pulmonary fibrosis. 2015-2019. Prof.dr. B.N. Melgert, Prof.dr. G.J. Poelarends, PhD student: L. Florez-Sampedro

Groningen Research Institute for Pharmacy (Erik Frijlink Patents): Role of MIF in pulmonary fibrosis. 2016-2020. Prof.dr. B.N. Melgert, Prof.dr. G.J. Poelarends, Prof.dr. P. Olinga. PhD student: S.S. Song

GSMS/CPE fellowship: Risky work: Association between airborne occupational exposures and lung function, blood pressure, and inflammatory biomarkers (neutrophils, eosinophil, and high-sensitivity C reactive protein) in blood. 2017-2020. Prof.dr. H.M. Boezen, Prof.dr. U. Bultmann, Dr. J.M. Vonk. PhD student: M.O. Faruque


GSMS/CSC: Functional studies on novel COPD susceptibility genes for environmental exposures. 2017-2021. Prof.dr. I.H. Heijink, Prof.dr. H.M. Boezen, Dr. M. de Vries. PhD student: Q. Chen

GSMS/University of Southampton: Functional characterisation of PCDH1, a novel gene for asthma and bronchial hyperresponsiveness. 2011-2017. Prof.dr. G.H. Koppelman, Prof.dr. J. Holloway, Dr. M.C. Nawijn, Dr. B.M. Willemse. PhD student: G. Faura Tellez

GSMS/Shantou University Medical College, China (Abel Tasman Talent Program). Proteomic and epigenetic analyses of cadmium-induced carcinogenesis in human bronchial epithelial cells. 2016-2020. Prof.dr. M.G. Rots, Dr. M.N. Hylkema, Prof.dr. A. Lau. PhD student: D. Wu

GSMS/UBC: Dysfunctional crosstalk between epithelial cells and fibroblasts contributes to abnormal tissue repair and remodeling processes in COPD. 2013-2017. Dr. C.A. Brandsma, Prof.dr. I.H. Heijink, Prof.dr. W. Timens, Prof.dr. D.S. Postma, Prof.dr. T.L. Hackett, Dr. S. Wadsworth. PhD student: E. Osei

GSMS/UBC: Accelerated lung ageing in COPD; epithelial barrier dysfunction as driver of abnormal lung tissue repair and remodelling. 2017-2021. Prof.dr. I. H. Heijink, Dr. C.A. Brandsma, Prof.dr. T.L. Hackett. PhD student: K. Muizer


GSMS/University of Newcastle (Australia): The role of β-catenin in the development of the asthmatic epithelial phenotype. 2016-2020. Prof.dr. I.H. Heijink, Dr. M.C. Nawijn, Prof.dr. D. Knight. Phd-student: V. Kuchibhotla

GSMS/University of Sydney: Lung ageing and tissue remodeling in COPD. 2016-2020. Dr. C.A. Brandsma, Prof.dr. W. Timens, Prof.dr. I.H. Heijink, Dr. M. de Vries, Dr. M. van den Berge, Dr. P. Horvatovich, Dr. V. Guryev, Dr. B. Oliver. Phd-student: R. Woldhuis

International Primary Care Respiratory Group. UNLOCK: Uncovering and Noting Long-term Outcomes in COPD to enhance Knowledge. 2010-2018. Dr. N. Chavannes, Dr. I. Tsiligianni, Prof.dr. D. Price, Prof.dr. T. van der Molen


International Primary Care Respiratory Group: Fresh Air Uganda: prevalence and burden of COPD in a rural area of sub-Saharan Africa. 2010-2017. Prof.dr. T. van der Molen, Dr. N.H. Chavannes, Dr. C. de Jong. PhD student: F.A. van Gemert


LPDP grant from the Indonesian Government: Role of the RANKL/OPG axis in pulmonary fibrosis. 2017-2021. Prof.dr. B.N. Melger. PhD student: H. Habibie

Lung Foundation Netherlands consortium grant 6.1.15.017. Mesenchymal stem cells in emphysema: finding the right niche for alveolar repair. 2015-2019. UMCG: Prof.dr. I.H. Heijink, Dr. N. ten Hacken. PhD-student: D.M.L.W. Kruk


Lung Foundation Netherlands 3.2.09.055: Protocadherin-1 expression in airway epithelium: Investigations into a novel cause of bronchial hyperresponsiveness and asthma. 2009-2017. Prof.dr. G.H. Koppelman, Dr. M.C. Nawijn, Prof.dr. D.S. Postma


Lung Foundation Netherlands 3.2.12.044: The functional relevance of microRNAs in COPD; elucidating their role in regulating pulmonary fibroblast function in COPD development. 2012-2017. Dr. C.A. Brandsma, Prof.dr. W. Timens, Prof.dr. DS Postma, Prof.dr. A. van de Berg, Dr. J. Kluiver. PhD-student: J. Ong


Lung Foundation Netherlands 3.2.12.079: Laminin α4 and α5 as regulators of airway inflammation and remodelling in allergic asthma. 2013-2017. Dr. B.G.J. Dekkers, Prof.dr. L.M. Sorokin, Prof.dr. H. Meurs. Post-doc: Dr. P. Prabhala


Lung Foundation Netherlands 1.14.001. Prevention of epigenetic programming of asthma. 2014 – 2018. Consortium grant in collaboration with University of Utrecht and RIVM. Prof. dr. G.H. Koppelman, Dr. U. Gehring, Prof.dr. H. A. Smit, Dr. A. Wiiga

Lung Foundation Netherlands 5.1.14.020 Identifying causal mechanisms of the inception of asthma through a novel experimental model for the interaction on the PCDH1 gene and environment. 2014 – 2017. Consortium grant in collaboration with University of Utrecht and University of Ghent. Dr. M. Nawijn, Prof.dr. G.H. Koppelman, Prof.dr. L. Bont, Prof.dr. B. Lambrecht


Lung Foundation Netherlands 4.1.15.002: Does high baseline oxidative stress attenuate macrophage function during exacerbations of COPD and asthma? 2015-2020. Prof.dr. B.N. Melgert, Dr. R. Lutter, Dr. F.O. Martinez, Prof.dr. H.A.M. Kerstjens; 2 PhD vacancies, 2 technician vacancies

Lung Foundation Netherlands junior investigator grant 4.2.15.039JO: Neuronal remodeling: a novel perspective on airway hyperresponsiveness in asthma. 2016-2019. Dr. L.E.M. Kistemaker

Lung Foundation Netherlands junior investigator grant 5.2.15.057JO: Treatment of chronic REspiratory failure in COPD patients with Non-invasive ventilation: Starting at home and selecting the Right Patient; the RECONSIDER study. 2016-2020. Dr. M.L. Duiverman

Lung Foundation Netherlands junior investigator grant 2.15.044JO: The role of the RAGE receptor and its ligands in abnormal lung tissue repair and injury in emphysema. 2017-2019. Dr. S.D. Pouwels

Lung Foundation Netherlands junior investigator grant 4.2.16.132JO: Understanding the genetic and epigenetic drivers of cigarette smoke susceptibility in COPD. 2017-2018. Dr. A. Faiz

MD/PhD: COPD in primary care and pulmonary rehabilitation: discovering the dynamics of the Minimal Clinically Important Difference (MCID) 2014-2018. Prof.dr. T van der Molen, Dr. C. de Jong. PhD student: H.J. Alma

MD/PhD: Insensitivity to glucocorticosteroid treatment in obstructive pulmonary diseases. 2009-2017. Dr. N.H.T. ten Hacken, Prof.dr. A.J.M. van Oosterhout, Prof.dr. I.H. Heijink. MD/PhD student: J. Zijlstra

MD/PhD: Translating asthma associated genetic variation in IL33 and IL1RL1 into pathophysiology and clinical expression of asthma. 2013 – 2017. Prof.dr. G.H. Koppelman, Dr. M.C. Nawijn. MD/PhD student: M. Ketelaar

MD/PhD: Genetics of food allergy. 2013-2018. Prof.dr. A.E.J. Dubois, Prof.dr. G.H. Koppelman. MD/PhD student: C.D. van Ginkel


MD/PhD: Severity of Anaphylaxis. 2015-2017. Prof.dr. A.E.J.Dubois, Prof.dr.G.H.Koppelman. MD/PhD student: M.E. Pettersson

MPDI Bursary project: The effects of extracellular matrix morphology and stiffness on macrophage function. 2016-2019. Prof. Dr. B.N. Melgert, Dr. P. van Rijn. PhD student: G. Vasse
National Health and Medical Research Council Australia (NHMRC): Elucidation of the Aetiology of Airway Remodelling in COPD; 2016-2020. Dr. B. Oliver, Prof.dr. I. Adcock, Dr. C.A. Brandsma. PhD student: R. Woldhuis

Novartis: Effects of a combination of the beta-adrenoceptor agonist indacaterol and the muscarinic receptor antagonist glycopyrrolate on intrapulmonary airway constriction. 2015-2017. Prof.dr. M. Schmidt. Post-doc: Dr. B. Han

Nuvaira, USA: A Sequential Two Phase Multicenter, Randomized Study to Optimize Dose Selection and Evaluate Safety After Treatment with the Holaira™ Lung Denervation System in Patients with Moderate to Severe COPD, 2014-2018 The AIRFLOW-1 trial. Dr. D.J. Slebos, Dr. J Hartman, Dr. K. Klooster

Pender Foundation for Pulmonary Fibrosis: Exchange of fresh human lung tissue of patients transplanted for pulmonary fibrosis between RUG/UMCG (Groningen) and Erasmus MC (Rotterdam). 2014-2018. Prof.dr. B.N. Melgert, Dr. B. van den Blink

Phadia; In vitro Diagnostiek en Eerstelijns Allergie Leidraad (IDEAL) 2009-2017. Prof.dr. A.E.J. Dubois, Prof.dr. T. van der Molen, Dr. B.M.J. Flokstra-de Blok

PneumRx/BTG, Inc. USA: Lung Volume Reduction Coil for Treatment in Patients with Emphysema (RENEW) Study, FDA-IDE RCT, PneumRx, Inc. USA. 2012-2018. Dr. D.J. Slebos, Dr. K. Klooster, Dr. J.E. Hartman, Dr. N.H.T. Ten Hacken

PneumRx/BTG: Lung Volume Reduction Coil for Treatment in Patients with Emphysema (RENEW-Crossover) Study, 2013-2018. Dr. D.J. Slebos, Dr. K. Klooster, Dr. J.E. Hartman, Dr. N.H.T. Ten Hacken


Roche (Basel, Switzerland): Pirfenidone in Crohn’s disease and other fibrotic disorders. 2016-2017. Prof.dr. B.N.Melgert, Prof.dr. G. Dijkstra


STW Open Technology Programme: Design, synthesis and validation of potent and isozyme selective arginase inhibitors for therapeutic use in asthma. 2015-2020. Prof.dr. A.S.S. Dömling, Prof.dr. H. Meurs, Prof.dr. P.H. Elsinga. PhD student: M.P.M. van den Berg

TEVA the Netherlands: Center for Translational Pediatric Pulmonology. 2016 - 2020. Prof.dr. G.H. Koppelman, Prof.dr. D.S. Postma, Dr. M.N. Nawijn, Dr. B.W.M. Willemse, Dr. E.T. Kersten


University of Groningen. Application of eHealth to improve care for asthma and COPD patients in primary care: from focus groups to data mining. 2012-2017. Prof.dr. T. van der Molen, Prof.dr. R. Sanderman. PhD student: E.I. Metting

University Medical Center Groningen: Work absence, productivity loss and indirect costs in patients with asthma, COPD and ACOS. 2016-2017. Dr. J.W.H. Kocks, Dr. B.M.J. Flokstra -de Blok, Dr. J.F.M. van Boven, Prof.dr. T van der Molen, M. Román-Rodriguez, Prof.dr. J.B. Soriano. PhD Student: B.J.H. Dierick

University Medical Center Groningen (Doelmatigheidsonderzoek). Improving Quality of Life and reducing length of stay for COPD exacerbations by protocolised care. 2014-2017. Prof.dr. H.A.M. Kerstjens, Dr. N.H.T. ten Hacken. PhD Student: M. Klijnsma. Research nurse: A. Niemeijer

University Medical Center Groningen (Doelmatigheidsonderzoek) & Stichting Vrienden van het Beatrixkinderziekenhuis (Grantnumber 671437): GERAS-project NeoLifes (prof dr AF Bos)/Neolifes-lungs. 2013-2020. Dr. E.J.L.E. Vrijlandt, W.Stalman, M. van Smaalen


ZonMW. Citrienfonds: Doen of laten? Terugdringen van onnodige zorg. Afbouwen onnodig gebruik van inhalatie corticosteroïden bij COPD. 2016-2018. Dr. J.W.H. Kocks, Dr. T Schermer, Dr. C. de Jong, Dr. J. van Boven, Prof.dr. T. van der Molen, Dr. R. Riemersma, E. Brill, Dr. M. van den Berge
ZonMW/Proefdiervrij; program Meer kennis met minder dieren. NEURO-Chip: neuronal control of internal organ pathophysiology. 2017-2021. Prof.dr. R. Gosens, Dr. A.M. Dolga, Dr. L.E.M. Kistemaker, Dr. K. Mathwig. Prof.dr. E.M. Verpoorte. PhD student: P. Goldsteen

Also a substantial contribution for several projects has been obtained from the Stichting Astma Bestrijding (SAB) and the Northern CARA Foundation (NCS).

**Research projects of the GRIAC spin-off company Aquilo:**

Aquilo: Evaluation of airway inflammation after TLD for COPD. 2016-2018. Prof.dr. R. Gosens, Dr. L.E.M. Kistemaker

Aquilo: Evaluation of airway inflammation after TLD for asthma. 2017-2019. Dr. L.E.M. Kistemaker, Prof.dr. R. Gosens

Publications 2017

Dissertations

A. Hazenberg
Innovation in home mechanical ventilation
08-03-2017
Promotores: Prof. Dr. P.J. Wijkstra, Prof. Dr. H.A.M. Kerstjens

B.J.P.R. Vos
Hymenoptera venom allergy. Challenges in diagnosis and treatment
13-03-2017
Promotores: Prof. Dr. A.E.J. Dubois, Prof. Dr. F. Ruëff
Co-promotor: Dr. J.N.G. Oude Elberink

F.A. van Gemert
Prevalence and impact of chronic obstructive pulmonary disease in a rural district of Uganda. FRESH AIR methodology for sub-Saharan Africa
10-04-2017
Promotores: Prof. Dr. T. van der Molen, Prof. Dr. N.H. Chavannes
Co-promotor: Dr. C. de Jong

S.D. Pouwels
DAMPs, endogenous danger signals fueling airway inflammation in COPD
10-05-2017
Promotores: Prof. Dr. H.I. Heijink, Prof. Dr. A.J.M. van Oosterhout
Co-promotor: Dr. M.C. Nawijn

M.A.E. Nieuwenhuis
Genetics of different asthma phenotypes
15-05-2017
Promotores: Prof. Dr. D.S. Postma, Prof. Dr. G.H. Koppelman
Co-promotor: Dr. J.M. Vonk

E.T. Osei
The role of epithelial-fibroblast communication in asthma and COPD
06-09-2017
Promotores: Prof. Dr. W. Timens, Prof. Dr. T-L. Hackett, Prof. Dr. H.I. Heijink
Co-promotor: Dr. C.A. Brandsma

X. Han
Internalization of Aspergillus fumigatus into pulmonary epithelial cells: joint action of host and pathogen.
15-09-2017
Promotores: Prof. Dr. M. Schmidt, Prof. Dr. L. Han

N.P. Tania
Developmental and pathological roles of BMP/follistatin-like 1 in the lung
06-10-2017
Promotores: Prof. Dr. R. Gosens, Prof. Dr. M. Schmidt
Co-promotor: Dr. H. Maarsingh
E.M. van Dijk
WNT pathway activation in COPD: a two way street between signalling and pathology
16-10-2017
Promotores: Prof. Dr. R. Gosens, Prof. Dr. H. Meurs

D.A. van der Plaat
Genes, DNA methylation and exposures underlying COPD in never-smokers
18-10-2017
Promotores: Prof. Dr. H.M. Boezen, Prof. Dr. D.S. Postma
Co-promotor: Dr. J.M. Vonk

T. Koopmans
WNT and β-catenin signalling in airway smooth muscle: emerging concepts for asthma
20-10-2017
Promotores: Prof. Dr. R. Gosens, Prof. Dr. H. Meurs

B. Honrath
On the impact of neuronal KCa channels & calcium signaling in neurodegeneration
08-12-2017
Promotor: Prof. Dr. M. Schmidt
Co-promotor: Dr. A.M. Dolga

K.F. Meyer
Smoking during pregnancy and prenatal programming - Consequences for DNA-methylation
13-12-2017
Promotor: Prof. Dr. W. Timens
Co-promotor: Dr. M.N. Hylkema

Publications SCI journals


Boven van JFM, Lavorini F, Dekhuijzen PNR, Blasi F, Price DB, Viegi G. Urging Europe to put non-adherence to inhaled respiratory medication higher on the policy agenda: a report from the First European Congress on Adherence to Therapy. Eur Respir J. 2017;49(5):1700076. PMID: 28526801.


Ipratropium Bromide in Male and Female Patients with Mild to Moderate Chronic Obstructive Pulmonary Disease. EBioMedicine. 2017;19:139-145. PMID: 28461224.


Nolte IM, van der Most PJ, Alizadeh BZ, de Bakker PI, Boezen HM, Bruinenberg M, Franke L, van der Harst P, Navis G, Postma DS, Rots MG, Stolk RP, Swertz MA, Wolffenbuttel BH,


Rijn van SP, Zuur MA, van Altena R, Akkerman OW, Proost JH, de Lange WC, Kerstjens HA, Touw DJ, van der Werf TS, Kosterink JG, Alffenaar JW. Pharmacokinetic Modeling and


Publications in Dutch


Book chapters


Contributions to other research institutes

Dissertations

Publications SCI journals


