

Groningen Research Institute for Asthma and COPD
Annual Report 2009



UMCG

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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. W. Timens

Prof. dr. H.M. Boezen

Visiting address:

University Medical Center Groningen
Hanzeplein 1
NL-9713 GZ Groningen

Website: www.griac.nl

Webmaster: Prof.dr. W. Timens

Secretariat:

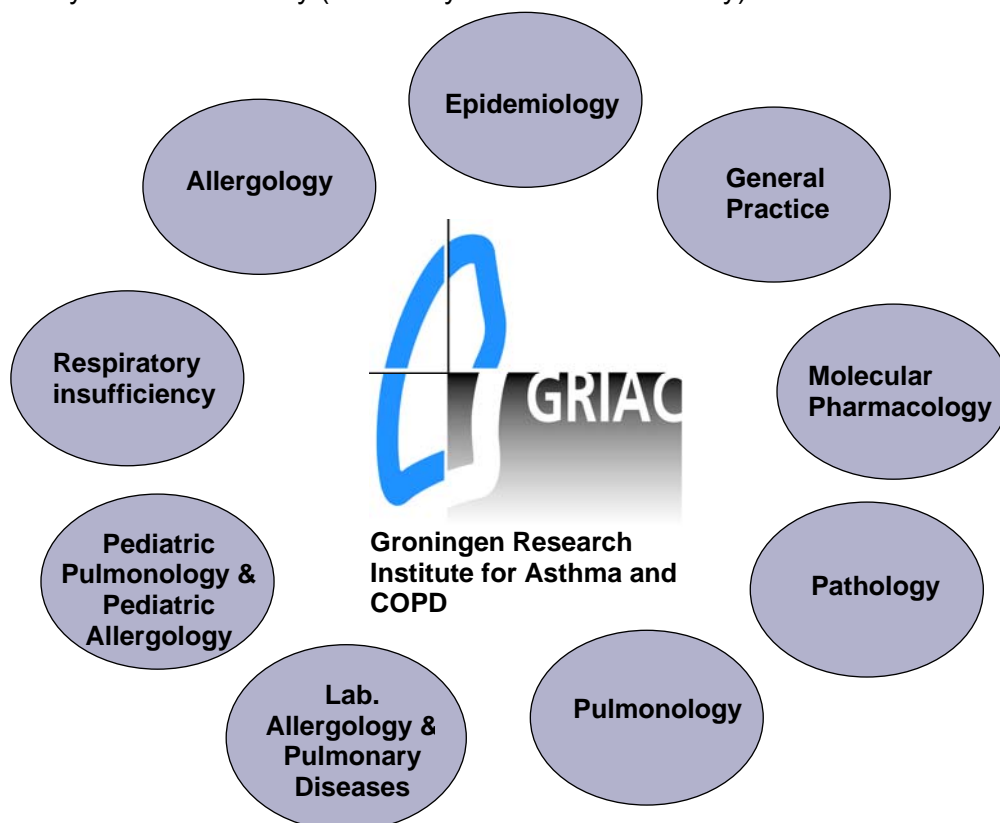
Dept. of Epidemiology
University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone: 31-50-361 0739
Fax: 31-50-361 4493
Email: w.timens@path.umcg.nl
and h.m.boezen@epi.umcg.nl

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 allergy, 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.

At every occasion of the defence of a Ph.D. thesis care is taken to also invite a top-researcher of particular research field. He or she is asked to judge the thesis and participate in the Ph.D. defence on site, and, in addition, to give a presentation. When these external visitors are present, workshops for exchange of ideas are always 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. Epidemiology and (genetic) statistical courses are being organised for participants 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.

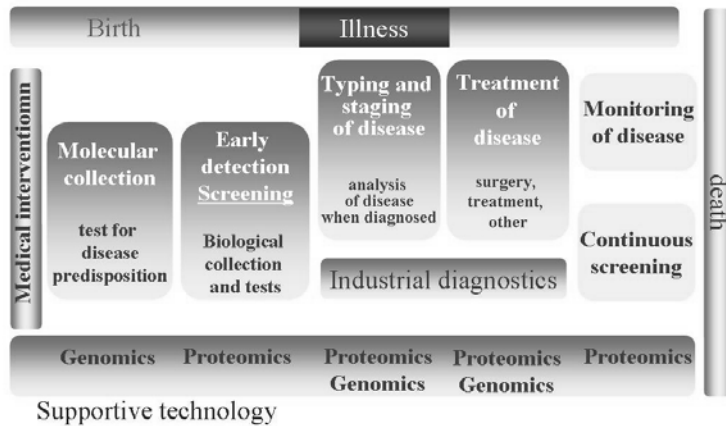
Research Program

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).

Translational medical management: From diagnosis to treatment



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.

Perspective

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

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

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

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

An area of importance in paediatric asthma is food allergy, which has recently been shown to be a risk factor for asthma exacerbations requiring ventilation in children. To explore this theme, the established food-challenge unit is carrying out double-blind placebo-controlled challenges.

Research in the rehabilitation programme has been recently reinforced with respect to asthma and COPD, and is expected to increase the input to and output of the GRIAC programme. This has been expanded by novel invasive techniques such as applying stents in airway walls, which dramatically improves exercise capacity in emphysema, thus allowing better rehabilitation as well.

The population for genetic analyses in asthma and COPD has been greatly expanded, and will be expanded still further, allowing replication and association studies. A number of international genome-wide association studies on asthma and COPD, including analysis on gene-environment interaction studies were started. 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. Functional studies on gene variations in asthmatic and healthy individuals have started, both in cells and in animal studies. Integration of epidemiological results with genetics will provide insight into genetic variants as risk factors for the development, progression or remission of asthma and COPD. Finally, the integration of newly discovered genes with the results of gene expression in relevant tissues that are available and/or cell cultures allows further research into functional relevance. It is envisaged that comparative genomics in animals, cell culture and humans will be initiated.

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 transmurial management of 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.

“Healthy Aging” has been adopted as the main theme for research and clinical profile of the UMCG. An important long term project fitting in with this, is “LifeLines” a planned 30-year survey on risk factors (obtained by objective physiologic, questionnaire, biologic end genomic markers) of disease development, COPD being one of the leading themes. This fits very well with the research agenda of GRIAC, including co-morbidity and systemic manifestations of COPD. We are and will be actively participating in development of this programme within the UMCG. In addition, we participate actively in the development of ERIBA, the program on aging in the UMCG that has important bearings on both fundamental and clinical research developments.

The year in review

All contributions to the scientific work in GRIAC are of importance and are appreciated. Nevertheless, without disrespect to the work of members who are not specifically mentioned, we like to highlight some topics that drew particular attention in 2009.

We are happy that Dr. R. Gosens has been appointed as tenure track Assistant Professor *Translational Pharmacology* at the Department of Molecular Pharmacology. In addition, Dr. H. Maarsingh and Drs. B. Dekkers have been appointed as lecturers at the Department of Molecular Pharmacology. Dr J.M.Vonk was appointed as Assistant Professor at the Department of Epidemiology.

Also in 2009, GRIAC had to accept the pass away of our secretary Annelies Drewes.

In particular in this year, the highly dynamic discipline-interactive feature of GRIAC was reflected upon the organization of several (inter)national symposia being held in the framework of the participating departments. From June 15th up to June 17th Bronchitis 8, entitled "Obstructive lung diseases from conception to old age", was held in the University Medical Center Groningen (UMCG), and attracted again scientific recognition by the world-wide renowned (inter)national experts in chronic obstructive lung disorders.

Chairs and speakers at the symposium were:

Prof. T. Bai (Toronto, Canada), Prof. P. Barnes (London, Great Britain), Prof. E. Bleeker (Winston-Salem, USA), Prof. H. Boezen (Groningen, The Netherlands), Prof. P. Boulet (Hamilton, Canada), Dr. G. Braunstahl (Rotterdam, The Netherlands), Prof. B. Brunekreef (Utrecht, The Netherlands), Prof. G. Brusselle (Gent, Belgium), Prof. A. Bush (London, Great Britain), Prof. P. O'Byrne (Hamilton, Canada), Prof. D. Davies (Southampton, Great Britain), Prof. J. Drazen (Boston, USA), Prof. A. Dubois (Groningen, The Netherlands), Prof. L. Fabbri (Modena, Italy), Prof. E. Gelfand (Boston, USA), Dr. R. Gosens (Groningen, The Netherlands), Dr. N. ten Hacken (Groningen, The Netherlands), Prof. S. Hirst (Melbourne, Australia), Prof. J. Hogg (Toronto, Canada), Prof. S. Holgate (Southampton, Great Britain), Dr. M. Hylkema (Groningen, The Netherlands), Dr. G. Koppelman (Groningen, The Netherlands), Prof. H. Magnussen (Hamburg, Germany), Prof. F. Martinez (Tucson, USA), Prof. D. Meyers (Kansas, USA), Prof. T. van der Molen (Groningen, The Netherlands), Prof. E. von Mutius (Munich, Germany), Prof. D. Postma (Groningen, The Netherlands), Prof. K. Rabe (Leiden, The Netherlands), Prof. O. van Schayck (Leiden, The Netherlands), Prof. A. Spira (Boston, USA), Prof. W. Timens (Groningen, The Netherlands), Prof. E. Wouters (Maastricht, The Netherlands),

On the occasion of the retirement of Dr. J.P. Schouten, Assistant Professor at the Department of Epidemiology, a Farewell symposium was held on October 30 in the UMCG. Dr. Schouten's expertise is on complex and longitudinal data analysis and reference equations for spirometric indices, and he has contributed largely to the international scientific body of knowledge in both fields. We are indebted to his scientific achievements, and his knowledge and expertise will be missed within GRIAC. Chairs and speakers at the symposium were: Prof.dr. H.M. Boezen (Groningen, The Netherlands), Prof.dr. D.S. Postma (Groningen, The Netherlands), Dr. J.M. Vonk (Groningen, The Netherlands), Prof.dr. W. Timens (Groningen, The Netherlands), Prof.dr. J.W. Groothoff (Groningen, The Netherlands) and Prof.dr. R.P. Stolk, (Groningen, The Netherlands). In addition, on the occasion of the inaugural lecture of Prof.dr. M. Schmidt, a (inter)national Symposium TopMaster Medical Pharmaceutical Drug Innovation, was held in the Department Pharmacie. Chair and speakers were: Prof.dr. M. Schmidt (Groningen, The Netherlands), Prof.dr. T. Wieland (Mannheim, Germany). Dr. M. van den Hoff (Amsterdam, The Netherlands), Dr. J. van den Born (Groningen, The Netherlands). Dr. M. Harmsen (Groningen, The Netherlands) and Dr. R. Gosens (Groningen, The Netherlands).

Visitors

Prof. I. Sabroe, University of Sheffield, UK: "Viruses, pollution, and the regulation of airway inflammation", November 23th, 2009.

Prof. Moritz Bünemann, University of Würzburg, Germany: '*FRET and FRAP shine new light on G protein-coupled receptor signaling*'. May 25, 2009.

Dr. Frank Lezoulc'h, Université Parix XI, France: '*Functional characterization of the cAMP binding protein Epac in cardiac myocytes*'. June 10, 2009.

Prof. Liliana Schaefer, University of Frankfurt, Germany: '*SLRP-signaling in inflammation and fibrosis*'. June 19, 2009.

Prof. Thomas Wieland, University of Mannheim-Heidelberg, Germany: 'The interaction of nucleoside diphospho (NDP) kinase B with G_{βγ} controls heterotrimeric G protein function. December 9, 2009.

Dr. Maurice van den Hoff, University of Amsterdam: '*Follistatin-like 1: what's your function?*'. December 9, 2009.

Other visitors were Prof. J. Vestbo, University of Copenhagen, Denmark, Prof. N. Probst, University of Basel, Switzerland, Prof. D. Meyers and Prof. E. Bleecker, Wake Forest University, School of Medicine, Winston-Salem, USA.

Prizes / Awards

The abstract by G. Koppelman describing the discovery of *PCDH1* as a novel gene for bronchial hyperresponsiveness and asthma was selected for the 'Scientific Breakthrough of the year' Symposium at the annual conference of the ATS.

M.J. Blacquièrè was awarded a short-term European Respiratory Society fellowship for the project: "Epigenetic regulation of farm dust-induced T cell differentiation" in collaboration with Prof. I. Adcock, London, UK.

C.A. Brandsma was awarded short-term research fellowships from the Dutch Asthma Foundation and the European Respiratory Society for the project; "Differential expression of remodelling genes in small airways and parenchymal lung tissue in relation to airway obstruction and emphysematous destruction in COPD" in collaboration with Prof. J.C. Hogg, Vancouver, Canada and Dr. A. Spira, Boston, USA.

S. Shirinbaik was awarded a short-term European Respiratory Society fellowship for the project: "Maternal transfer of allergen specific tolerance induced by immunotherapy to the progeny and protection from allergic asthma", which will be carried out in the group of Dr.V. Julia, Nice, France.

D.S. Postma received the presidential award of the European Respiratory Society.

HOT TOPICS

Special Topic 1:

Food allergy and quality of life: Development, validation and outcomes of health-related quality of life questionnaires for food allergic patients.

Bertine Flokstra – de Blok

Introduction

Food plays an important role in our social and cultural life. In patients with food allergy the ingestion of a particular food may provoke an allergic reaction, which may be fatal for some patients¹⁻³. The only proven form of treatment is strict avoidance of the food(s) involved and medications for emergency treatment⁴. Food allergic patients thus need to be continuously alert as to what they are eating in numerous situations and settings. Consequently, daily life of these patients may be seriously disrupted by the required continuous vigilance, the threat of accidental exposure and fear of an allergic reaction and this may have a negative impact on their health-related quality of life (HRQL).

Although food allergy might have a considerable impact on HRQL, no valid disease-specific HRQL questionnaires were available to measure the impact of food allergy on the patient's quality of life at the beginning of this study (June 2005). The only well-validated HRQL questionnaire for food allergy available at that time, was the Food Allergy Quality of Life – Parental Burden (FAQL-PB) questionnaire⁵. This questionnaire is completed by parents and measures the parental burden of having a child with food allergy. Although being useful and well designed, this questionnaire is not able to measure the impact of food allergy on HRQL as experienced by the patients themselves. Therefore, our aim was to develop and validate the first disease-specific HRQL questionnaires for food allergic children 8-12 years, adolescents 13-17 years, and adults 18 years and older. This study was part of the EuroPrevall project, a European multi-centre research project on food allergy.

Development

The development phase started with the generation of items for the new questionnaires. The main sources for items were food allergic patients. In semi-structured interviews patients were asked about troublesome aspects of having a food allergy in daily life. In addition, we searched the literature on food allergy and asked clinical experts for additional items. When no important new items emerged, the item generation was considered as complete. This item generation phase was followed by the item reduction phase, in which the obtained long lists of items concerning food allergy were given to other groups of food allergic patients. These patients were asked to indicate whether an item was applicable to them and if so, to rate on a five-point scale how troublesome that particular item was. By following this method, also named as the clinical impact method, we could select the most important items for the questionnaires. This resulted in the following three questionnaires:

- Food Allergy Quality of Life Questionnaire - Child Form (FAQLQ-CF)⁶,
- Food Allergy Quality of Life Questionnaire - Teenager Form (FAQLQ-TF)⁷,
- Food Allergy Quality of Life Questionnaire - Adult Form (FAQLQ-AF)⁸.

Validation

The development phase was followed by the cross-sectional validation, in which the newly developed questionnaires were investigated as to their validity. Construct validity is usually evaluated by comparing the HRQL questionnaire with an objective measurement of the extent or severity of the disease. However, in disorders not characterized by chronic symptoms, as in food allergy, such an independent measure is not available. It has been shown that the perceived expectation of what will happen following exposure can be used as independent

measure to evaluate construct validity and instruments developed in this way have proved to be useful and consistent in measuring HRQL^{5; 9;10}. Therefore, in order to investigate construct validity of the FAQLQs, correlation coefficients were calculated for the FAQLQs with the Food Allergy Independent Measure (FAIM). The FAIM contains four Expectation of Outcome (EO) questions and two additional Independent Measure (IM) questions¹¹. The EO questions are based on the perceived expectation of patients of what will happen following exposure, which is likely to be a driving force of quality of life. The IM questions are based on the same principle and query about the perceived number of foods one needs to avoid and perceived impact on social life. By calculating correlation coefficients between the FAQLQs and the FAIM we showed acceptable levels of construct validity for all three FAQLQs (Table 1) and by calculating correlation coefficients between the FAQLQs and the generic HRQL questionnaire we showed acceptable levels of convergent and discriminant validity for all three questionnaires^{6,7,8}. By administrating the FAQLQs two times to the same patients within a 10-14 day interval, we found that all three questionnaires showed good test-retest reliability¹². Such reliability measures are important to ensure that what the questionnaire is measuring is reproducible.

Table 1: Spearman’s correlation coefficients of the FAQLQs with the FAIM

	FAIM	
FAQLQ-CF	0.60	p<0.001
FAQLQ-TF	0.57	p<0.001
FAQLQ-AF	0.76	p<0.001

Outcomes

In two additional studies we investigated HRQL of food allergic patients with generic HRQL questionnaires. Measurement of generic and disease-specific HRQL in the same group of food allergic patients had never been done before. The aim of the first study was to compare generic HRQL of food allergic patients with the general population and other diseases (asthma, irritable bowel syndrome (IBS), diabetes mellitus type I (DM) and rheumatoid arthritis (RA))¹³. The aim of the second study was to compare HRQL of food allergic patients as measured with generic and disease-specific questionnaires¹⁴. We found that food allergic children reported the least impact of food allergy on generic HRQL, which was even better than in children in the general population in some respects (Role functioning - Behaviour). Food allergic adolescents and adults reported overall poorer generic HRQL than the general population. In addition, we found that the generic HRQL impact of food allergy is intermediate in magnitude between DM and asthma, IBS and RA (Figure 1 and 2). Moreover, we found very high ceiling effects for some generic scales, which may indicate that generic HRQL questionnaires are not sufficiently sensitive to measure disease-specific clinically important impairments in food allergy. Thus, generic HRQL questionnaires may be useful to compare the impact of food allergy on HRQL in the general population and other chronic diseases. However, for measuring disease-specific effects in food allergic patients, it is preferable to use disease-specific questionnaires.

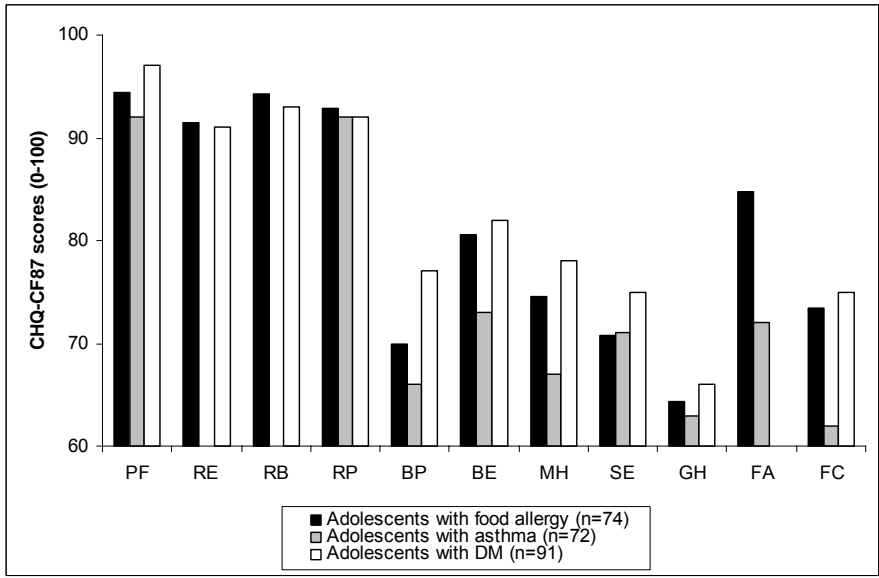


Figure 1. Generic CHQ-CF87 scores of adolescents with food allergy, asthma and diabetes mellitus type 1 (DM). *p<0.05; **p<0.01. Higher scores indicate better HRQL. RE and RB not available for asthma, FA not available for DM. Physical functioning (PF), Role functioning-emotional (RE), Role functioning-behaviour (RB), Role functioning-physical (RP), Bodily pain (BP), General behaviour (BE), Mental health (MH), Self-esteem (SE), General health (GH), Family activities (FA), Family cohesion (FC).

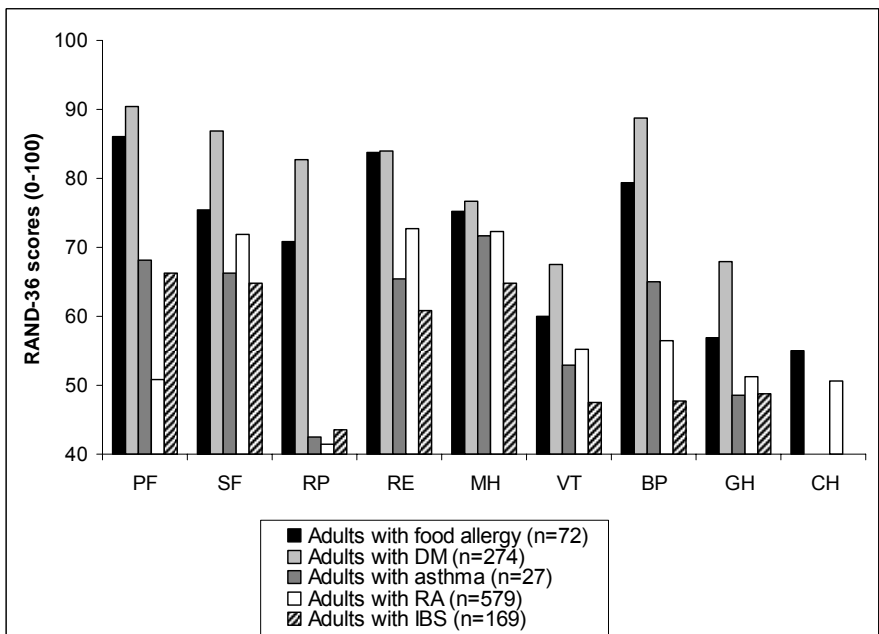


Figure 2 Generic RAND-36 scales scores of adults with food allergy, diabetes mellitus type 1 (DM), asthma, rheumatoid arthritis (RA) and irritable bowel syndrome (IBS). *p<0.05; **p<0.01; ***p<0.001. Higher scores indicate better HRQL. CH not available for asthma, IBS and DM. Physical functioning (PF), Social functioning (SF), Role functioning-physical (RP), Role functioning-emotional (RE), Mental health (MH), Vitality (VT), Bodily pain (BP), General health (GH), Change in health (CH).

Conclusion

We have developed and validated 3 disease-specific HRQL questionnaires for food allergic children 8-12 years, adolescents 13-17 years, and adults 18 years and older. In addition and concomitantly to these questionnaires, a parent-administered questionnaire has been developed (Food Allergy Quality of Life Questionnaire – Adult Form)¹⁵. Hence, validated disease-specific HRQL questionnaires are now available for food allergic patients of all age groups. These HRQL questionnaires may be used in clinical studies to measure the effects of an intervention on the patient's quality of life and HRQL questionnaires may be used by clinicians to get insight in the specific problems patients have to face.

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Special Topic 2:

Identification of Protocadherin-1 (PCDH1) as a novel gene for Bronchial Hyperresponsiveness

Gerard Koppelman

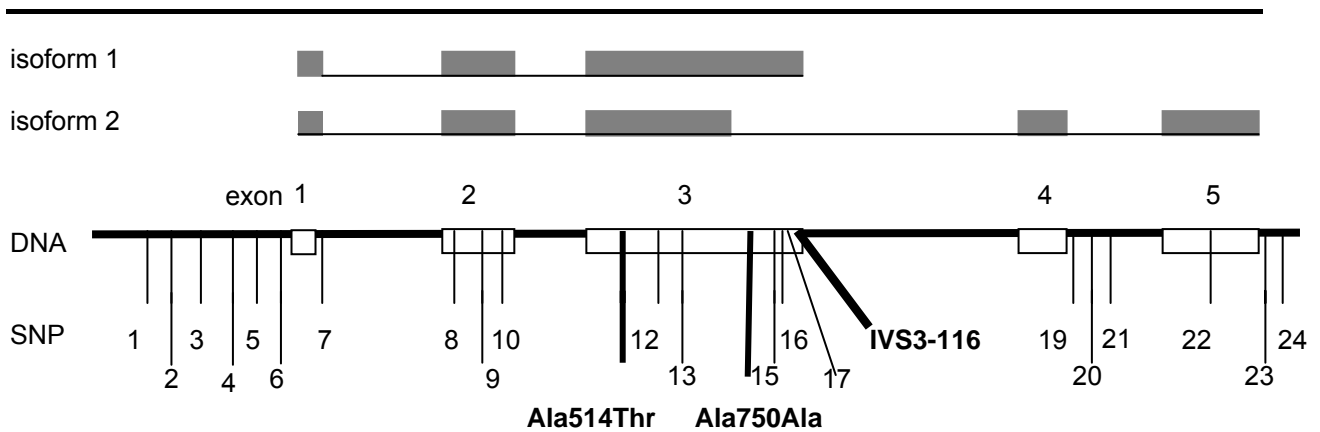
Introduction

Asthma is a chronic inflammatory airway disease that affects over 300 million of individuals worldwide. It is characterized by respiratory symptoms, variable airway obstruction, and bronchial hyperresponsiveness (BHR). BHR has a considerable genetic component and constitutes a risk factor for asthma. Genetic approaches, including positional cloning and more recently, genome wide association studies, have led to the identification of multiple novel genes for asthma, resulting in more insight into the complex pathogenesis of this disease.

The identification of PCDH1 as a novel BHR susceptibility gene

We initially reported linkage of BHR to chromosome 5q31-q33 in Dutch asthma families. [1].

Figure 1. Protocadherin-1: Gene, mRNA expression and SNPs



Legend: SNPs that were identified through resequencing are numbered 1 – 24. In exon 3, Ala514Thr, Ala750Ala and IVS3_116 (in bold) are associated with asthma and BHR in multiple populations.

PCDH1 was discovered using linkage analysis and fine mapping in Dutch asthma families, and replication studies in 7 populations from the Netherlands, USA and UK. Three genetic variants were found to be associated with BHR and asthma (table 1). First, the association found between Ala750Ala and BHR was observed consistently in parents and children of the Dutch family study. Ala750Ala was also significantly associated with asthma in this study ($p=0.003$). The association of Ala750Ala and BHR was strictly [2] replicated in 11-year-old children participating in the population-based Children's Respiratory Study in Tucson, Arizona, USA (Prof Martinez) [3]. Moreover, Ala750Ala was associated with the development of BHR in adults from the Dutch population-based study Vlagtwedde-Vlaardingen. [4] Second, a three base pair insertion/deletion polymorphism (IVS3 -116) in the 3' UTR region of exon 3 was associated with BHR in two Dutch populations and with asthma and BHR in two US case-control populations collected as part of the CSGA (Prof Meyers and Prof Bleecker). [5] Third, Ala514Thr was associated with BHR in the US Children's Respiratory Study, and in a UK population of 341 families ascertained through two affected siblings with asthma (dr Holloway, Prof Holgate). [6] Thus, three *PCDH1* gene variants in exon 3 are associated with BHR and asthma in 7 different populations.

Table 1. Association of *PCDH1* gene variants with bronchial hyperresponsiveness in 8 populations (n=6,168)

SNP	Rs number	Risk allele	Allele frequency (Dutch)	Dutch 200 Asthma families	Dutch 200 Asthma parents (case-control)	Dutch 407 asthma trios	Dutch General population, adults	Tucson, US General population, children	Southampton, UK 341 asthma families	US – Caucasian (C); Hispanic (H) and Afro-American (A) Case-control	
								age 11	age 16		
N				1259	401	1221	418	318	329	1508	665C 246 H 522 A
Ala514Thr	RS3822357	A	0.92	0.47	0.11	0.72	0.58	0.07	0.005	0.009	Ns
Ala750Ala	RS3797054	T	0.67	0.005	0.02	0.49	0.05	0.04	0.28	0.19	Ns
IVS3-116	-	Del TTC	0.08	0.04	0.25	0.05	0.95	0.40	1.0	0.58	0.02 (H, asthma) 0.02 (C, BHR)

PCDH1: gene, expression and function

PCDH1 spans 5 exons and encodes multiple mRNA isoforms through alternative splicing in exon 3 (figure 1). There are two isoforms of *PCDH1* annotated in Genbank, one containing 3 exons and one spanning all 5 exons. Both isoforms encode the extracellular and transmembrane domains, but only the longer isoform also encodes intracellular signalling domains. *PCDH1* belongs to the δ 1-protocadherin family of transmembrane proteins. [7] δ 1-protocadherins are members of the large protocadherin family within the superfamily of cadherins, and are characterized by 6 or 7 cadherin repeats in the extracellular region, and three highly conserved regions CM1, -2 and -3 in the intracellular domain [8]. CM2 interacts with protein phosphatase 1 α (PP1 α) [9], whereas the function and interaction partners of the conserved domains CM1 and CM3 is unknown. Overexpression of *PCDH1* induces calcium dependent cell-cell adhesion and membrane expression of *PCDH1* in a mouse fibroblast L cell assay [10]. Thus, *PCDH1* is thought to have homologous adhesion properties. Another function of *PCDH1* was suggested by studies of a skin keratinocyte wounding model. In this model, *PCDH1* mRNA was significantly upregulated 24 hours after wounding, compatible with a role of *PCDH1* in epithelial repair [11]. Within the airways, *PCDH1* expression is confined to airway epithelial cells and alveolar macrophages. Thus, *PCDH1* may play a role in the chronic epithelial repair process that is thought to contribute to airway remodelling in asthma. We plan to perform further research on *PCDH1* isoform expression, and function, within the Groningen Research Institute for Asthma and COPD and are currently developing *PCDH1* mouse models.

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Reference:

Identification of PCDH1 as a novel susceptibility gene for bronchial hyperresponsiveness. Gerard H. Koppelman¹, Deborah A. Meyers², Timothy D. Howard², S. Lilly Zheng², Greg A. Hawkins², Elizabeth J. Ampleford², Jianfeng Xu², Henk Koning^{1,3}, Marcel Bruinenberg⁴, Ilija M. Nolte⁵, Cleo C van Diemen⁵, H. Marike Boezen⁵, Wim Timens⁵, Paul A Whittaker⁷, O. Colin Stine⁶, Sheila J. Barton⁹, John W. Holloway⁹, Stephen T. Holgate¹⁰, Penelope E. Graves¹¹, Fernando D. Martinez¹¹, Martijn C. Nawijn³, Antoon van Oosterhout³, Eugene R. Bleeker² and Dirkje S. Postma¹². *Am J Respir Crit Care Med*. 2009 Nov 15;180(10):929-35

Department of (1) Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, (3) Medical Biology, (4) Genetics, (5) Epidemiology, (6) Pathology and (12) Pulmonology and Tuberculosis, University Medical Center Groningen, University of Groningen, The Netherlands; (2) Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem, NC, USA; (7) Respiratory Disease Area, Novartis Institutes for Biomedical Research, Horsham, UK; (8) Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD, USA; (9) Human Genetics Research Division; (10) Respiratory, Cell and Molecular Biology, Infection, Inflammation and Repair, Research Division, School of Medicine, University of Southampton, Southampton, UK; (11) Arizona Respiratory Center, University of Arizona, Tucson, AZ, USA.

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Special Topic 3:

Farm dust exposure decreases allergic airway inflammation but induces non-allergic airway inflammation

Anne Blacquièrè, Wim Timens, Dirkje Postma and Machteld Hylkema

The incidence of asthma has increased over the past decades worldwide. An explanation for this increased incidence was proposed by D. Strachan who put forward the hygiene hypothesis in 1989 [1]. This hypothesis states that infections and microbial exposure in early life may confer protection towards development of allergies and asthma. This is underlied by the observation that the immature immune system at birth is biased in a T_H2 direction, which, when persisting, may lead to development of allergies and asthma. Thus, maturation of T_H1 immune competence has to occur in early childhood to protect against the development of an imbalance between T_H1 and T_H2 immunity as seen in allergic asthma. However, the incidence of typically T_H1 oriented diseases has also increased in the past decades [2,3]. Therefore, a sub-hypothesis was put forward, stating that a lack of microbial exposure early in life has a negative effect on development of T regulatory cells that down regulate both excessive T_H1 and T_H2 responses [4].

To study the mechanisms that contribute to farm dust induced down regulation of allergic airway inflammation we studied the effects of farm dust in our mouse model of allergic asthma. Allergic airway inflammation was induced by intranasal administration of house dust mite (HDM), a natural allergen to the majority of allergic asthma patients, without adjuvant for four times per week during five weeks. Farm dust was administered intranasally one minute before every HDM administration.

Airway responsiveness and allergic airway inflammation, characterized by eosinophil accumulation in lung tissue, inflammatory cytokines IL-5 and IL-13 in lung tissue (data not shown) and HDM-specific IgE in serum, were down regulated when mice were treated with farm dust (Figure 1 A-C).

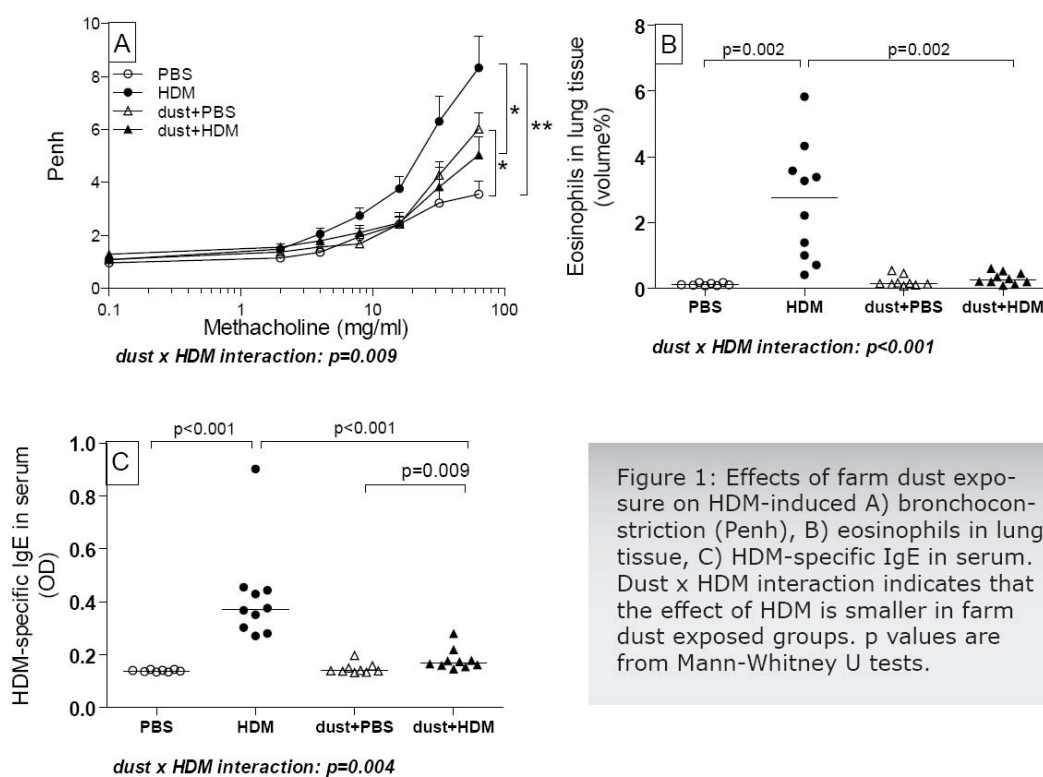


Figure 1: Effects of farm dust exposure on HDM-induced A) bronchoconstriction (Penh), B) eosinophils in lung tissue, C) HDM-specific IgE in serum. Dust x HDM interaction indicates that the effect of HDM is smaller in farm dust exposed groups. p values are from Mann-Whitney U tests.

The effects of farm dust on HDM-induced allergic airway inflammation could not be explained by increased numbers of T regulatory cells (which were increased in both HDM and dust exposed groups) or increased T_H1 responses (the T_H1 cytokine IFN γ was down regulated in farm dust exposed mice compared with HDM exposed mice). However, a marked difference between the HDM exposed mice and farm dust exposed mice was that farm dust exposed mice had larger and more inflammatory infiltrates in lung tissue (Figure 2A). Additionally, farm dust exposed mice showed T_H17 cells in lung tissue, which were totally absent in HDM exposed mice (Figure 2B).

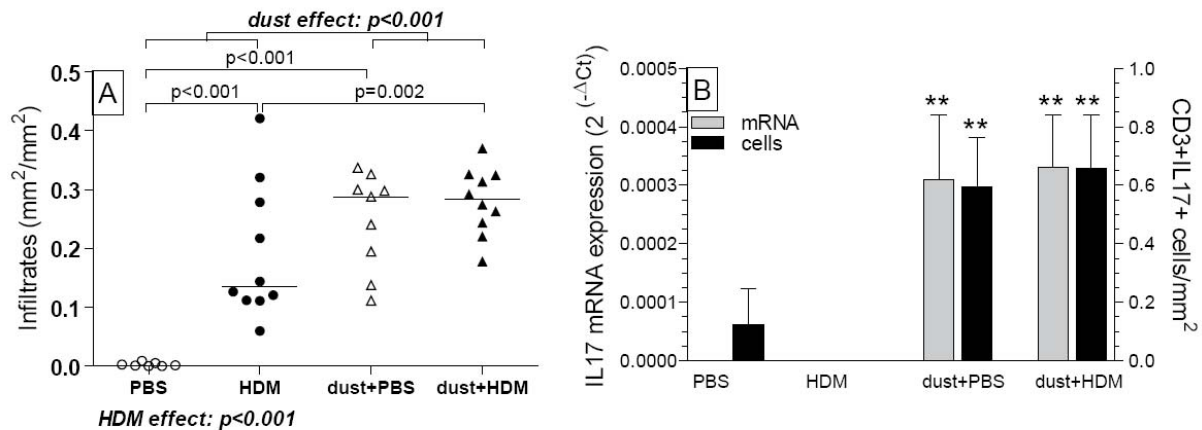


Figure 2: Effects of farm dust exposure on HDM-induced A) infiltrate size and B) IL-17 mRNA and number of Th17 cells in lung tissue. HDM effect indicates an effect of HDM exposure, dust effect indicates an effect of dust exposure. p Values are from Mann-Whitney U tests, ** p<0.01 compared with PBS or HDM groups.

In conclusion this study indicates that farm dust can down regulate allergic airway inflammation, as also described in epidemiological studies. The results show that instead of an increase in regulatory T cell numbers or the counterbalancing T_H1 response, as hypothesized by the hygiene hypothesis, the T_H17 response may play a key role in this protective effect. Although farm dust exposed mice seem to be protected from allergic airway inflammation, they do develop non-allergic airway inflammation and airway responsiveness. We therefore hypothesize that the T_H17 response can contribute to down regulation of the allergic airway inflammation but can increase non-allergic airway inflammation as well. Since agricultural workers show a decreased risk for allergic airway symptoms but do have non-allergic airway complaints [5], we currently investigate the dual role of the Th17 response in allergic and non-allergic airway inflammation in mice and human blood.

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Special Topic 4:

Endogenous activation of RGD-binding integrins enhances airway smooth muscle remodelling in chronic asthma

Bart Dekkers, Sophie Bos, Reinoud Gosens, Andrew Halayko, Johan Zaagsma and Herman Meurs.

Airway wall remodelling is a characteristic feature of chronic asthma, which is considered to contribute importantly to decreased airway diameter and airway hyperresponsiveness in asthma. Increased airway smooth muscle (ASM) mass and altered deposition of extracellular matrix (ECM) proteins – including increased expression of collagen I, fibronectin and laminin $\alpha 2/\beta 2$ chains¹ – are characteristic features of airway remodelling^{2,3}. The ECM is a dynamic macromolecular structure that surrounds tissue cells and provides structural support. In addition, ECM proteins have also been shown to regulate the function of the cells embedded therein. Recently, an important role for collagen I and fibronectin in increasing ASM cell proliferation was found, whereas laminin inhibited growth factor-induced proliferation and preserved contractile function^{4,5}, indicating that ECM proteins may be actively involved in airway remodelling.

Interaction of cells with the surrounding matrix is mainly mediated by integrins, a group of heterodimeric transmembrane glycoproteins, which interact with specific sequences within the ECM proteins⁶. One of these sequences, the Arg-Gly-Asp (RGD) binding motif, is present in ECM proteins like fibronectin, collagen I and laminin. Studies investigating the role of integrins in ASM function have indicated that the RGD-binding integrin $\alpha 5\beta 1$ is importantly involved in regulation of ASM cell proliferation *in vitro*³.

Collectively, these findings indicate that ECM proteins and their integrins are major modulators of ASM remodelling in asthma. To test this hypothesis *in vivo*, we investigated the effects of the integrin blocking peptide RGDS (Arg-Gly-Asp-Ser) and its negative control GRADSP (Gly-Arg-Ala-Asp-Ser-Pro) on ASM remodelling in a guinea pig model of allergic asthma⁷. The animals were challenged with either saline or ovalbumin once weekly for 12 weeks and treated with intranasally administered saline, RGDS (2.5 mM) or GRADSP (2.5 mM), 30 min prior to and 5,5 hr after each challenge. As parameters for ASM remodelling, ASM area, ASM cell size, pulmonary expression of proliferating cell nuclear antigen (PCNA) and smooth muscle myosin heavy chain (*sm*-MHC), as well as ASM contractility were evaluated *ex vivo*. In addition, airway inflammation was quantified by assessing eosinophilic and neutrophilic cell numbers in the different airway compartments. Airway fibrosis was estimated by a hydroxyproline assay, using total lung homogenates.

The results showed that intranasal instillation of RGDS attenuated allergen-induced ASM hyperplasia, increased pulmonary expression of *sm*-MHC and ASM hypercontractility, whereas no effects were observed in saline-challenged animals (Figure 1)⁸. In addition, RGDS inhibited the allergen-induced increase in pulmonary expression of PCNA (not shown)⁸. No effects were observed for GRADSP. The RGDS effects appeared to be ASM-selective, as allergen-induced eosinophil and neutrophil infiltration as well as fibrosis were unaffected (not shown)⁸.

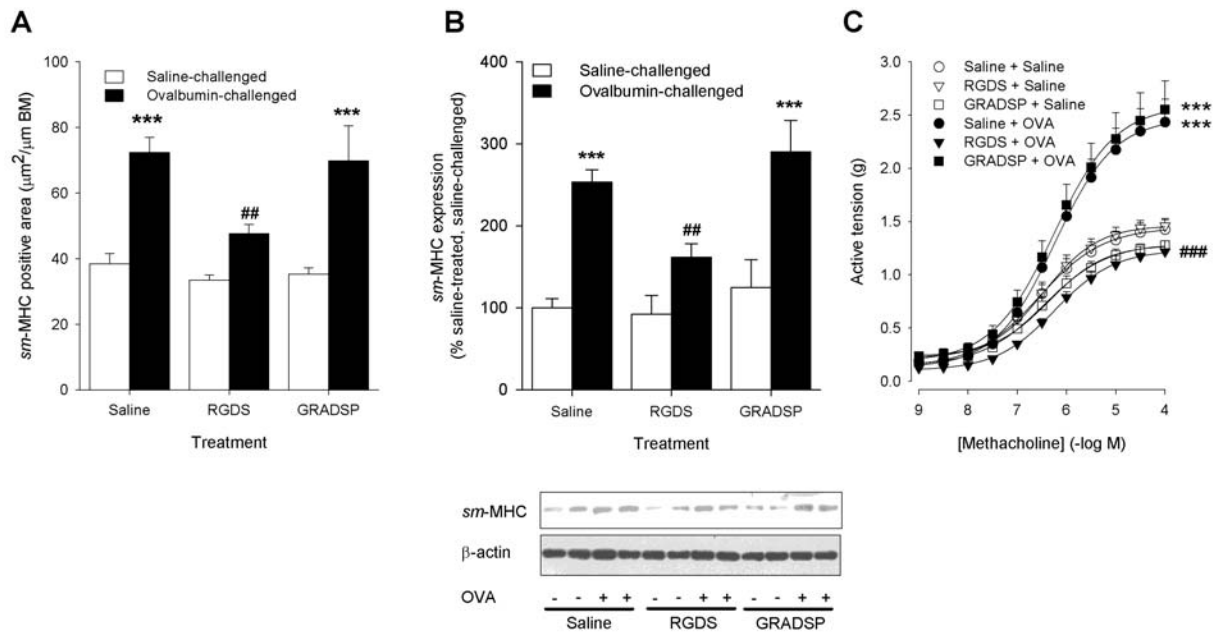


Figure 1 The integrin blocking peptide RGDS inhibits allergen-induced ASM remodelling in vivo. (A) Treatment with RGDS inhibited ovalbumin-induced increase in ASM mass (hyperplasia⁸) in cartilaginous airways. No effect was observed for GRADSP. (B) RGDS inhibited ovalbumin-induced accumulation of sm-MHC in guinea pig lung, whereas treatment with GRADSP had no effect. Representative western blots of sm-MHC and β-actin are shown. (C) Treatment with RGDS, but not with GRADSP, fully normalized the ovalbumin-induced increase in maximal methacholine-induced isometric contraction of epithelium-denuded ASM preparations. ***P<0.001 compared to saline-treated, saline-challenged controls; **P<0.01, ****P<0.001 compared to saline-treated, ovalbumin-challenged controls. Data represent means ± SEM of 6-8 animals.

In cultured human ASM cells, we demonstrated that collagen I- and fibronectin-induced proliferation requires signalling via RGD-binding integrins, particularly of the α5β1 subtype (not shown)⁸. RGDS also inhibited proliferation induced by serum (Figure 2A) and platelet-derived growth factor (not shown)⁸. In addition, the additive effects of collagen I and fibronectin on serum-induced proliferation were fully inhibited (Figure 2A). Moreover, RGDS inhibited smooth muscle α-actin (sm-α-actin) accumulation, induced by serum deprivation for 7 days (Figure 2B).

In conclusion, our results indicate a significant role for RGD-binding integrins in allergen-induced ASM remodelling in chronic asthma. Based on these findings, RGD-binding integrins may represent a novel target in the treatment of airway remodelling in asthma.

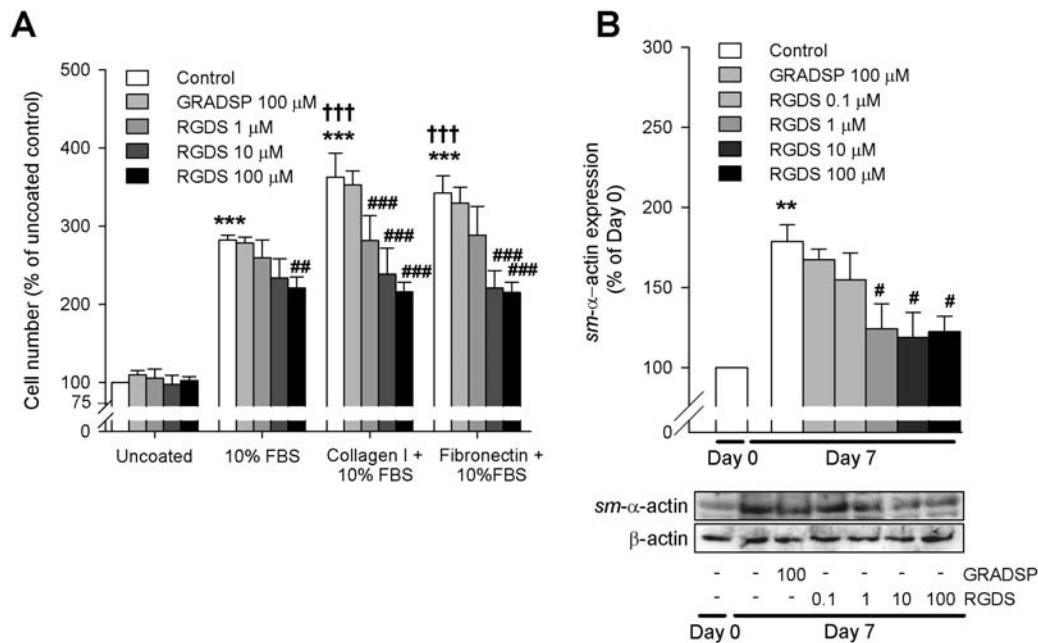


Figure 2 RGD-binding integrins are involved in ASM cell proliferation and ASM contractile protein accumulation in vitro. (A) Inhibition of fetal bovine serum (FBS)-induced ASM cell proliferation by RGDS. The additive effects of collagen I or fibronectin on FBS-induced proliferation were fully normalized by RGDS. *** $P < 0.001$ compared to control cells on uncoated surface. ## $P < 0.01$, #### $P < 0.001$ compared to cells stimulated with mitogens in the absence of inhibitor. ††† $P < 0.001$ compared to FBS-stimulated cells grown on uncoated surface. Data represent means \pm SEM of 6 experiments of 3 donors, performed in duplicate. (B) RGDS concentration-dependently inhibited sm- α -actin accumulation induced by serum deprivation for 7 days. Representative western blots of sm- α -actin and β -actin are shown. ** $P < 0.01$ compared to day 0 (10% serum). # $P < 0.05$ compared to sm- α -actin accumulation in the absence of inhibitor. Data represent means \pm SEM of 4 independent experiments of three different donors.

This study was supported by the Netherlands Asthma Foundation (NAF grant 3.2.03.36)

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Special Topic 5:

Alternatively activated macrophages in the development of male and female asthma

Barbro Melgert and Machteld Hylkema

The immune system is an important component in asthma and it has distinct sex-specific dimorphic responses. Women have higher humoral immunity and cellular immunity than men, resulting in more vigorous antibody responses to exogenous antigens and better resistance against microbial infections (1, 2). The downside of this greater immune responsiveness is the increased susceptibility to autoimmune diseases (3) and asthma (4-6). Asthma not only occurs more frequently among adult women in the reproductive years of their lives, but female asthmatics often suffer from more severe disease than males (7-9).

We and others have shown in mouse models of asthma that female mice are also more susceptible to the development of airway inflammation than male mice (10-12). We have used this model to elucidate which processes leading up to asthma are different between males and females. Our study indicated that the differences between males and females may lie in the adaptive immune response, e.g. differences in regulatory T cell (Treg) function (10). In follow-up work we tried to pinpoint which part of the immunological cascade leading up to asthma is different between males and females. As shown in figure 1, we could not show that there are functional or numerical differences in Tregs between males and females (13). Male and female mice had comparable Treg numbers in lung tissue and comparable Treg function, but effector T cells had expanded to a greater extent in lungs of females after allergen exposure (ovalbumin).

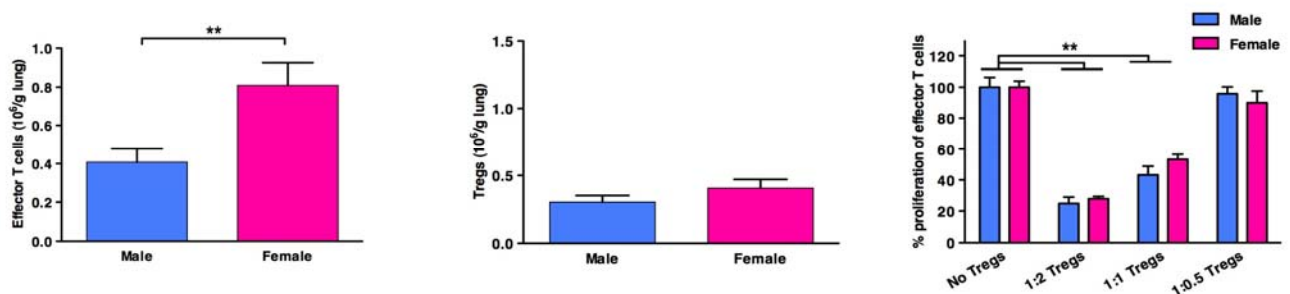


Figure 1: Female mice (n=14) with ovalbumin-induced airway inflammation have more than twice as many effector T cells (left panel) in lung tissue than their male counterparts (n=13), but have similar numbers of Tregs in lung tissue (middle panel). Effector T cells were defined as $CD4^+CD25^+Foxp3^-$ lymphocytes and Tregs as $CD4^+CD25^+Foxp3^+$ lymphocytes. **: $p < 0.01$ in Mann Whitney U test. Right panel: male and female Tregs (n=3) isolated from mice tolerized against ovalbumin are equally effective in suppressing α -CD3 ϵ -stimulated proliferation of naive male effector T cells in the presence of naive male irradiated APC. Cells were isolated from 4 spleens per group. **: $p < 0.01$ in a one-way ANOVA with Dunnet post-test.

This difference in T cell expansion was therefore not the result of lack of Treg control but appeared to be driven by a greater number of inflammatory myeloid dendritic cells (mDC) migrating from the lungs to lymph nodes in females. Resident lung cells can influence mDC migration and macrophages in lung tissue were found to be involved. Macrophages are part of the innate immune system and this system is emerging as an important component in asthma pathogenesis (14). Until recently, it was just regarded as the first-line defense against microbes and allergens, but it has become increasingly clear that macrophages and other cells of the innate immune system actively orchestrate adaptive immune responses (14-16). Macrophages are among the most abundant cells of the innate immune system present in lungs and have a crucial role in maintaining tissue homeostasis. They have a flexible phenotype that not only allows them to respond quickly to pathogens entering the lung, but also to suppress inflammatory responses and induce tissue repair (17, 18). Additionally, the alternatively activated phenotype that is responsible for tissue repair has been implicated in asthma

development. Exciting new data show that markers of alternative activation are associated with the induction and clinical expression of asthma (19-23). We have subsequently shown that artificially elevating the number of alternatively activated macrophages in lung tissue of mice increased the migration of mDC and amplified airway inflammation (figure 2).

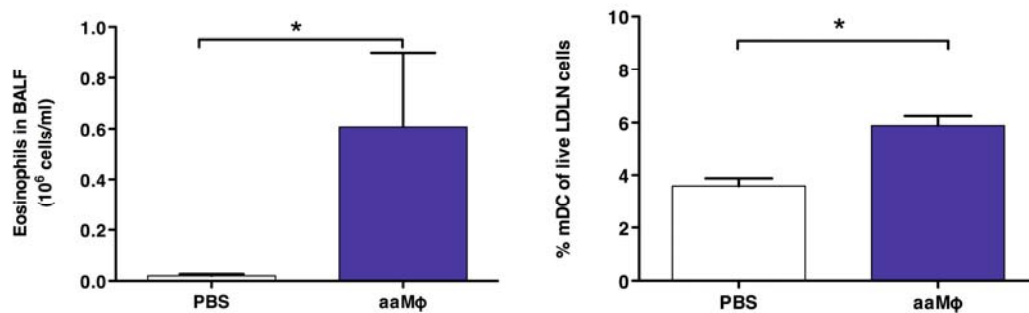


Figure 2: Left panel: intratracheal instillation of alternatively activated macrophages (aaMΦ, n=4) as compared to phosphate-buffered saline (PBS, n=4) before ovalbumin challenges significantly increases the number of eosinophils found in bronchoalveolar lavage fluid (BALF). Right panel: after aaMΦ instillation (n=4), lung-draining lymph nodes (LDLN) contain twice as many mDC as compared to instillation with PBS (n=4). *: p<0.05 in Mann Whitney test.

In addition, we found greater numbers of alternatively activated macrophages in female lungs than in males (figure 3), we therefore postulate that AAMΦ are involved in increased airway inflammation found in female mice.

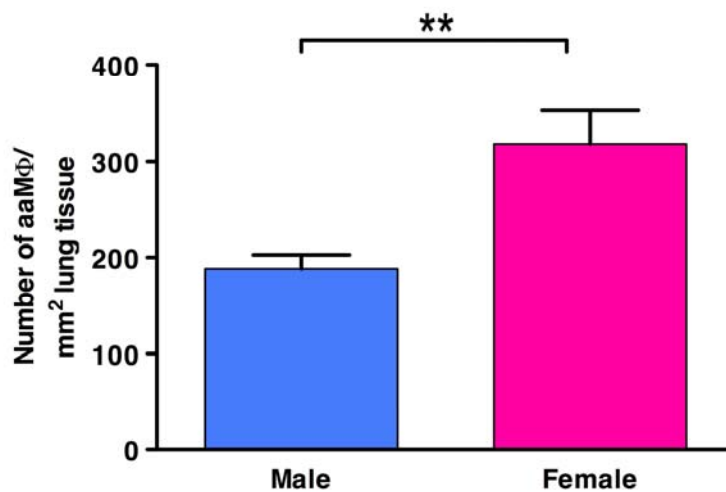


Figure 3: Female mice (n=11) with ovalbumin-induced airway inflammation have significantly more alternatively activated macrophages (aaMΦ) in lung tissue than their male counterparts (n=12). **: p<0.01 in Mann Whitney U test.

Conclusions

Our data suggest that macrophages may play an active role in female asthma and possibly constitute an interesting new target for therapy. Studying how female sex hormones subsequently affect macrophage responses in the lung is an interesting novel approach in trying to explain gender differences in asthma.

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Members Griac 2009

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Volbeda F., MD

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Beverdam, H.R.
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Wierda, F.
Zijlstra, J
Zonderland, J.
Zuidhof, A.B.



Dept. General Practice

University of Groningen, Faculty of Medical Sciences
A. Deusinglaan 1
NL-9713 AV Groningen
Phone 31-50-363 2963
Fax 31-50-363 2964
Principal Investigator: Prof. T. van der Molen

Dept. Epidemiology

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

Dept. Internal Medicine, div. Allergology

University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone: 31-50-361 2976
Fax: 31-50-3121576
Principal Investigator: Prof. J.G.R. de Monchy

Lab. Allergology and Pulmonary Diseases

University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone: 31-50-361 8043
Fax: 31-50-361 9911
Principal Investigator: Prof. A.J.M. van Oosterhout

Dept. Pulmonary Diseases and Tuberculosis

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

Dept. Pathology and Medical Biology

University Medical Center Groningen
Hanzeplein 1
P.O. Box 30.001
NL-9700 RB Groningen
Phone: 31-50-361 4684
Fax: 31-50-363 2510
Principal Investigators: Dr. M.N. Hylkema, Prof. W. Timens

Dept. Pediatric Pulmonology and Pediatric Allergy

University Medical Center Groningen

Hanzeplein 1

P.O. Box 30.001

NL-9700 RB Groningen

Phone: 31-50-361 2748

Fax: 31-50-361 4235

Principal Investigators: Dr. G. Koppelman, Prof. E.J. Duiverman, Prof. A.E.J. Dubois

Working group on Respiratory Insufficiency

University Medical Center Groningen

Hanzeplein 1

P.O. Box 30.001

NL-9700 RB Groningen

Phone: 31-50-361 3235

Fax: 31-50-361 9320

Principal Investigators: Dr. P.J. Wijkstra

Dept. Molecular Pharmacology, University Centre for Pharmacy

University of Groningen

A. Deusinglaan 1

NL-9713 AV Groningen

Phone 31-50-363 3197

Fax: 31-50-363 6908

Principal Investigators: Prof. M.A. Schmidt, Prof. H. Meurs, Dr. R. Gosens

International collaboration GRIAC

(As far as related to joint publications in 2009)

Prof E.R. Bleecker	Wake Forest University School of Medicine	Winston-Salem, USA
Prof A.W Burks	Duke's University	USA
Dr. J.M. Foster	Clinical Management Group, Woolcock Institute of Medical Research	Camperdown, Sydney, Australia
Prof. W.T. Gerthoffer	University of Nevada	Reno, USA
Prof. G.H. Guyatt	Mcmaster University	Hamilton, Ontario, Canada.
Prof. A.J. Halayko	University of Manitoba	Winnipeg, Canada
Dr. J.W. Holloway	University of Southampton	Southampton, UK
Prof. J.O. Hourihane	University of Cork	Cork, Ireland
Prof. D.A. Meyers	Wake Forest University School of Medicine	Winston-Salem, USA
Dr. T. Tran	University of Singapore	Singapore
Dr. H.K. Reddel	Clinical Management Group, Woolcock Institute of Medical Research	Camperdown, Sydney, Australia
Dr. C. Venter	Isle of Mann	U.K

Seminar program 2009

Date	Speaker	Title
6-01-2009	Dr. M. Nawijn Medical Biology UMCG	Mouse models of asthma susceptibility – from gene towards function
20-01-2009	F. Volbeda, MD Pulmonary Diseases UMCG	Control of asthma
3-02-2009	Prof. A.E. Dubois Pulmonary Pediatrics UMCG	IgE heterogeneity.
17-02-2009	Dr. M. Dentener Pulmonary Diseases UMC Maastricht	Remodelling in COPD, studies on hyaluronan.
03-03-2009	Prof. D.S. Postma Pulmonary Diseases UMCG	Inflammation and inhaled steroid treatment in COPD, a role in progression of disease.
17-03-2009	M.J. Blacquièrè, MSc Pathology UMCG	The hygiene hypothesis tested in a house dust mite mouse model of allergic asthma.
07-04-2009	B. Dekkers, MSc Molecular Pharmacology University of Groningen	“The matrix reloaded”: novel effects of extracellular matrix-integrin interactions on airway smooth muscle function.
21-04-2009	Dr. I. Wouters IRAS Utrecht	The hygiene hypothesis: from cradle to worksite
02-06-2009	Prof. D. Price Centre of academic primary care University of Aberdeen	“More than just RCP! – Effectiveness trials in respiratory disease“
01-09-2009	Dr. D.J. Slebos Pulmonary Diseases UMCG	New technologies for treatment of COPD
06-10-2009	Dr. B. Kaptein Wilhelmina Pediatric Hospital UMC Utrecht	“Early recognition of persistent wheezing using gene expression profiles”.
28-10-2009	Prof. J. Vestbo University of Copenhagen, Denmark	COPD and drug adherence - trial and epi
03-11-2009	Prof.dr. M. Schmidt Molecular Pharmacology University of Groningen	The novel cAMP effector Epac: new avenues in the treatment of airway diseases.

17-11-2009	Prof. K. Racké University Hospital Bonn, Germany	Differential role of cAMP effectors epac and pka in the control of pro-fibrotic features in human lung fibroblasts: cAMP effectors and their potential to modulate lung cell plasticity.
01-12-2009	Dr. I Tsiligianni General Practitioner Heraklion Greece	Factors that influence health status in patients with COPD.
23-11-2009	Prof. I. Sabroe Academic unit of respiratory Medicine University of Sheffield	Viruses, pollution, and the regulation of airway inflammation.
15-12-2009	Dr. M. Broekema Pathology UMCG	Unraveling the pathological background of asthma: new insights from bronchial biopsy studies.

Research projects in 2009

AstraZeneca; Symbicort Management of Asthma compared to Regular Therapy (SMART study). Prof.dr. T. van der Molen, Prof.dr. D.S. Postma, Prof.dr. B. Meyboom-de Jong. 2001-2010. Res. Fellow: R.A. Riemersma, MD.

AstraZeneca/MSD: The development of a questionnaire for the assessment of bronchial hyperresponsiveness. Prof.dr. T. van der Molen, Prof.dr. D.S. Postma. 2001-2010. Res. Fellow: R. Riemersma, MD.

AstraZeneca/Pfizer/MSD/GSK; Using health status in daily clinical practice. Prof. T. van der Molen. 2003-2009. Res. Fellow: J.W.H. Kocks, MD.

AstraZeneca; Health status guided-COPD care; the MARCH study. Prof.dr. T. van der Molen, Prof.dr. H.A.M. Kerstjens. 2008-2011. Res. Fellow: J.W.H. Kocks, MD.

AstraZeneca; Evaluation of unexplained exercise induced dyspnea in mild to moderate COPD . Prof. T. van der Molen, Prof.dr. H.A.M. Kerstjens, Dr. L.H. Steenhuis. 2008-2012. Res Fellow: J.S. Vroegop, MD.

AstraZeneca; The Clinical COPD Questionnaire: International survey of real life data. Prof T. van der Molen, 2009-2011, Res. Fellow: I. Tsiligianni, MD, PhD.

Asthmatx Inc. Safety and Effectiveness of the Alair® System for the Treatment of Asthma: A Multicenter Randomized Clinical Trial (AIR2-trial) Dr. N.H.T. ten Hacken, Dr. D.J. Slebos. 2006-2011. Lung function technician: K. Klooster.

Boehringer Ingelheim GmbH: 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. 2006-2009. Res fellow: L. Bossenbroek, MSc.

Boehringer Ingelheim Pharma GmbH; Muscarinic receptors as master switches of airway smooth muscle phenotype and function. Dr. R. Gosens, Prof.dr. H. Meurs. 2008-2012. PhD student: T.A. Oenema MSc.

Boehringer Ingelheim International GmbH: Role of muscarinic receptors in increased extracellular matrix deposition by fibroblasts in COPD. 2009-2011. Prof. H. Meurs, Dr. R. Gosens, Prof.dr. J. Zaagsma, Prof.dr. W. Timens, Prof.dr. D.S. Postma. Fellow: B. Dekkers, MSc, Pharm D, 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 µg/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. Technicians A. van der Laan-Boers, M.R. van der Eems.

Broncus Technologies Inc. A Randomized, Double-blind Study to Evaluate the Safety and Effectiveness of the Exhale® Drug-Eluting Stent in Homogeneous Emphysema Subjects with Severe Hyperinflation (EASE-trial). Dr. D.J. Slebos, Drs. P.H.W. Vennik, Prof.dr. H.A.M. Kerstjens. 2006-2012. Res. fellow: S.L. Snijders, MD. Studycoordinator K. Klooster.

Broncus Technologies Inc. A Clinical Product Evaluation of the Yield™ Tissue Sampler and the Yield Mini Doppler System, Broncus Tech Inc. 2009. Dr. D.J. Slebos PI.

CBN/Boehringer Ingelheim International GmbH; Development and properties of a new animal model of chronic obstructive pulmonary disease (COPD). Prof.dr. H. Meurs, Prof.dr. J. Zaagsma. 2006-2010. PhD-student: T. Pera, MSc.

CBN; Airway smooth muscle transition and its impact on the progression of chronic obstructive pulmonary disease. Prof.dr. M. Schmidt, 2006-2010; PhD-student: S.S. Roscioni, MSc.

European Community, ISA FRUIT, 584394. A multicenter study on apple allergy. Prof.dr. A.E.J. Dubois, 2006-2010.

European Community (FP6), GABRIEL LSH-2004-1.2.5-1 A multidisciplinary study to identify the genetic and environmental causes of asthma in the European Community. Prof.dr. D.S. Postma, Dr. G.H. Koppelman, Dr. M.N. Hylkema, Prof.dr. A.J.M. van Oosterhout, Prof.dr. H.M. Boezen. 2006-2010. PhD student: B. Piavaux, technician: M. Geerlings, post-doc: S. Scholtens.

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 stud: H. Koning.

European Community, EUROPREVAL 584386. A multidisciplinary, multicenter study on food allergy. Prof.dr. A.E.J. Dubois; 2005-2009; PhD-stud: B. Flokstra-de Blok.

European Community (FP6): MUGEN Network of Excellence 'Integrated Functional Genomics in Mutant Mouse Models as Tools to Investigate the Complexity of Human Immunological Disease (MUGEN)'. Dr. M. Nawijn (MUGEN LSHG-CT-2005-005203). Technician: U. Brouwer.

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. PhD Students: A.E. Dijkstra, A. Smolonska

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

GlaxoSmithKline; Predictors and surrogate markers for Control of Asthma. Dr. N.H.T. ten Hacken, Prof.dr. W. Timens, Prof.dr. D.S. Postma, 2005-2010; Res. Fellow: F. Volbeda, MD. Post-doc: Dr. M. Broekema. Technician: M. Lodewijk.

GlaxoSmithKline: CoE project: Dysregulation of epithelial cells and fibroblasts in the pathogenesis of COPD. Prof.dr. D.S. Postma, Prof.dr. W. Timens, Prof.dr. A.J.M. van Oosterhout. 2007-2009. Technicians: S. Brandenburg; M.R. Jonker.

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. 2005-2010. S. Schokker, PhD.

GUIDE; Newly granted but not yet started project by GUIDE: Genetics of COPD in LifeLines, Dr. J.M. Vonk, Prof.dr. H.M. Boezen, Prof.dr. D.S. Postma.

GUIDE; Effects of maternal smoking during pregnancy on the development of the foetal lung and susceptibility for development of asthma. Dr. M.N. Hylkema, Prof.dr. W. Timens and Prof.dr. D.S. Postma. 2005-2009. PhD-student: M.J. Blacquièrè, MSc.

GUIDE; Cigarette smoke induced mitochondrial dysfunction in COPD: "Powerhouse of disease" .M. van der Toorn, Prof.dr. A.J.M. van Oosterhout, Dr. D.J. Slebos. 2007-2010. PhD-student: D. Rezayat, MSc.

GUIDE Ubbo Emmius: Linking gene polymorphisms with COPD pathology and pathophysiology in mild to moderate COPD patients (GLUCOLD study). 2007-2011. Prof.dr. H.M. Boezen, Prof.dr. W. Timens, Prof.dr. D.S. Postma, PhD-student : S. Budulac MD.

GUIDE Ubbo Emmius; Prevention of COPD through dietary intake and smoking abstinence in genetically susceptible subgroups. Prof.dr. H.M. Boezen, Dr. H.A. Smit, Prof.dr. D.S. Postma. 2006-2010. PhD-student: M.I. Siedlinski MSc.

GUIDE Ubbo Emmius; The role of dietary iron in the development of IgE-mediated allergies. Prof.dr. A.J.M. van Oosterhout, Dr. N. Bloksma. 2005-2009. PhD-student: H. Maazi.

GUIDE Ubbo Emmius; Allergen immunotherapy, mechanisms and improvements. Prof.dr A.J.M. van Oosterhout. 2005-2009. PhD-student: S. Shirinbaik.

GUIDE Ubbo Emmius; Efficacy of allergen specific immunotherapy determined by an immunoregulatory pathway consisting of regulatory T-cells and indoleamine 2,3 dioxygenase. Prof.dr A.J.M. van Oosterhout, J.N.G. Oude-Elberink MD. 2005-2009. PhD-stud: D. van Hemelen MSc.

GUIDE Ubbo Emmius; Genetic research on asthma symptoms in young children: the ALLERGENIC study. Dr. M. Kerkhof, Dr. G.H. Koppelman, Prof.dr. D.S. Postma. 2008-2012. PhD student: O. Savenije MSc.

GUIDE: Effect of maternal smoking during pregnancy on susceptibility for development of COPD. Dr. M.N. Hylkema, Prof.dr. W. Timens and Prof.dr. D.S. Postma. 2008-2012. PhD student: A. Lech, MSc.

GUIDE: An old dilemma: Asthma with irreversible airway obstruction or COPD? Dr. N.H.T. ten Hacken, Dr. M.N. Hylkema, Prof.dr. W. Timens and Prof.dr. D.S. Postma. 2009-2013. PhD student: F. Fattahi MD.

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

MSD; Bronchial hyperresponsiveness in daily practice in patients treated with the leucotriene antagonists montelukast Prof.dr. T. van der Molen. 2006-2010. PhD-student: R. Riemersma, MD.

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

NAF3.2.08.21: Autoimmunity in Chronic Obstructive Pulmonary Disease. 2009-2011. Dr. H.P.J. Bonarius, Prof.dr. W. Timens, Prof.dr. H.A.M. Kerstjens, Dr. M. Nawijn. Post-doc: T. Mes; technician: T. Bijma.

NAF 08.014: The role of acetylcholine in chronic inflammation and remodelling in asthma and COPD. Dr. R. Gosens, Prof.dr. H.A.M. Kerstjens, Prof.dr. P.S. Hiemstra. 2009-2013. PhD student vacancy.

NAF 3.2.0.49: Smoking: short and long standing effects in asthma. Dr. N.H.T. ten Hacken, Prof.dr. W. Timens, Prof.dr. D.S. Postma. 2004-2009. Res. Fellow: Drs. F. Volbeda, MD, post-doc: Dr. M. Broekema, technician: M. Lodewijk.

NAF 03.4.05.041: The role of estrogen and estrogen receptors in the pathogenesis of asthma. Prof.dr. W. Timens, Prof.dr. D.S. Postma, Dr. M.N. Hylkema, 2006-2009; Post Doc: B.N. Melgert.

NAF 03.55: Identification of susceptibility gene(s) in an experimental asthma locus in the mouse. Prof.dr. A.J.M. van Oosterhout. 2005-2009. PhD-stud: B. Piavaux.

NAF 03.36: Effect of extracellular matrix proteins on airway smooth muscle contractility and proliferation in chronic asthma. Prof.dr. H. Meurs, Dr. SA Nelemans, Prof.dr. J. Zaagsma. 2005-2009. PhD-stud: B.G.J. Dekkers.

NAF 03.2.07.019: Cutting down on E-cadherin; Evaluating E-cadherin as a key regulator of allergic asthma. Dr. H.I. Heijink, Dr. M. Nawijn, Prof.dr. A.J.M. van Oosterhout. 2008-2010. PhD-stud: S. Post MSc.

NAF 07.034: 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 MSc.

NAF 07.023: Beta-catenin/GSK-3 signalling axis: a central transducer of chronic airway remodelling and emphysema in COPD. Dr. R. Gosens, Prof.dr. H.A.M. Kerstjens. 2008- 2012. PhD student. H.A. Baarsma.

NAF 07.036: Physical and psychological predictors of daily physical activity in COPD. 2008-2011. Dr. N.H.T. ten Hacken, Dr. M.H.G. de Greef, Prof.dr. H.M. Boezen. PhD Student: J. E. Hartman.

NAF 3.4.06.044: The effect of chronic non-invasive ventilation at home after treatment of acute respiratory failure in hypercapnic COPD patients. 2007-2011. Dr. P.J. Wijkstra, Prof.dr.H.A.M. Kerstjens. Fellows: F. Struik and G. Bladder.

NAF 3.2.06.75: Role of the B-cell in the pathogenesis of COPD. 2007-2009. Prof.dr. W. Timens, Prof.dr. H.A.M. Kerstjens. Post-doc: C.A. Brandsma; technician: M. Geerlings.

NAF, special grant for translational research in Pediatric Pulmonology: Asthma phenotypes. 2009-2015. Dr. GH Koppelman and Prof. JC de Jongste. 2 PhD students. N. Grotenboer

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

NAF 3.2.09.034: The novel cAMP effector Epac: new avenues in the treatment of inflammation, tissue remodelling and airway narrowing in COPD. 2009-2013. Prof.dr. M. Schmidt, Prof.dr. W. Timens, Prof.dr. H. Meurs. PhD student: A. Oldenburger MSc.

NAF 3.2.09.036: Th17 responses in asthma: Protection against atopy versus development of non-allergic asthma. Dr. M.N.Hylkema and Dr. I. Wouters. 2009-2011. Post-doc: M.J. Blacquièrre, Technician.

Nycomed; Development of the Clinical Short-form Inhaled Corticosteroid Questionnaire Scale. Prof.dr. T. van der Molen, Prof.dr. R. Sanderma, Prof.dr. D.S. Postma. 2008-2009. Post-doc: J.M. Foster, PhD.

Pfizer/Boehringer Ingelheim; Measuring functional status in primary care setting. Prof.dr. T. van der Molen. 2008-2009. Res. Fellow: J.W.H. Kocks, MD.

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, B.J. Vlieg-Boerstra. 2009 – 2013. PhD student: J. van Duijvenvoorde, MD.

PneumRx, Inc. Feasibility Study of the PneumRx, Inc. Lung Volume Reduction Coil for the Treatment of Emphysema. 2009-2011. Dr. D.J. Slebos PI

Rosetta Inpharmatics ; LKR57970 (2009-2011): Identification of key mechanistic drivers of lung disease. W. Timens, D.S. Postma. (Lung Cohort Study, together with University of British Columbia, Vancouver (P. Pare) and Hospital Laval, Quebec (Y. Bosse)).

Schering-Plough; 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, 2008-2010 Post doc: Dr. H. Maarsingh.

Stichting Koala (Stichting Menzis Beheer, Stichting Sensire Thuiszorg Groningen, KPN); Health status in telemonitoring in COPD, the KOALA project. 2007-2009. Prof.dr. T. van der Molen, J.W.H. Kocks.

STW 08008; A chemical proteomics approach towards profiling and imaging of metalloprotease activity. Prof.dr. R. Bischoff, Prof.dr. H. Overkleeft, Prof.dr. A.J.M. van Oosterhout, Prof.dr. R. Dierckx. 2008-2012. PhD student: D. Rozeveld MSc.

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. 2008-2012. 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. 2007-2012. technician; J. van der Leij. PhD student: S.J.M. Hoonhorst, Research nurse. R.G.A. Hiltermann-Tilanus.

Top Instituut Pharma 1-201; Groningen, Maastricht, Utrecht; Transition of systemic inflammation into multiorgan pathology. 2008-2012. Prof.dr. A.M.W.J. Schols, Prof.dr. E.F.M. Wouters, Prof.dr. W. Buurman, Prof.dr. W. Lamers, Dr. E. Blaak, Dr. R. Langen, Dr. H. Gosker, Prof.dr. L. Koenderman, Prof.dr. J.W.J. Lammers, Dr. L. Ulfman, Prof.dr. D.S. Postma. 2007-2012. PhD student: R. Hoffmann, Technician: S. Brandenburg.

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). 2006-2009. Res. fellow: W. Altenburg.

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

Zorgverzekeraars Nederland/ RESMED / VIVISOL / UMCG doelmatigheid; EOLUS : Initiation of chronic ventilatory support outside the hospital. Dr. P.J. Wijkstra , Prof.dr. H.A.M. Kerstjens. Fellows : A. Hazenberg.

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

PUBLICATIONS 2009

Dissertations

N. Abello

Chemical Labeling for the analysis of proteins, peptides and metabolites by mass spectrometry
(May 11, 2009)

Promotores: Prof.dr. R.P.H. Bischoff and Prof.dr. D.S. Postma

M. Brusse-Keizer

COPD exacerbations. Treatment and outcome. Universiteit Twente
(April 16, 2009)

Promotores: prof. dr. J. van der Palen Prof. Dr. H.A.M. Kerstjens

Copromotor; Dr. P.D.L.P.M. van der Valk.

T. Dijkstra

Contributing risk factors and genetic polymorphisms
(December 14, 2009)

Promotores: Prof.dr. D.S. Postma and Prof.dr. W. Timens

Copromotores: Dr. N.H.T. Hacken and Dr. J.M. Vonk

T.Effing

Self-management in patients with COPD. The COPE studie. Radboud Universiteit Nijmegen
(April 15, 2009)

Promotores: Prof. dr. Ir. G.A. Zielhuis, Prof. Dr. H.A.M. Kerstjens

Copromotores: Dr. J. van der Palen, Dr. P.D.L.P.M. van der Valk.

B. Flokstra-de Blok. Development, validation and outcome of health-related quality of life questionnaires for food allergic patients.

(May 27, 2009)

Promotores: Prof.dr. A.E.J. Dubois and Prof.dr. E.J. Duiverman

J.G.N. Oude Elberink

(November 11, 2009)

Quality of life in insect venom allergy.

Promotores: Prof.dr. A.E.J. Dubois and Prof.dr. J.G.R. de Monchy

N.E. Reijmerink

A search for missing pieces of the puzzle, the development of asthma and atopy
(November 23, 2009)

Promotores: Prof.dr. D.S. Postma and Prof.dr. Ir. B. Brunekreef

Copromotores: Dr. G.H. Koppelman, Dr. M. Kerkhof and Dr. J. Gerritsen

M.I. Siedlinski, Genetic and environmental determinants of lung function in the general population.

(October 28, 2009, Cum laude)

Promotores: Prof.dr. H.M. Boezen, Prof.dr. D.S. Postma, Prof.dr. H.A. Smit

M. van der Toorn Cigarette smoke-induced mitochondrial dysfunction and oxidative stress in epithelial cells.

(February 11, 2009)

Promotores: prof. dr. H.F. Kauffman, Prof. dr. R.O.B. Gans, Prof. Dr. G.H. Koëter

Copromotores: Dr. D.J. Slebos, Dr. S.J.L. Bakker

Publications SCI journals

- Abello N, Kerstjens HA, Postma DS, Bischoff R. Protein Tyrosine Nitration: Selectivity, Physicochemical and Biological Consequences, Denitration, and Proteomics Methods for the Identification of Tyrosine-Nitrated Proteins. *J Proteome Res* 2009 Jun 1: 3222-38.
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