

Editorial

Important questions in allergy: novel research areas

**J. Bousquet¹, T. Bieber²,
W. Fokkens³, M. L. Kowalski⁴,
M. Humbert⁵, B. Niggemann⁶,
H.-U. Simon⁷, P. Burney⁸, P. van
Cauwenberge⁹, T. Zuberbier¹⁰,
C. A. Akdis¹¹, P. Demoly¹²**

¹University Hospital and Inserm, Montpellier, France; ²Department of Dermatology and Allergy, University of Bonn, Bonn, Germany; ³Department of Otorhinolaryngology, University of Amsterdam, the Netherlands; ⁴Department of Immunology, Rheumatology and Allergy, Medical University of Lodz, Lodz, Poland; ⁵Service de Pneumologie, Hôpital Antoine-Béclère, Université Paris-Sud, Clamart, France; ⁶German Red Cross Hospital, Berlin, Germany; ⁷Institute of Pharmacology, University of Bern, Bern, Switzerland; ⁸Imperial College, London, UK; ⁹Department of Otorhinolaryngology, Ghent University, Ghent, Belgium; ¹⁰Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany; ¹¹Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland; ¹²University Hospital of Montpellier – Inserm U657 – France

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Jean Bousquet
University Hospital and Inserm
Hôpital Arnaud de Villeneuve
Service des Maladies Respiratoires
34295 Montpellier Cedex 5
France

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By definition, allergy is a multifactorial disease (1), which can no longer be studied by single research groups. Networks are therefore essential to achieve optimal research outcome. However, the results of this research need to be translated for physicians, patients, the public and policy makers. The networks should, therefore, include all experts, researchers, physicians of different

specialties, general practitioners, other health care professionals and patients to accomplish these tasks. In these networks, dissemination of research is the key to their success.

The European Union, having been at the forefront of allergy research for more than a decade, has led several networks, concerted actions and integrated projects. Projects commenced before 2002 have been reviewed in previous papers of the journal (2, 3). The European Community Respiratory Health Survey was one of the first and most successful assignments (4). Some projects like European Network For Understanding Mechanisms

Abbreviations: EuroPrevall, The Prevalence, Cost and Basis of Food Allergy across Europe; *Sens-it-iv*, novel testing strategies for *in vitro* assessment of allergens.

of Severe Asthma (5–7) and biomarkers in severe chronic airway diseases were related to severe asthma. The Sixth Framework programme has funded several large assignments.

The Global Allergy and Asthma European Network (GA²LEN) is a consortium of 25 leading European research centres including over 500 researchers specialized in allergic diseases. The Global Allergy and Asthma European Network addresses the growing public health concerns of allergic diseases. Research teams were chosen for their scientific excellence, their record regarding multidisciplinary work and international collaboration as well as their educational activities. Since its launch, the Network has grown to include an additional 54 collaborating centres making GA²LEN one of the largest multidisciplinary networks of researchers in allergy and asthma worldwide (8–22). The GA²LEN epidemiology study is currently being carried out on 110 000 adolescents and adults in the general population. This study, along with the birth cohort work package, may prove to be the cornerstone of many of the research proposals concerning novel research areas.

EuroPrevall is a project, which brings together over 53 research centres to investigate the complex interactions between food intake, metabolism, the immune system, genetic background and socioeconomic factors. The objective is to identify the key risk factors involved in food allergy and to provide the information and tools needed to manage food allergies across Europe effectively to improve the quality of life for food-allergic consumers (23–25).

The European Food Information Resource Network, the world-leading European Network of Excellence on Food Composition Databank systems, is a partnership involving 46 universities, research institutes and small-to-medium sized enterprises from 25 European countries. The European Food Information Resource Network will provide the first comprehensive pan-European food information resource, using state-of-the-art database linking, to facilitate effective management, updating, extending and comparability within the Network.

The GABRIEL project involves over 150 scientists from 14 European countries and uses the latest research across a variety of disciplines, including genetics, epidemiology and immunology to identify key factors in the development of asthma. Scientists believe that rural environments are strongly protective against the disease and that increasing urbanization may contribute to the rise in the numbers affected. In addition to looking at genetic and environmental interactions, GABRIEL will study the molecular basis for environmental factors, which can increase the risk of industrial asthma. It will also identify the agents, which protect strongly against asthma in rural and farming communities and will use genetics, genomics and proteomics to discover novel genetic and microbial factors that cause or protect against asthma (26).

Allergies to sensitizing agents are steadily increasing. The risk assessment for potential skin- or lung-sensitizers depends entirely on animal testing. The overall objective of *Sens-it-iv* is to produce *in vitro* alternatives for these assays and to develop them up to the level of prevalidation. Besides reducing animal experimentation, an increase in the accuracy of predicting the sensitizing potency of tested agents is expected.

In the USA, the Immune Tolerance Network of the National Institute of Allergy and Infectious Diseases (<http://www.niaid.nih.gov>; accessed 27 November 2007) (27, 28) has received a contract renewal. This contract will be used to continue research to advance the clinical application of immune tolerance by performing high-quality clinical trials of emerging therapeutics integrated with mechanism-based research, in particular for allergic diseases. Other research programmes include the Food Allergy Research Consortium, the Inner-City Asthma Consortium (29) and, in collaboration with the National Heart, Lung, and Blood Institute, the Immune System Development and the Genesis of Asthma program.

In Canada, in 2005, AllerGen NCE Inc. (<http://www.allergen-nce.ca>), the Allergy, Genes and Environment Network, was launched to improve the quality of life for allergic and related immune disease sufferers. Currently comprising more than 150 researchers at 30 universities and research facilities plus over 70 Canadian and international partners, AllerGen will support national and global initiatives and partnerships in the struggle against the developed world's most prevalent chronic condition. It will also support research, multidisciplinary scientific and health networking, knowledge translation, commercialization and capacity building to ensure expertise and preparedness of the next generation of Canadian allergic and immune disease researchers and entrepreneurs. AllerGen will attempt to mobilize Canadian science to reduce the illness, mortality and socioeconomic costs related to allergic disease.

However, there are still unanswered questions in Allergy. It is clear that these questions should be considered globally in a network and, if possible, using previous networks, which could be extended for specific projects. An Allergy Series will provide insight into some of these unanswered questions and will attempt to delineate how the current research of European groups can be beneficially embedded in these research questions.

Drug allergy

Drugs can induce several types of immunological reactions, which represent 15% of adverse drug reactions and can also be the cause of postmarketing withdrawal. Currently, drug allergies are barely predictable during the different drug development phases. So far, only a few drug allergen determinants and mechanistic pathways have been identified. Although a lot remains to be learnt,

current knowledge should allow a transfer to industry to predict immuno-toxicology better during the drug development process. Translational multidisciplinary projects to understand the mechanisms of allergic diseases are required and these may use epidemiology (30), experimental models, cell biology and molecular biology techniques as well as biobanking. Standardized diagnostic procedures have been published under the aegis of the European Network of Drug Allergy, the core group of the European Academy of Allergology and Clinical Immunology interest group of drug allergy and a member of GA²LEN. The development of drug hypersensitivity databases at the European level would enable all observations to be collated (suspected and diagnosed) and would facilitate epidemiologic, risk factor and pharmacosurveillance analyses (31, 32).

Nonallergic rhinitis

Allergic rhinitis is the most common form of noninfectious rhinitis (33). However, many patients present symptoms that mimic allergic rhinitis with no clear cut causal factor and with a lack of demonstrated IgE-mediated allergy by skin prick tests and serum IgE (34). These patients have nonallergic rhinitis, which is common and probably affects over 200 million people worldwide. Both children and adults are affected. However, its exact prevalence remains unknown and its phenotypes need to be characterized using appropriate methods to diagnose and manage nonallergic rhinitis. It is important to differentiate nonallergic rhinitis and chronic rhinosinusitis as their management differs. Mechanistic studies should be carried out to understand the disease(s) and risk factors better, and for the guidance towards an improved therapy.

Severe asthma

The common disease asthma is probably not a single disease, but rather a complex of multiple, separate syndromes that overlap (35). Control of the disease is the aim of all guidelines (36). The term severe refractory asthma in adults applies to patients who remain difficult to control despite extensive re-evaluation of diagnosis and management by a specialist following an observational period of at least 6 months. Factors that influence asthma control should be recognized and adequately addressed prior to confirming the diagnosis of severe refractory asthma. Important issues remain to be explored such as a better understanding of severe asthma phenotypes (including the possible role of gender, obesity, atopy and smoking habits), better knowledge of inducers (such as occupational sensitizers, allergens and viruses) and better approach of severe asthma pathophysiology (inflammatory, epithelial and smooth muscle cells all

contribute to airway narrowing, and both large and small airway wall thickening is observed, but parenchymal abnormalities may also influence airway limitation). Patients with severe refractory asthma who remain uncontrolled despite the best standard of care represent a challenge to clinicians and a niche for novel therapies (37).

Nonallergic eczema

Atopic dermatitis, allergic contact dermatitis and drug reactions are the most important forms of hypersensitivity targeting the skin. As for rhinitis, the nonallergic variant of eczema (formerly the intrinsic form, affecting up to 30% of the patients) remains a pathophysiological enigma. There is a great need for further progress in this field to answer a series of fundamental questions about the origin of inflammation in dermatitis. Furthermore, the role of innate immunity of the epidermal barrier function in atopic dermatitis (38) and in other allergic skin conditions has been underestimated and will be the focus of intensive research in forthcoming years.

T-cell regulation

Patients with allergic rhinitis have an IgE-mediated response involving Th2 and T-regulatory cells. The interaction of migrating T cells with resident tissue cells such as epithelial cells represents an important mechanism in allergic rhinitis (39). The function of a new type of T-cell subset characterized by the secretion of IL-17A, named Th17 cells (40), may be the key in the progression of allergic and nonallergic rhinitis. T-regulatory cells are essential in the regulation of allergic diseases and more data are needed to understand the regulation of allergic diseases by these T-cell subsets in addition to the established role of Th1 and Th2 cells.

Inflammatory cells

Several important questions concerning inflammatory cells contributing to allergic responses still remain to be answered. These include the cells limiting inflammatory responses and their regulation, a possible defect in regulatory cells in allergy, the possibility to induce physiological anti-inflammatory molecular and cellular events, the activation of dendritic cells and the role of eosinophils, which is still unclear. Another important problem is the lack of appropriate biomarkers to diagnose and monitor allergic patients. This is particularly obvious when clinical trials are designed to explore the potential anti-inflammatory effect of new drugs.

These questions will be addressed in a series of papers published in *Allergy*.

References

- Bousquet J, Bieber T, Fokkens W, Humbert M, Kowalski M, Niggemann B et al. Themes in allergy. *Allergy* 2006;**61**:1–2.
- van Ree R. The CREATE project: EU support for the improvement of allergen standardization in Europe. *Allergy* 2004;**59**:571–574.
- Bousquet J, Ansotegui IJ, van Ree R, Burney PG, Zuberbier T, van Cauwenberge P. European Union meets the challenge of the growing importance of allergy and asthma in Europe. *Allergy* 2004;**59**:1–4.
- Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994;**7**:954–960.
- Gaga M, Papageorgiou N, Yiougioti G, Karydi P, Liapikou A, Bitsakou H et al. Risk factors and characteristics associated with severe and difficult to treat asthma phenotype: an analysis of the ENFUMOSA group of patients based on the ECRHS questionnaire. *Clin Exp Allergy* 2005;**35**:954–959.
- The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for understanding mechanisms of severe asthma. *Eur Respir J* 2003;**22**:470–477.
- Romagnoli M, Caramori G, Braccioni F, Ravenna F, Barreiro E, Siafakas NM et al. Near-fatal asthma phenotype in the ENFUMOSA Cohort. *Clin Exp Allergy* 2007;**37**:552–557.
- Van Cauwenberge P, Watelet JB, Van Zele T, Bousquet J, Burney P, Zuberbier T. Spreading excellence in allergy and asthma: the GA²LEN (Global Allergy and Asthma European Network) project. *Allergy* 2005;**60**:858–864.
- Munoz-Lopez F. Ga²Len: coordinated research. *Allergol Immunopathol* 2005;**33**:243–244.
- Frew AJ. GA²LEN – The Global Allergy and Asthma European Network. *Clin Exp Allergy* 2005;**35**:122–125.
- Warner JO. Global Allergy and Asthma European Network (GA²LEN) – a focus for paediatric allergy research. *Pediatr Allergy Immunol* 2006;**17**: 163.
- Bonini S, Bonini M, Bousquet J, Brusasco V, Canonica GW, Carlsen KH et al. Rhinitis and asthma in athletes: an ARIA document in collaboration with GA²LEN. *Allergy* 2006;**61**:681–692.
- Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczynska M, Dahlen B, Dahlen S et al. Aspirin provocation tests for diagnosis of aspirin sensitivity. EAACI/GA²LEN guideline. *Allergy* 2007;**62**:1111–1118.
- Keil T, Kulig M, Simpson A, Custovic A, Wickman M, Kull I et al. European birth cohort studies on asthma and atopic diseases: II. Comparison of outcomes and exposures – a GALEN initiative. *Allergy* 2006a;**61**:1104–1111.
- Keil T, Kulig M, Simpson A, Custovic A, Wickman M, Kull I et al. European birth cohort studies on asthma and atopic diseases: I. Comparison of study designs – a GALEN initiative. *Allergy* 2006;**61**:221–228.
- Papadopoulos NG, Xepapadaki P, Mallia P, Brusselle G, Watelet JB, Xatzipsalti M et al. Mechanisms of virus-induced asthma exacerbations: state-of-the-art. A GA²LEN and Inter-Airways document. *Allergy* 2007;**62**:457–470.
- Turjanmaa K, Darsow U, Niggemann B, Rance F, Vanto T, Werfel T. EAACI/GA²LEN position paper: present status of the atopy patch test. *Allergy* 2006;**61**:1377–1384.
- Werfel T, Ballmer-Weber B, Eigenmann PA, Niggemann B, Rance F, Turjanmaa K et al. Eczematous reactions to food in atopic eczema: position paper of the EAACI and GA²LEN. *Allergy* 2007;**62**:723–728.
- Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM et al. EAACI/GA²LEN/EDF guideline: management of urticaria. *Allergy* 2006;**61**:321–331.
- Zuberbier T, Bindslev-Jensen C, Canonica W, Grattan CE, Greaves MW, Henz BM et al. EAACI/GA²LEN/EDF guideline: definition, classification and diagnosis of urticaria. *Allergy* 2006;**61**:316–320.
- Bousquet J, van Cauwenberge P, Ait Khaled N, Bachert C, Baena-Cagnani CE, Bouchard J et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update (in collaboration with GALEN). *Allergy* 2006;**61**:1086–1096.
- Watelet JB, Van Zele T, Gjomarkaj M, Canonica GW, Dahlen SE, Fokkens W et al. Tissue remodelling in upper airways: where is the link with lower airway remodelling? *Allergy* 2006;**61**:1249–1258.
- Asero R, Ballmer-Weber BK, Beyer K, Conti A, Dubakiene R, Fernandez-Rivas M et al. IgE-mediated food allergy diagnosis: current status and new perspectives. *Mol Nutrition Food Res* 2007;**51**:135–147.
- de Blok BM, Vlieg-Boerstra BJ, Oude Elberink JN, Duiverman EJ, DunnGalvin A, Hourihane JO et al. A framework for measuring the social impact of food allergy across Europe: a EuroPrevall state of the art paper. *Allergy* 2007;**62**:733–737.
- Mills EN, Mackie AR, Burney P, Beyer K, Frewer L, Madsen C et al. The prevalence, cost and basis of food allergy across Europe. *Allergy* 2007;**62**:717–722.
- Moffatt MF, Kabesch M, Liang L, Dixon AL, Strachan D, Heath S et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007;**448**:470–473.
- Rotrosen D, Matthews JB, Bluestone JA. The immune tolerance network: a new paradigm for developing tolerance-inducing therapies. *J Allergy Clin Immunol* 2002;**110**:17–23.
- Saxon A. What impact will the immune tolerance network have on the future treatment of allergic diseases? *Clin Exp Allergy* 2004;**34**:1657–1659.
- Liu AH. Optimizing childhood asthma management: the role of national institutes of health-sponsored study groups. *Allergy Asthma Proc* 2004;**25**:365–369.
- Messaad D, Sahla H, Benahmed S, Godard P, Bousquet J, Demoly P. Drug provocation tests in patients with a history suggesting an immediate drug hypersensitivity reaction. *Ann Intern Med* 2004;**140**:1001–1006.
- Bousquet PJ, Co-Minh HB, Arnoux B, Daures JP, Demoly P. Importance of mixture of minor determinants and benzylpenicilloyl poly-L-lysine skin testing in the diagnosis of beta-lactam allergy. *J Allergy Clin Immunol* 2005;**115**:1314–1316.
- Bousquet PJ, Kvedariene V, Co-Minh HB, Martins P, Rongier M, Arnoux B et al. Clinical presentation and time course in hypersensitivity reactions to beta-lactams. *Allergy* 2007;**62**:872–876.
- Bousquet J, Van Cauwenberge P, Khaltayev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001;**108**(Suppl. 5):S147–S334.

34. van Rijswijk JB, Blom HM, Fokkens WJ. Idiopathic rhinitis, the ongoing quest. *Allergy* 2005;**60**:1471–1481.
35. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet* 2006;**368**:804–813.
36. Humbert M, Holgate S, Boulet LP, Bousquet J. Asthma control or severity: that is the question. *Allergy* 2007;**62**: 95–101.
37. Tarantini F, Baiardini I, Passalacqua G, Braidò F, Canonica GW. Asthma treatment: ‘magic bullets which seek their own targets’. *Allergy* 2007;**62**: 605–610.
38. Bieber T. Atopic dermatitis. *N Engl J Med* 2008, in press.
39. Schleimer RP, Kato A, Kern R, Kuperman D, Avila PC. Epithelium: at the interface of innate and adaptive immune responses. *J Allergy Clin Immunol* 2007; DOI: 10.1016/j.jaci.2007.08.046.
40. Schmidt-Weber CB, Akdis M, Akdis CA. TH17 cells in the big picture of immunology. *J Allergy Clin Immunol* 2007;**120**:247–254.