REVIEW ARTICLE

MeDALL (Mechanisms of the Development of ALLergy): an integrated approach from phenotypes to systems medicine

J. Bousquet[1,2,*], J. Anto[3,4,5,6*], C. Auffray[7], M. Akdis[8,*], A. Cambon-Thomsen[9,*], T. Keil[10,*], T. Haahtela[11,*], B. N. Lambrecht[12,*], D. S. Postma[13], J. Sunyer[3,4,5,6,*], R. Valenta[14,*], C. A. Akdis[8,*], I. Annesi-Maesano[15,16], A. Arno[17], C. Bachert[18,*], F. Ballester[19], X. Basagana[3,4,5,*], U. Baumgartner[20], C. Bindslev-Jensen[21,*], B. Brunekreef[22,*], K. H. Carlsen[23,*], L. Chatzi[24], R. Crameri[8,*], E. Eveno[7], F. Forastiere[25], J. Garcia-Aymerich[3,4,5,6,*], S. Guerra[3,4,5,26], H. Hammad[12,*], J. Heinrich[27,*], D. Hirsch[28], B. Jacquemin[2,29], F. Kauffmann[2,29,*], M. Kerkhof[30], M. Kogevinas[3,4,5,31,*], G. H. Koppelman[32], M. L. Kowalski[33,*], S. Lau[34,*], K. C. Lodrup-Carlsen[23,*], M. Lopez-Botet[35,36], J. Lotvall[37,*], C. Lupinek[14,*], D. Maier[38], M. J. Makela[11,*], F. D. Martinez[26], J. Mestres[39], I. Momas[40], M. C. Nawijn[41], A. Neubauer[20], S. Oddie[42,43], S. Palkonen[44,*], I. Pin[45], C. Pison[7,46], F. Rancé[47], S. Reitamo[11,*], E. Rial-Sebbag[48], M. Salapatas[44,*], V. Siroux[49], D. Smagghe[28,*], M. Torrent[50,51,52], E. Toskala[53,*], P. van Cauwenberge[54,*], A. J. M. van Oosterhout[41], R. Varraso[2,29], L. von Hertzen[11,*], M. Wickman[55,*], C. Wijmenga[56], M. Worm[57,*], J. Wright[42] & T. Zuberbier[57,58,*]

[1]University Hospital, Department of Respiratory Diseases, Hôpital Arnaud de Villeneuve, Montpellier; [2]Inserm, CESP Centre for research in Epidemiology and Population Health, U1018, Respiratory and Environmental Epidemiology team, Villejuif, France; [3]Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain; [4]Municipal Institute of Medical Research (IMIM-Hospital del Mar), Barcelona, Spain; [5]CIBER Epidemiología y Salud Pública (CIBERESP), Spain; [6]Universitat Pompeu Fabra (UPF), Barcelona, Spain; [7]Functional Genomics and Systems Biology for Health, CNRS Institute of Biological Sciences, Villejuif, France; [8]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland; [9]Epidémiologie et analyses en santé publique : risques, maladies chroniques et handicap. UMR Inserm, U558, and University Paul Sabatier Toulouse 3, Faculty of Medicine, Toulouse, France; [10]Institute of Social Medicine, Epidemiology and Health Economics, Charité - Universitätsmedizin Berlin, Berlin, Germany; [11]Department of Dermatology, Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland; [12]Laboratory of Immunoregulation and Mucosal Immunology, University Hospital Gent, Ghent, Belgium; [13]Department of Pulmonology, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [14]Christian Doppler Laboratory for Allergy Research, Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria; [15]EPAR U707 INSERM, Paris; [16]EPAR UMR-S UPMC, Paris VI, Paris, France; [17]Onmedic Networks, Barcelona, Spain; [18]URL (Upper Airways research Laboratory), University Hospital Ghent, Ghent, Belgium; [19]Environment and Health Area, Centre for Public Health Research (CSISP); CIBERESP, Department of Nursing, University of Valencia, Valencia, Spain; [20]Biomay AG, Vienna, Austria; [21]Odense University Hospital, Odense, Denmark; [22]Institute for Risk Assessment Sciences and Julius Center for Health Sciences and Primary Care, University of Utrecht, Utrecht, the Netherlands; [23]Department of Paediatrics, University of Oslo; Oslo University Hospital, Oslo, Norway; [24]Department of Social Medicine, Faculty of Medicine, University of Crete, Crete, Greece; [25]Department of Epidemiology, Lazio Regional Health Service, Rome, Italy; [26]Arizona Respiratory Center, University of Arizona, Tucson, AZ, USA; [27]Institute of Epidemiology, Helmholtz Zentrum Munchen, Germany; [28]Inserm-Transfert, Paris, France; [29]University Paris Sud 11, UMRS 1018, Villejuif, France; [30]Department of Epidemiology, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [31]Department of Nutrition, National School of Public Health, Athens, Greece; [32]Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [33]Department of Immunology, Rheumatology and Allergy, Medical University of Lodz, Lodz, Poland; [34]Charité Campus Virchow, Department of Pneumology and Immunology, Berlin, Germany; [35]Immunology Unit, Universitat Pompeu Fabra, Barcelona, Spain; [36]IMIM-Hospital de Mar, Barcelona, Spain; [37]University of Gothenburg, Gothenburg, Sweden; [38]Biomax Informatics AG, Planegg, Germany; [39]Chemotargets SL and Chemogenomics Laboratory, GRIB Unit, IMIM-Hospital del Mar and University Pompeu Fabra, Barcelona, Catalonia, Spain; [40]Department of Public health and biostatistics, Paris Descartes University, EA 4064 and Paris municipal Department of social action, childhood, and health, Paris, France; [41]Laboratory of Allergology and Pulmonary Diseases, Department of Pathology and Medical Biology, GRIAC Research Institute, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [42]Bradford Institute for Health Research, Bradford Teaching Hospitals Foundation Trust, Bradford, UK; [43]Bradford Neonatology, Bradford Royal Infirmary, Bradford, UK; [44]EFA European Federation of Allergy and Airways Diseases Patients' Associations, Brussels, Belgium; [45]CHU de Grenoble; INSERM, U823, Institut Albert Bonniot, University Joseph Fourier, Grenoble, France; [46]Department of Pulmonology, University Hospital of Grenoble; Inserm 884, University of Grenoble, Grenoble, France; [47]INSERM U563, Allergolgie – Pneumologie, Pole Medico-Chirurgical de Pédiatrie, Hopital des Enfants, Toulouse, France; [48]Genetics and Society Platform, INSERM U 558, Faculty of Medicine, Toulouse, France; [49]INSERM, U823, Team of Environmental Epidemiology applied to Reproduction and Respiratory Health, Université Joseph Fourier, Grenoble, France, [50]Area de Salut de Menorca, ib-salut, Spain; [51]Fundació Caubet-CIMERA, Mallorca, Spain; [52]CIBER Epidemiologia y Salud Pública (CIBERESP), Barcelona, Spain; [53]Finnish Institute of Occupational Health, Helsinki, Finland; [54]Department of Otorhinolaryngology, Ghent University, Ghent, Belgium; [55]Sachs' Children's Hospital, Stockholm; Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden; [56]Department of Genetics, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands; [57]Allergy-Centre-Charité at the Department of Dermatology, Charité - Universitätsmedizin Berlin, Berlin, Germany;

[58]Secretary General of the Global Allergy and Asthma European Network (GA^{2}LEN), Network of Excellence, Charité - Universitätsmedizin Berlin, Berlin, Germany

To cite this article: Bousquet J, Anto J, Auffray C, Akdis M, Cambon-Thomsen A, Keil T, Haahtela T, Lambrecht BN, Postma DS, Sunyer J, Valenta R, Akdis CA, Annesi-Maesano I, Arno A, Bachert C, Ballester F, Basagana X, Baumgartner U, Bindslev-Jensen C, Brunekreef B, Carlsen KH, Chatzi L, Crameri R, Eveno E, Forastiere F, Garcia-Aymerich J, Guerra S, Hammad H, Heinrich J, Hirsch D, Jacquemin B, Kauffmann F, Kerkhof M, Kogevinas M, Koppelman GH, Kowalski ML, Lau S, Lodrup-Carlsen KC, Lopez-Botet M, Lotvall J, Lupinek C, Maier D, Makela MJ, Martinez FD, Mestres J, Momas I, Nawijn MC, Neubauer A, Oddie S, Palkonen S, Pin I, Pison C, Rancé F, Reitamo S, Rial-Sebbag E, Salapatas M, Siroux V, Smagghe D, Torrent M, Toskala E, van Cauwenberge P, van Oosterhout AJM, Varraso R, von Hertzen L, Wickman M, Wijmenga C, Worm M, Wright J, Zuberbier T. MeDALL (Mechanisms of the Development of ALLergy): an integrated approach from phenotypes to systems medicine. *Allergy* 2011; **66**: 596–604.

Keywords
allergy; early diagnosis; epigenetics; framework programme 7; IgE; mechanisms; mechanisms of the development of allergy; prevention; proteomics; systems medicine; transcriptomics.

Correspondence
J. Bousquet, Hôpital Arnaud de Villeneuve, Service des Maladies Respiratoires, Montpellier Cedex 05, France.
Tel.: +33 467 336105
Fax: +33 467 416701
E-mail: jean.bousquet@inserm.fr

*Member of GA^{2}LEN (Global Allergy and Asthma European Network), supported by the Sixth EU Framework program for research, contract n° FOOD-CT-2004-506378.
This work was supported by the European Commission's Seventh Framework Programme under grant agreement No. 261357 (MeDALL).

Accepted for publication 1 December 2010

DOI:10.1111/j.1398-9995.2010.02534.x

Edited by: Hans-Uwe Simon

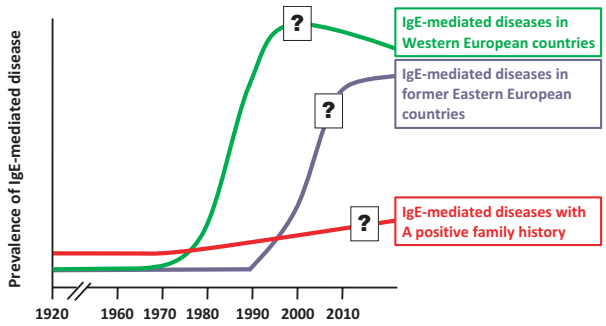
Abstract

The origin of the epidemic of IgE-associated (allergic) diseases is unclear. MeDALL (Mechanisms of the Development of ALLergy), an FP7 European Union project (No. 264357), aims to generate novel knowledge on the mechanisms of initiation of allergy and to propose early diagnosis, prevention, and targets for therapy. A novel phenotype definition and an integrative translational approach are needed to understand how a network of molecular and environmental factors can lead to complex allergic diseases. A novel, stepwise, large-scale, and integrative approach will be led by a network of complementary experts in allergy, epidemiology, allergen biochemistry, immunology, molecular biology, epigenetics, functional genomics, bioinformatics, computational and systems biology. The following steps are proposed: (i) Identification of 'classical' and 'novel' phenotypes in existing birth cohorts; (ii) Building discovery of the relevant mechanisms in IgE-associated allergic diseases in existing longitudinal birth cohorts and Karelian children; (iii) Validation and redefinition of classical and novel phenotypes of IgE-associated allergic diseases; and (iv) Translational integration of systems biology outcomes into health care, including societal aspects. MeDALL will lead to: (i) A better understanding of allergic phenotypes, thus expanding current knowledge of the genomic and environmental determinants of allergic diseases in an integrative way; (ii) Novel diagnostic tools for the early diagnosis of allergy, targets for the development of novel treatment modalities, and prevention of allergic diseases; (iii) Improving the health of European citizens as well as increasing the competitiveness and boosting the innovative capacity of Europe, while addressing global health issues and ethical issues.

IgE-associated allergic diseases represent a global health problem that is increasing in prevalence and severity. In some European countries, up to 50% of children have an IgE sensitization to inhalant or food allergens. An epidemic of IgE-associated allergic diseases has occurred over the past decades in all parts of Europe (Fig. 1) (1). A wide variety of mechanisms are associated with allergic diseases. The most common diseases are linked with an IgE immune response. IgE-associated allergic diseases are complex multifactorial disorders, with both genetic and environmental components. Their complex genetic and additional epigenetic interactions determine disease expression and lead to different and frequently coexisting phenotypes. These interactions are likely to start *in utero* and during perinatal development and then develop in infancy and childhood (2). Adult allergic phenotypes are largely influenced by these earlier developments (3). The different manifestations of allergic diseases involve the respiratory system (asthma, rhinoconjunctivitis), the skin (atopic eczema) (4), and the gastrointestinal tract [food allergy and eosinophilic gastroenteritis (5)] and may have a generalized expression involving different organs (anaphylaxis). These are not separate diseases but are linked by complex and currently insufficiently defined interrelationships that occur during childhood and persist throughout life.

Surprisingly, and despite developments in epidemiology, immunology, and human genomics, our understanding of the trends depicted in Fig. 1 is limited and the answers to the

Abbreviations
EU, European Union; FP, Framework Programme (European Union); EAACI, European Academy of Allergy and Clinical Immunology; EFA, European Federation of Allergy and Airways Diseases Patients' Associations; GA^{2}LEN, Global Allergy and Asthma European Network (FP6); IPR, Intellectual Property Rights; MeDALL, Mechanisms of the Development of ALLergy (FP7); SCID, Severe Combined Immunodeficiency.



Q1- Why is allergy increasing in European countries ?
Q2- Why is allergy increasing with delay in some countries ?
Q3- Is allergy decreasing in some countries ?
Q4- Is « atopy » with heredity different from « allergy » without heredity in onset, persistence and possible decreased prevalence ?
Q5- Are they different phenotypes of allergic diseases in these different situations ?

Figure 1 Trends in IgE-associated allergic diseases and some of the questions raised.

relevant questions raised are still largely unknown. The significant increase in prevalence over a relatively short period of time strongly suggests the influence of environmental determinants. The hygiene hypothesis has attempted to explain the epidemic of allergy, but it does leave some relevant facts unexplained, like the epidemic increase in allergy in large cities in Latin America (6). Although the reasons explaining the epidemic of IgE-associated diseases are likely to be environmental, the influence of interactions between environmental factors and genes has to be considered. In the last decade, much effort has been put into genetic studies, but the results have been largely limited by the lack of replication. The arguments for this apparent failure may involve many different factors such as the limitations in genomic studies, i.e. the presence of complex genetic modulation of environmental exposures on the inception of allergies (7), the small effects contributed by many different genes and environmental factors (8), the lack of information on the role of the epigenetic regulation in the allergic phenotypes (9), the heterogeneity of allergy-related diseases and their interrelationships (currently addressed by splitting single complex diseases into several sub-entities) (10), genetic differences depending on the age of onset [like the role of the region of the *ORMDL3/GSDML* gene in childhood asthma (11)], or the uncovered complexity in the interactions between genes and environmental exposures (e.g. pathway analyses) (12).

In utero and early life events appear to be critical. The risk and protective factors for allergic diseases during pregnancy and early life include airborne allergens, air pollution, indoor air including molds and chemicals (e.g. pesticides, herbicides, cleaning products, hormonal disruptors such as phthalates), nutrition, drugs, lifestyle, stress, psychosocial factors, obesity, and/or exercise.

There are several reasons justifying a joint effort within the EU to mobilize the critical mass of expertise in understanding the onset of allergic diseases. These include the following:

- The reasons for the recent epidemic in IgE-associated allergic diseases are still largely unknown. The difficulty to understand the distribution of the epidemic over the recent decades may be linked to the approach that is being followed rather than to the type of determinants and mechanisms that are being sought.
- Although most patients with allergic diseases may be controlled by current treatment, there is a need for the discovery and development of preventive approaches. Research is required to better understand the mechanisms underlying the onset of allergy, to develop biomarkers of early diagnosis and severity of allergy, and to develop prevention strategies and targets for therapy, particularly in children.
- This area of research is currently fragmented, leading to a lack of integrated studies. Whereas individual mechanistic investigations will most likely continue to provide limited insight, we propose that an integrative approach is necessary to understand the current epidemic of allergic diseases. This integrative approach can only be obtained by a network of complementary experts in all disciplines from clinicians to systems biology and should also involve the analysis of the societal dimension of the questions.

A new integrative approach is needed to understand how a complex network of genetic and environmental factors leads to a complex allergic phenotype. Mechanisms of the Development of ALLergy (MeDALL) will provide the platform of a large multidisciplinary integrative effort that is required to overcome the limitations of current research.

Objectives

This project (MeDALL) aims to generate novel knowledge on the origin and mechanisms of the IgE-associated allergic diseases (asthma, allergic rhinitis, atopic dermatitis, and food allergy, particularly in children) to understand how and which environmental factors influence the initiation of allergy and how changes in these factors have induced an epidemic increase in IgE-associated allergic diseases without having changed the hereditary genetic predisposition.

An innovative integrative research strategy complex model will combine several approaches making this consortium particularly comprehensive. The MeDALL consortium includes experts from a wide range of fields.

Overall strategy

The strategy is based on information and samples (already available and obtained during the project) obtained from a large network of existing birth cohorts (Table 1). Birth cohorts have been stratified into younger and older cohorts depending on the length of study.

Based on the participating birth cohorts, classical and novel phenotypes will be established. A wide range of mechanistic studies will build up on the samples provided by the birth cohorts. Methods and tools used in systems biology will be applied to facilitate an effective knowledge management strategy and to integrate the findings of the different mechanistic approaches. The information from the mechanistic studies will be used to validate the classical and novel phenotypes and to assess interactions with relevant environ-

Table 1 Birth cohorts included in MeDALL

Acronym of birth cohort	Name of birth cohort	Country	Recruitment of subjects	Number recruited at birth	Age at new examination (in 2012–2013)
AMICS-Menorca* (13)	Asthma Multicenter Infant Cohort Study	Spain	1997–1998	482	15–16 year
BAMSE* (14)	Children, Allergy, Milieu, Stockholm	Sweden	1994–1996	4089	16–18 year
BIB† (15)	Born in Bradford	UK	2007–2009	1000	4–6 year
DARC* (16)	Danish Allergy Research Council	Denmark	1998–1999	562	14–15 year
ECA* (17)	Environment and Childhood Asthma	Norway	1992–1993	3754	16–17 year (in 2009; no field work in MeDALL)
EDEN† (18)	Etude des Déterminants pré et post natals du développement et de la santé de l' Enfant	France	2003–2005	1900	8–10 year
GINI* (19)	German Infant Nutritional Intervention Study	Germany	1995–1998	5991	16–18 year
INMA† (20)	Infancia y medio ambiente	Spain	2004–2008	2500	5–8 year
LISA* (21)	Lifestyle-related Factors on the Immune System and Development of Allergies. In Childhood	Germany	1997–1998	3097	15–16 year
PARIS† (22)	Birth cohort in Paris	France	2005	2700	8 year
PIAMA-NHS* (23)	Prevention and Incidence of Asthma and Mite Allergy - Natural History Study	NL	1996–1997	3291	16–17 year
RHEA†(24)	Mother–Child cohort in Crete	Greece	2007–2008	1500	7–8 year
ROBIC† (25)	Roma-Bologna birth cohort	Italy	2003–2004	1400	9–10 year
Total				22 900 21 127	

MeDALL, Mechanisms of the Development of ALLergy.
*Older cohorts.
†Younger cohorts.

mental factors. Finally, a translational strategy will be developed to maximize the preventive and therapeutic impact of MeDALL (Fig. 2).

The overall strategy of MeDALL will be developed in four steps (Fig. 3):

First step: identification of 'classical' and 'novel' phenotypes in existing population-based birth cohorts

The identification of classical phenotypes will be based on experts' criteria. A review of the literature will include the following relevant topics: the definition of allergic phenotypes, the heterogeneity of the different allergic diseases, and their interrelationships. The review will be used in an expert meeting for the definition of IgE-associated allergic diseases. The expert meeting will agree on the relevant classical phenotypes that will be used to define the samples to be assayed in the participating birth cohorts for the mechanistic studies (second step). To identify the novel phenotypes, the same data sets as those used for the classical phenotypes will be analyzed using hypothesis-free methods such as latent class (for categorical data) and cluster analysis (both hierarchical and k-means). The applicability of scale-free network analysis to the existing databases will be explored. The population included in these analyses will consist of 22 900 children from six young birth cohorts and 21 127 subjects from seven older cohorts.

In addition to using existing data sets of European birth cohorts, all participating cohorts will be followed up with a standardized protocol. The population invited to participate in the follow-up will include 6000 children aged 4–8 years from the six younger cohorts and 11 900 subjects aged 14–18 years from the older cohorts.

Second step: building discovery of the relevant mechanisms in IgE-associated allergic diseases in the European birth cohorts and Karelian children (26)

Once defined, both classical and novel phenotypes will be sampled following prespecified criteria and these samples

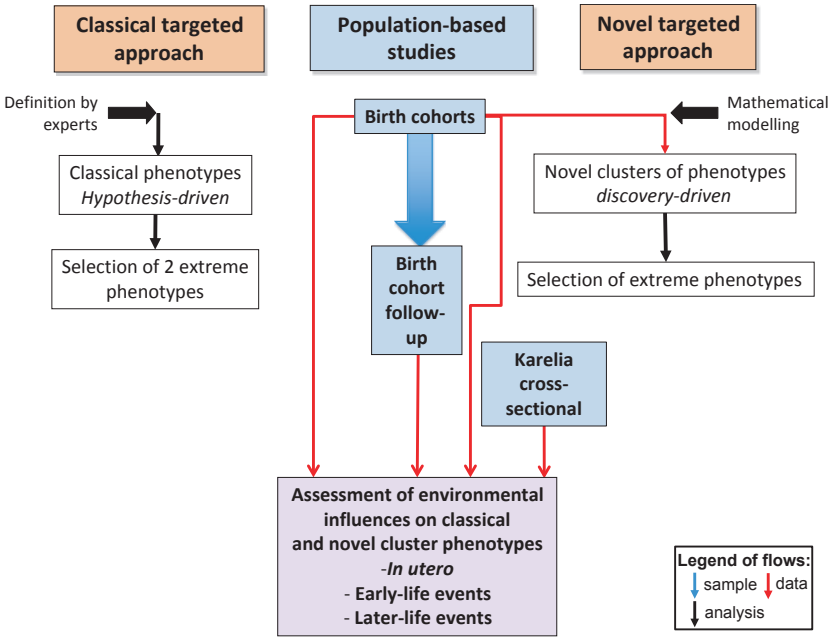


Figure 2 Approaches used in Mechanisms of the Development of ALLergy.

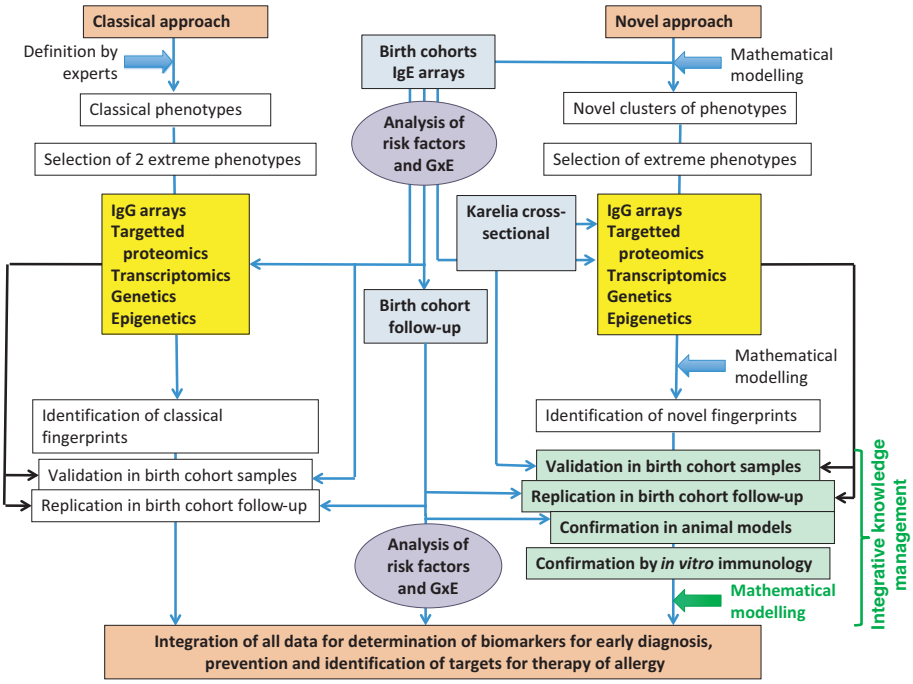


Figure 3 Overview of Mechanisms of the Development of ALLergy.

will be used in a wide range of mechanistic studies. These studies will also use samples obtained in the follow-up. The overall aim of the mechanistic studies is to identify fingerprints of relevance in the disease course from initiation to persistence. In addition, the mechanistic studies will test a wide range of relevant specific hypotheses. The mechanistic approach in MeDALL will include the following types of studies:

1. Characterization of inhalant and food allergens using an allergen microarray containing the most relevant respiratory and food allergens to measure the levels of specific IgE, IgG subclass, IgA and IgM antibodies.

2. Epigenetics and targeted proteomics including a genome-wide and specifically gene-targeted assessment of methylation status, the analysis of a large set of serum biomarkers, and the assessment of gene-methylation-biomarker-interactions. Gene by environment interactions will also be assessed.
3. Transcriptomics and systems biology to identify and validate transcriptomic fingerprints and integrated network phenotype handprints.
4. *In vitro* human immunological studies to investigate the mechanisms of allergen-specific T-cell tolerance and allergen-specific T-cell and B-cell regulation.
5. The previous investigations in children's samples will be complemented with experiments in animal models including naive mice, gene-modified mice, and humanized severe combined immunodeficiency (SCID) mice.

Third step: validation and redefinition of the novel and classical phenotypes of IgE-associated allergic diseases

Findings from the mechanistic studies will be integrated, and relevant fingerprints will be validated as markers and predictors of allergic diseases. The validation analysis will include the analysis of the novel fingerprints in the full sample of the historical birth cohorts and in the follow-up data of the birth cohorts.

Fourth step: translational integration of systems biology outcomes into health care

In this final step, all relevant MeDALL findings will be examined and their potential use for improving prevention, prediction, and treatment will be considered (Fig. 4). This step will include the following activities:
1. Definition of novel approaches for prevention, addressing the relevant environmental exposures, to lead to national preventive plans.
2. Identification of new opportunities for early diagnosis (including biomarkers: threshold levels for disease expression using classical and novel phenotypes).
3. Characterization of risk groups in the population, leading to risk charts for allergic diseases.
4. Identification of innovative targets for therapy.
5. Estimation of the MeDALL research outcomes into societal and economic impacts in a European context.

The MeDALL project includes a specific strategy to guarantee the dissemination of the results to all stakeholders and education, in collaboration with the European Academy of Allergy and Clinical Immunology (EAACI), GA^{2}LEN, and patients (the European Federation of Allergy and Airways Diseases Patients' Associations (EFA)), and to deal with the ethical problems and intellectual property rights issues.

Overall progress beyond the state-of-the-art of the MeDALL consortium

The long-term solution to the allergy and asthma epidemic is thought to be prevention rather than treatment of established disease (27). A large number of studies have attempted to prevent the onset of allergic diseases, but results are inconsistent and at best modest. The reasons explaining the failure of these interventions are unclear but may be because of the incomplete understanding of the phenotypes and of the

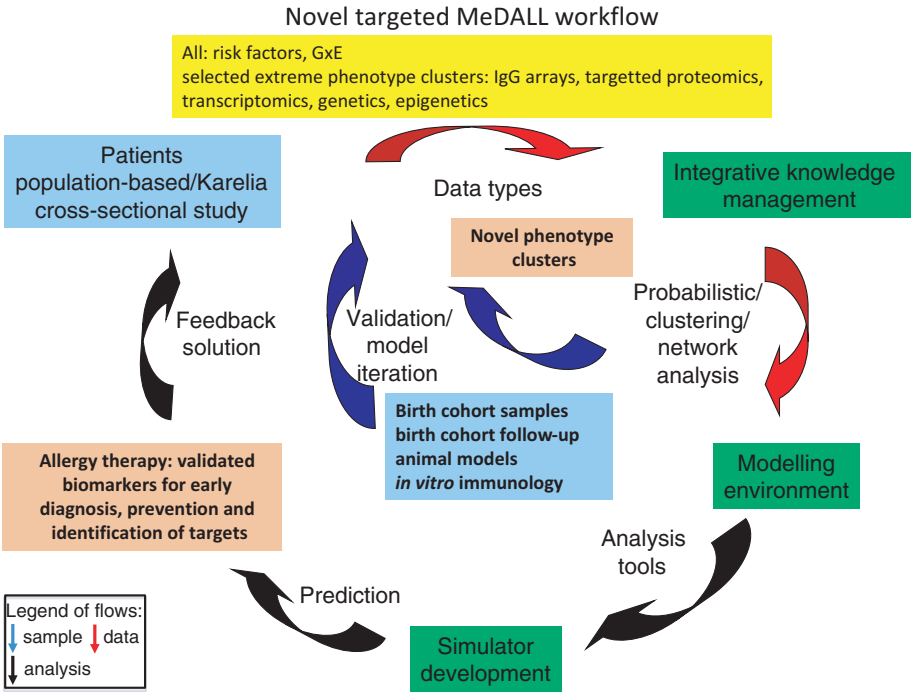


Figure 4 Illustration of knowledge improvement by iterative modeling.

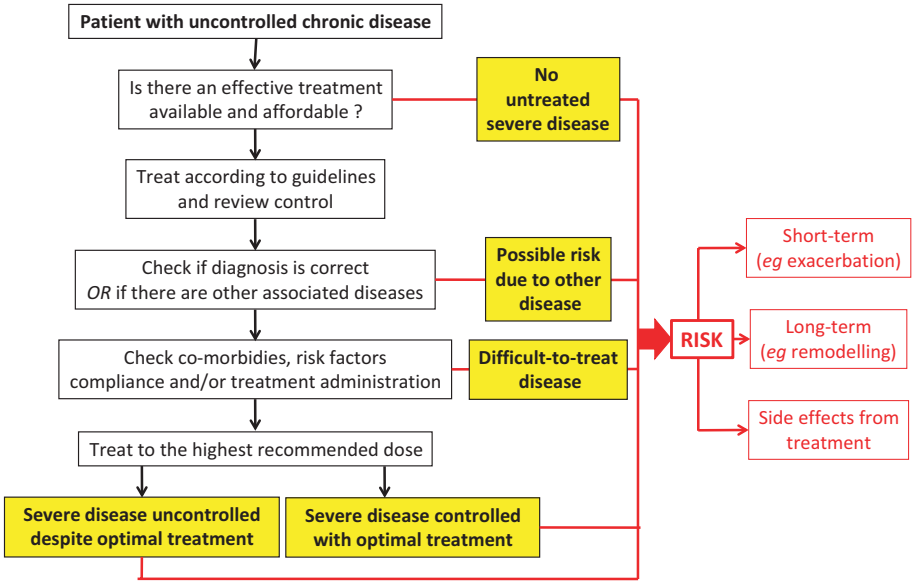


Figure 5 Uniform definition of severe chronic disease (the example of asthma) [based on (32)].

mechanisms underlying the allergy epidemic. The MeDALL project will increase our knowledge on complex interactions and lead to more efficient preventive strategies. Besides considering the ethical issues of the research involving children cohorts and biomaterial (28, 29), it will also carefully address the epistemological health system and societal implications of the newly identified types of biomarkers (30).

MeDALL will also propose a uniform definition of severe allergic diseases based on the definition of severe asthma proposed to WHO, and which can be extended to all chronic diseases. It is based on control and future risks (short, medium, and long term) (31) (Fig. 5).

MeDALL will advance the current state-of-the-art knowledge of the mechanisms underlying the epidemic of IgE-associated allergic diseases. It will be based on previous EU projects that have helped to design this innovative integrated research strategy. It will provide new insights into epigenetics, biomarkers, and immunologic mechanisms.

More specifically, with an integrative translational approach, it will be possible to identify opportunities for prevention, prediction, diagnosis, and treatment

1. To define the different allergic/atopic phenotypes;
2. To determine early markers of the development of IgE-associated allergic diseases (diagnosis before clinical expression);
3. To provide novel insight into the individual susceptibility of developing IgE-associated allergic diseases;
4. To determine risk prediction algorithms for allergy in children;
5. To propose novel preventive measures for the development and clinical expression of IgE-associated allergic diseases;
6. To propose new targets for therapy.

The progress expected beyond the state-of-the-art is summarized in Fig. 6.

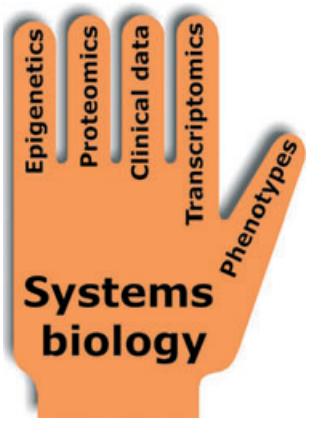


Figure 6 Allergy phenotype handprints developed through an integrative systems biology approach *(adapted from U-BIOPRED)*.

Impact

This project is aimed at improving the health of European citizens as well as increasing the competitiveness and boosting the innovative capacity of Europe, while addressing the global health issues of a major public health problem. It is designed to develop novel diagnostic tools, treatment modalities, and methods for the prevention of allergic diseases, from childhood to adolescence. The feasibility and achievability of MeDALL have been carefully examined.

Dissemination of the MeDALL results and intellectual property (IP) management will be extensive and will also involve carefully redacted public health messages prepared in collaboration with scientists and stakeholders including patients' associations and, if possible, a larger public. Proper interaction with national health agencies and public health

societies at national and European level will be promoted, as well as visibility to the Health and Consumer General Directorate of the EU Commission.

The 'foreground' of MeDALL will be extensively promoted. It will consist of results, including information, materials, and knowledge generated during the project, whether or not results can be protected, intellectual property rights (IPRs such as rights resulting from copyright protection, related rights, design rights, patent rights, plant variety rights, rights of creators of topographies of semiconductor products), similar forms of protection (e.g. *sui generis* right for databases), and unprotected know-how (e.g. confidential material).

MeDALL outcomes will hold a significant benefit for society and human interaction including health and environmental implications. The ultimate goal of MeDALL is to increase our knowledge and understanding of the causes of asthma and allergic disease. The results of the program will help to improve early diagnosis, target primary and secondary prevention strategies, and develop novel cost-effective treatments for allergic disorders. The project is likely to have a major impact on health and costs, and to reduce health inequities in Europe because it is expected to abate the allergy epidemic.

Acknowledgement

The authors would like to thank Ms Anna Bedbrook for her help in the preparation of this manuscript.

References

1. 2008-2013 Action plan for the global strategy for the prevention and control of non communicable diseases. Prevent and control cardiovascular diseases, cancers, chronic respiratory diseases, diabetes. http://wwwwhoint/nmh/Actionplan-PC-NCD-2008pdf. 2008.
2. Martinez FD. Genes, environments, development and asthma: a reappraisal. *Eur Respir J* 2007;**29**:179–184.
3. Martinez FD. Heterogeneity of the association between lower respiratory illness in infancy and subsequent asthma. *Proc Am Thorac Soc* 2005;**2**:157–161.
4. Spergel JM, Paller AS. Atopic dermatitis and the atopic March. *J Allergy Clin Immunol* 2003;**112**(Suppl. 6):S118–S127.
5. Simon HU, Rothenberg ME, Bochner BS, Weller PF, Wardlaw AJ, Wechsler ME et al. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol* 2010;**126**:45–49.
6. Cooper PJ, Rodrigues LC, Cruz AA, Barreto ML. Asthma in Latin America: a public heath challenge and research opportunity. *Allergy* 2009;**64**:5–17.
7. Martinez FD. Gene-environment interaction in complex diseases: asthma as an illustrative case. *Novartis Found Symp* 2008;**293**:184–192. discussion 92–7.
8. von Mutius E. Gene-environment interactions in asthma. *J Allergy Clin Immunol* 2009;**123**:3–11. quiz 2–3.
9. Bousquet J, Jacot W, Yssel H, Vignola AM, Humbert M. Epigenetic inheritance of fetal genes in allergic asthma. *Allergy* 2004;**59**:138–147.
10. Freimer NB, Sabatti C. Human genetics: variants in common diseases. *Nature* 2007;**445**:828–830.
11. Bouzigon E, Corda E, Aschard H, Dizier MH, Boland A, Bousquet J et al. Effect of 17q21 variants and smoking exposure in early-onset asthma. *N Engl J Med* 2008;**359**:1985–1994.
12. Bottema RW, Postma DS, Reijmerink NE, Thijs C, Stelma FF, Smit HA et al. Interaction of T-cell and antigen presenting-cell costimulatory genes in childhood IgE. *Eur Respir J* 2010;**35**:54–63.
13. Garcia Algar O, Pichini S, Basagana X, Puig C, Vall O, Torrent M et al. Concentrations and determinants of NO2 in homes of Ashford, UK and Barcelona and Menorca, Spain. *Indoor Air* 2004;**14**:298–304.
14. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol* 2002;**13**(Suppl. 15):11–13.
15. Raynor P. Born in Bradford, a cohort study of babies born in Bradford, and their parents: protocol for the recruitment phase. *BMC Public Health* 2008;**8**:327.
16. Host A, Halken S, Jacobsen HP, Christensen AE, Herskind AM, Plesner K. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. *Pediatr Allergy Immunol* 2002;**13**(Suppl 15):23–28.
17. Lodrup Carlsen KC. The environment and childhood asthma (ECA) study in Oslo: ECA-1 and ECA-2. *Pediatr Allergy Immunol* 2002;**13**(Suppl. 15):29–31.
18. Slama R, Thiebaugeorges O, Goua V, Aussel L, Sacco P, Bohet A et al. Maternal personal exposure to airborne benzene and intrauterine growth. *Environ Health Perspect* 2009;**117**:1313–1321.
19. Laubereau B, Brockow I, Zirngibl A, Koletzko S, Gruebl A, von Berg A et al. Effect of breast-feeding on the development of atopic dermatitis during the first 3 years of life–results from the GINI-birth cohort study. *J Pediatr* 2004;**144**:602–607.
20. Aguilera I, Guxens M, Garcia-Esteban R, Corbella T, Nieuwenhuijsen MJ, Foradada CM et al. Association between GIS-based exposure to urban air pollution during pregnancy and birth weight in the INMA Sabadell Cohort. *Environ Health Perspect* 2009;**117**:1322–1327.
21. Heinrich J, Bolte G, Holscher B, Douwes J, Lehmann I, Fahlbusch B et al. Allergens and endotoxin on mothers' mattresses and total immunoglobulin E in cord blood of neonates. *Eur Respir J* 2002;**20**:617–623.
22. Clarisse B, Demattei C, Nikasinovic L, Just J, Daures JP, Momas I. Bronchial obstructive phenotypes in the first year of life among Paris birth cohort infants. *Pediatr Allergy Immunol* 2009;**20**:126–133.
23. Wijga A, Smit HA, Brunekreef B, Gerritsen J, Kerkhof M, Koopman LP et al. Are children at high familial risk of developing allergy born into a low risk environment? The PIAMA Birth Cohort Study. Prevention and Incidence of Asthma and Mite Allergy. *Clin Exp Allergy* 2001;**31**:576–581.
24. Chatzi L, Plana E, Daraki V, Karakosta P, Alegkakis D, Tsatsanis C et al. Metabolic syndrome in early pregnancy and risk of preterm birth. *Am J Epidemiol* 2009;**170**:829–836.
25. Porta D, Forastiere F, Di Lallo D, Perucci CA. Enrolment and follow-up of a birth cohort in Rome. *Epidemiol Prev* 2007;**31**:303–308.
26. Pekkarinen PT, von Hertzen L, Laatikainen T, Makela MJ, Jousilahti P, Kosunen TU et al. A disparity in the association of asthma, rhinitis, and eczema with allergen-specific IgE between Finnish and Russian Karelia. *Allergy* 2007;**62**:281–287.
27. Sly PD, Boner AL, Bjorksten B, Bush A, Custovic A, Eigenmann PA et al. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008;**372**:1100–1106.
28. Ries NM, LeGrandeur J, Caulfield T. Handling ethical, legal and social issues in birth cohort studies involving genetic research: responses from studies in six countries. *BMC Med Ethics* 2010;**11**:4.

29. Cambon-Thomsen A, Rial-Sebbag E, Knoppers BM. Trends in ethical and legal frameworks for the use of human biobanks. *Eur Respir J* 2007;**30**:373–382.
30. Bauer S. Societal and ethical issues in human biomonitoring–a view from science studies. *Environ Health* 2008;**7**(Suppl. 1):S10.
31. Expert panel report 3: Guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program. National Heart, Lung and Blood Institute. US Department of Health and Human Services. 440 pages. 2007. http://www.nhlbi.nih.gov/guidelines/index.htm
32. Bousquet J, Mantzouranis E, Cruz A, AÏt-Khaled N, Baena-Cagnani C, Bleecker E et al. Uniform definition of asthma severity, control and exacerbations. Paper presented to WHO for a consultation on severe asthma. *J Allergy Clin Immunol* 2010;**126**: 926–938.