Mechanisms of the Development of Allergy (MeDALL): Introducing novel concepts in allergy phenotypes

Josep M. Anto, PhD,[a,b,c,d]* Jean Bousquet, MD,[e,f,g]* Mubeccel Akdis, MD,[h] Charles Auffray, MD,[i] Thomas Keil, MD,[j] Isabelle Momas, PhD,[k] Dirkje S. Postma, MD,[l] Rudolf Valenta, MD,[m] Magnus Wickman, MD,[n] Anne Cambon-Thomsen, MD,[o] Tari Haahtela, MD,[p] Bart N. Lambrecht, MD,[q] Karin C. Lodrup Carlsen, MD,[r] Gerard H. Koppelman, PhD,[s] Jordi Sunyer, MD,[a,b,c,d] Torsten Zuberbier, MD,[t] Isabelle Annesi-Maesano, MD,[u] Albert Arno, MD,[v] Carsten Bindslev-Jensen, PhD,[w] Giuseppe De Carlo,[x] Francesco Forastiere, MD,[y] Joachim Heinrich, PhD,[z] Marek L. Kowalski, MD,[aa] Dieter Maier, PhD,[bb] Erik Melén, MD,[cc] Henriette A. Smit, PhD,[dd] Marie Standl, PhD,[z] John Wright, FRPC,[ee] Anna Asarnoj, MD,[ff] Marta Benet, MSc,[a] Natalia Ballardini, MD,[n,gg] Judith Garcia-Aymerich, MD,[a,b,c,d] Ulrike Gehring, PhD,[hh] Stefano Guerra, MD,[a] Cynthia Hohmann, Dipl Psych,[ii] Inger Kull, PhD,[n,jj] Christian Lupinek, MD,[m] Mariona Pinart, PhD,[a] Ingebjorg Skrindo, MD,[r] Marit Westman, MD,[kk] Delphine Smagghe, MSc,[ll] Cezmi Akdis, MD,[h] Niklas Andersson, MSc,[mm] Claus Bachert, MD,[nn] Stephane Ballereau, PhD,[i] Ferran Ballester, MD,[oo] Xavier Basagana, PhD,[a] Anna Bedbrook, MSc,[f] Anna Bergstrom, PhD,[mm] Andrea von Berg, MD,[pp] Bert Brunekreef, PhD,[dd,hh] Emilie Burte, MSc,[g] Kai-Hakon Carlsen, MD,[qq] Leda Chatzi, MD,[rr] Jonathan M. Coquet, PhD,[q] Mirela Curin, PhD,[m] Pascal Demoly, MD,[ss] Esben Eller, MD,[w] Maria Pia Fantini, MD,[tt] Leena von Hertzen, PhD,[p] Vergard Hovland, MD,[qq] Benedicte Jacquemin, MD,[a] Jocelyne Just, MD,[uu] Theresa Keller, MSc,[ii] Renata Kiss, MSc,[m] Manolis Kogevinas, MD,[a,b,c,d] Sibylle Koletzko, MD,[vv] Susanne Lau, MD,[ww] Irina Lehmann, PhD,[xx] Nicolas Lemonnier, PhD,[yy] Mika Mäkelä, MD,[p] Jordi Mestres, PhD,[zz] Peter Mowinckel, MSc,[qq] Rachel Nadif, PhD,[g] Martijn C. Nawijn, PhD,[s] Johan Pellet, MSc,[i] Isabelle Pin, MD,[aaa] Daniela Porta, MD,[y] Fanny Rancière, PhD,[k] Emmanuelle Rial-Sebbag, PhD,[o] Yvan Saeys, PhD,[q] Martijn J. Schuijs, MSc,[q] Valerie Siroux, PhD,[bbb] Christina G. Tischer, PhD,[z] Mathies Torrent, MD,[a,ccc] Raphaelle Varraso, PhD,[g] Kalus Wenzel, MD,[bb] and Cheng-Jian Xu, PhD[s]

Barcelona, Valencia, and Menorca, Spain; Montpellier, Villejuif, Montigny le Bretonneux, Lyon, Paris, Toulouse, and Grenoble, France; Davos, Switzerland; Berlin, Wuerzburg, Neuherberg, Munich, Wesel, and Leipzig, Germany; Groningen and Utrecht, The Netherlands; Vienna, Austria; Stockholm, Sweden; Helsinki, Finland; Ghent and Brussels, Belgium; Oslo, Norway; Odense, Denmark; Rome and Bologna, Italy; Lodz, Poland; Bradford and London, United Kingdom; and Crete, Greece

Asthma, rhinitis, and eczema are complex diseases with multiple genetic and environmental factors interlinked through IgE-associated and non–IgE-associated mechanisms. Mechanisms of the Development of ALLergy (MeDALL; EU FP7-CP-IP; project no: 261357; 2010-2015) studied the complex links of allergic diseases at the clinical and mechanistic levels by linking epidemiologic, clinical, and mechanistic research, including *in vivo* and *in vitro* models. MeDALL integrated 14 European birth cohorts, including 44,010 participants and 160 cohort follow-ups between pregnancy and age 20 years. Thirteen thousand children were prospectively followed after puberty by using a newly standardized MeDALL Core Questionnaire. A microarray developed for allergen molecules with increased IgE sensitivity was obtained for 3,292 children. Estimates of air pollution exposure from previous studies were available for 10,000 children. Omics data included those from historical genome-wide association studies (23,000 children) and DNA methylation (2,173), targeted multiplex biomarker (1,427), and transcriptomic (723) studies. Using classical epidemiology and machine-learning methods in 16,147 children aged 4 years and 11,080 children aged 8 years, MeDALL showed the multimorbidity of eczema, rhinitis, and asthma and estimated that only 38% of multimorbidity was attributable to IgE sensitization. MeDALL has proposed a new vision of multimorbidity independent of IgE sensitization, and has shown that monosensitization and polysensitization represent 2 distinct phenotypes. The translational component of MeDALL is shown by the identification of a novel allergic phenotype characterized by polysensitization and multimorbidity, which is associated with the frequency, persistence, and severity of allergic symptoms. The results of MeDALL will help integrate personalized, predictive, preventative, and participatory approaches in allergic diseases. (J Allergy Clin Immunol 2017;139:388-99.)

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Asthma, rhinitis, and eczema are among the most common chronic diseases. One of the most challenging characteristics is their complexity, with multiple genetic and environmental factors interlinked through IgE-associated and non–IgE-associated mechanisms.[1] These diseases generally begin very early in life and can persist into adult life.[2] As in patients with other chronic

diseases, they often occur in the same subjects (multimorbidity) more often than expected by chance.[3]

During the last decade, increasing recognition of the challenges associated with the complexity of many chronic diseases has stimulated interest in applying ***systems biology*** approaches to biomedical research.[4] Personalized, predictive, preventative, and participatory (P4) medicine has been advocated to integrate personalized, predictive, preventative, and participatory approaches.[5]

An important milestone in this process was that the 7th Framework Programme of the European Union (EU) promoted research to develop systems medicine to better understand chronic diseases. Mechanisms of the Development of ALLergy (MeDALL; EU FP7-CP-IP; project no: 261357; 2010-2015)

From [a]ISGLoBAL, Centre for Research in Environmental Epidemiology (CREAL), Barcelona; [b]IMIM (Hospital del Mar Research Institute), Barcelona; [c]CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona; [d]Universitat Pompeu Fabra (UPF), Barcelona; [e]University Hospital, Montpellier; [f]MACVIA-France, Contre les MAladies Chroniques pour un Vieillissement Actif en France, European Innovation Partnership on Active and Healthy Ageing Reference Site, Montpellier; [g]INSERM, U1168, Ageing and chronic diseases Epidemiological and public health approaches, Villejuif, and UVSQ, UMR-S 1168, Univ Versaille St-Quentin-en-Yvelynes, Montigny le Bretonneux; [h]the Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos; [i]the European Institute for Systems Biology and Medicine, CNRS-ENS-UCBL, Université de Lyon; [j]the Institute of Social Medicine, Epidemiology and Health Economics, Charité–Universitätsmedizin Berlin, Berlin, and the Institute for Clinical Epidemiology and Biometry, University of Wuerzburg; [k]the Department of Public health and health products, Paris Descartes University–Sorbonne Paris Cité, EA 4064, and Paris Municipal Department of Social Action, Childhood, and Health, Paris; [l]the University of Groningen, University Medical Center Groningen; [m]the Division of Immunopathology, Department of Pathophysiology and Allergy Research, Center for Pathophysiology, Infectiology and Immunology, Medical University of Vienna; [n]Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm, and Institute of Environmental Medicine, Karolinska Institutet, Stockholm; [o]UMR Inserm U1027 and Université de Toulouse III Paul Sabatier, Toulouse; [p]the Skin and Allergy Hospital, Helsinki University Hospital; [q]VIB Inflammation Research Center, Ghent University; [r]the Department of Paediatrics, Oslo University Hospital, and the Faculty of Medicine, Institute of Clinical Medicine, University of Oslo; [s]the Department of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, GRIAC Research Institute, University Medical Center Groningen, University of Groningen; [t]Allergy-Centre-Charité at the Department of Dermatology, Charité–Universitätsmedizin Berlin, and Secretary General of the Global Allergy and Asthma European Network (GA^{2}LEN); [u]EPAR U707 INSERM, Paris and EPAR UMR-S UPMC, Paris VI; [v]Onmedic Networks, Barcelona; [w]the Department of Dermatology and Allergy Centre, Odense University Hospital; [x]EFA European Federation of Allergy and Airways Diseases Patients' Associations, Brussels; [y]the Department of Epidemiology, Regional Health Service Lazio Region, Rome; [z]the Institute of Epidemiology I, Helmholtz Zentrum München—German Research Center for Environmental Health, Neuherberg; [aa]the Department of Immunology, Rheumatology and Allergy, Medical University of Lodz; [bb]Biomax Informatics AG, Munich; [cc]Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm, and Institute of Environmental Medicine, Karolinska Institutet, Stockholm; [dd]the Julius Center of Health Sciences and Primary Care, University Medical Center Utrecht, University of Utrecht; [ee]the Bradford Institute for Health Research, Bradford Royal Infirmary; [ff]the Clinical Immunology and Allergy Unit, Department of Medicine Solna, Karolinska Institutet, Stockholm, and Astrid Lindgren Children's Hospital, Department of Pediatric Pulmonology and Allergy, Karolinska University Hospital, Stockholm; [gg]St John's Institute of Dermatology, King's College London; [hh]the Institute for Risk Assessment Sciences, Utrecht University; [ii]the Institute of Social Medicine, Epidemiology and Health Economics, Charité–Universitätsmedizin, Berlin; [jj]the Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm; [kk]the Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, and Department of ENT diseases, Karolinska University Hospital, Stockholm; [ll]Inserm Transfert, Paris; [mm]the Institute of Environmental Medicine, Karolinska Institutet, Stockholm; [nn]the ENT Department, Ghent University Hospital; [oo]the Environment and Health Area, Centre for Public Health Research (CSISP); CIBERESP, Department of Nursing, University of Valencia; [pp]the Research Institute, Department of Pediatrics, Marien-Hospital, Wesel; [qq]the Department of Paediatrics, Oslo University Hospital and University of Oslo; [rr]the Department of Social Medicine, Faculty of Medicine, University of Crete; [ss]the Department of Respiratory Diseases, Montpellier University Hospital; [tt]the Department of Medicine and Public Health, Alma Mater Studiorum–University of Bologna; [uu]the Allergology Department, Centre de l'Asthme et des Allergies, Hôpital d'Enfants Armand-Trousseau (APHP), and Sorbonne Universités, UPMC Univ Paris Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe EPAR, Paris; [vv]the Division of Paediatric Gastroenterology and Hepatology, Ludwig-Maximilians-Universität of Munich; [ww]the Department for Pediatric Pneumology and Immunology, Charité Medical University, Berlin; [xx]the Department of Environmental Immunology/Core Facility Studies, Helmholtz Centre for Environmental Research–UFZ, Leipzig; [yy]Institut Albert Bonniot à Grenoble (Institute for Advanced Biosciences), Grenoble; [zz]Chemotargets SL and Chemogenomics Laboratory, GRIB Unit, IMIM-Hospital del Mar and University Pompeu Fabra, Barcelona; [aaa]Département de pédiatrie, CHU de Grenoble; [bbb]Inserm, U823, Grenoble; and [ccc]ib-salut, Area de Salut de Menorca.

*These authors contributed equally to this work.

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Corresponding author: Josep M. Anto, ISGlobal Barcelona, Health Services Research Unit, IMIM, Barcelona, Spain. E-mail: jmanto@isglobal.org. Or: Jean Bousquet, CHU Montpellier, 34295 Montpellier Cedex 5, France. E-mail: jean.bousquet@orange.fr.

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Terms in boldface and italics are defined in the glossary on page 390.