Global Allergy Forum and Second Davos Declaration 2013 Allergy: Barriers to cure – challenges and actions to be taken

Allergic diseases like asthma, eczema, hay fever, anaphylaxis, and food and drug hypersensitivity affect approximately 1 billion people in the world and represent the most prevalent and most costly noncommunicable and chronic diseases of childhood (both direct and indirect costs) (1). The epidemic increase in the prevalence of allergic disease (2), which first started in the industrialized countries in the 1960s, may have reached a peak in the developed world and an end is not in sight (3). Allergic diseases continue to rise in developing countries and developing parts of industrialized countries (4). The reasons for this are not well understood, and unfortunately, there is no established way to prevent allergic diseases. The major unmet needs include public health concerns (such as the very high burden to healthcare costs), inadequate control of the severe and complex allergic diseases, and the lack of curative treatments and preventative strategies.

Allergies create a high burden of suffering not only due to the life-threatening conditions such as anaphylaxis or asthma, but also due to the tremendous impairment in quality of life that occurs in the affected patients, for example in skin allergy due to intense itch sensation and stigmatization. In spite of great progress in experimental research in allergology and immunology, there are still many barriers to developing curative therapies for these chronic and relapsing diseases.

Therefore, a group of 40 scientists and clinicians from four continents and various fields of allergy and related disciplines gathered under the sponsorship of the Christine Kühne – Center for Allergy Research and Education (CK-CARE) for the second Global Allergy Forum from 16 to 19 June 2013 in Davos, Switzerland. Based on the conclusions reached at the first Global Allergy Forum in 2011 (5), the participants formed four working groups to discuss and define the most urgent problems and to propose practical suggestions for interventions.

Role of the environment

Allergy can be defined as a typical 'environmental disease' on a specific genetic background, whereby environment is defined as the sum of exposure to physical, biological, and psychosocial factors. It has become clear that the rise in the prevalence of allergy occurs sequentially over time and is multifactorial in origin. Genetic background and modulation of genes (epigenetics) (6) play critical roles in individual responses to allergens and other environmental factors. Accordingly, exposure to allergens is a necessary, but not sufficient, requirement for the development of allergy. The context of antigen presentation in the micro-milieu of body surfaces, such as the skin, airways, and gastrointestinal tract is crucial. Stress and the psychosocial environment also can modulate the development of allergic sensitization, as well as influence exacerbations and remissions during established disease in sensitized subjects (7). The actual origin of allergenicity (8), including the extent to which it reflects physical, biochemical, or functional properties of the allergen molecules, and the roles of co-exposure to other molecules still remain to be fully elucidated, as does the role of exposure (route, dose, duration).

While there has been significant progress made in the field of allergy in recent years, numerous challenges remain. Some of these are highlighted below.

- The key features of the indoor environment, where one is exposed to domestic mites, molds, and animal products, as well as those of the outdoor environment, where one is exposed to pollens and other sources of allergens, are not very well characterized in molecular terms, nor is there sufficient knowledge regarding dose–response curves and thresholds for sensitization and elicitation of symptoms.
- New and improved existing methodologies for measuring allergen concentrations in indoor and outdoor environments, as well as modeling of pollen and allergen distributions over large geographical regions, are essential in quantifying the exposure. Sustainable monitoring and modeling of allergen content in the indoor and outdoor air will allow more accurate correlation of such data with symptom scores and will therefore provide a better understanding of the relationship between exposure to allergen and the development of allergic diseases.
- The interplay between multiple factors in the internal and external environment which influence allergy is poorly understood at the molecular level. The roles in allergy development and progression of individual microbiomes and environmental microbes, and the potential impact of the widespread clinical and agricultural use of drugs such as antibiotics, are unknown.
- Climate change likely has an impact on allergy development, but this needs further investigation. Tools to predict the impact of future changes in climate and related changes in environmental exposure need to be developed.
- New strategies for reducing environmental factors contributing to allergies, and rational recommendations for prevention, can only be developed once the mechanisms

of environmental influences upon allergy induction and exacerbation are better understood. Relevant environmental factors include air quality (of chemical and biological nature), nutrition, climate, UV radiation, and environmental chemicals of natural or human (industrial) origin, as well as psychosocial interactions.
- The rising prevalence of allergy in developing countries requires further research to identify key contributing factors related to environmental, social, and industrial changes in these countries, and among immigrant populations in developed countries.
- Psychosocial factors are known to play an important role in the development and exacerbation of allergic diseases and should be included as possible risk factors in epidemiological studies.

Mechanisms of allergic inflammation or protection

Within a given environment, not every organism reacts in the same way. It is still a major problem why, under the same conditions, only some individuals develop allergic sensitization or, when sensitized, then manifest disease.

However, there has been much recent progress in efforts to understand the regulation of inflammation and to advance knowledge about protection from allergic disorders (9). This progress includes:
- The identification of mammalian host factors that influence innate and adaptive immune responses, including innate lymphoid cells (ILCs) as 'new' players in allergic disorders and appreciation of the importance of epithelial functions in such settings;
- Appreciation of the heterogeneity of tissue-/organ-associated responses to the environment and in their manifestations of chronic allergic inflammation;
- The application of high-throughput, unbiased approaches for data acquisition, which have markedly increased the information we have about complex biological responses, including potentially important 'subtypes' of disease and their 'biomarkers';
- Increased understanding of the roles of microbiomes and infections (e.g., *S. aureus,* rhinoviruses) in modifying the risk for allergic disorders, including effects on disease initiation, persistence, and exacerbation;
- The identification of examples of the utility of certain 'biomarkers' (in addition to antigen-specific IgE) for identifying subtypes of patients who are likely to respond to targeted therapy based on disease subclassification, thus expanding the scope of personalized/stratified or 'precision medicine' in allergy (10, 11).

Despite such progress, much remains to be done.

We must enhance our understanding of the mechanisms by which microbiomes and metabolic factors (including diet), and neuroimmune interactions, can influence innate and adaptive immune responses and immune tolerance to allergens and thereby promote or curtail the development or severity of allergic (and autoimmune) diseases.

We need to understand the composition and stability of microbiomes (in the upper and lower respiratory tract, skin, gut, etc.) (12), their ability to influence innate and adaptive immune responses, and their susceptibility to short- or long-term changes induced by antibiotics, probiotics, or hygiene practices (e.g., in the skin). There is a need to develop multiplex assay platforms for analyzing immune responses to microbes.

We have to define the importance of colonization versus infection by microbes (e.g., *S. aureus*) in triggering or sustaining allergic disease, and understand by what mechanisms they alter host responses to allergens (e.g., via effects on IgE, effector cells, T regulatory cells, and epithelia). These efforts will be enabled by the development and application of better approaches to quantify microbial exposure and virulence factors and to assess the efficacy and consequences of antibiotic treatment. These will enable progress in understanding epithelial barrier functions in general, and how such functions are influenced by the environment.

We need to understand whether natural anti-inflammatory mechanisms (e.g., epithelial barrier functions, production of antimicrobial molecules or certain cytokines, and lipid mediators) can be modulated for therapeutic benefit, such as for limiting or resolving inflammation, and, if so, define how this best can be achieved safely and effectively.

Many of the gaps in current knowledge of mechanisms of allergic inflammation or protection can be closed by establishing and appropriately employing open biorepositories and data repositories of well-characterized populations (with data linked to individual subjects) to provide environmental (i.e., 'exposome') and clinical (i.e., 'omics') data, and response-to-treatment data, that can be used to advance understanding of:
- The causes of allergic diseases;
- Clinically relevant subtypes of allergic diseases and/or disease predispositions (and related biomarkers);
- Molecular mechanisms of spontaneous healing, remissions, and exacerbations;
- The responses and biomarkers to various treatments (including the induction of immune tolerance).

One framework approach for meeting this need, in allergic disorders and in all types of disease, recently has been described in detail by a committee of the National Research Council in the US (NRC) (11).

In the case of allergic diseases, we must develop and apply robust analytical algorithms that can be used to mine 'omics' and other 'big data' in order to identify 'subtypes' of allergic diseases or disease predispositions that are clinically relevant, that is, that are useful in deciding how to prevent or treat allergic disorders in individual subjects, and to inform definitive mechanistic studies of allergy and allergic diseases.

Finally, it will be critical to increase support for long-term interventional studies to test approaches for preventing the development of allergic disorders, as well as to ameliorate disease in those who have developed such disorders.

Allergy prevention

Regarding research into allergy prevention, the group recommended that new and specific patient cohorts (key cohorts)

should be established to enable the investigation of many of the questions mentioned above.

Adequate biorepositories and data repositories are a prerequisite for these studies.

In addition to analyses of genomes, proteomes, and metabolomes, the multitude of environmental exposure factors (the 'exposome') has to be studied longitudinally and quantitatively. The environmental exposome needs better characterization at the molecular level.

Well-designed interdisciplinary studies of individual patients receiving standard ongoing clinical care, as well as carefully selected patient cohorts, may each provide useful information. It is likely that a system biology approach, which attempts to integrate and analyze complex, interdisciplinary data sets, will be helpful in discerning clues regarding approaches which may be effective in preventing allergies. Studies in emerging countries may be particularly helpful in identifying new factors contributing to the development of allergies.

Allergy diagnostics

Regarding diagnostics, the group found that robust clinical endophenotyping (13) has substantial promise in helping to define more precisely clinically important 'subtypes' of allergic diseases in order to devise more effective, individually tailored, therapeutic strategies.

The development of clinically useful cellular or humoral biomarkers of allergic disease and subtypes of allergic disease is an important, albeit challenging, goal. Success in this effort may require systematic searches using data derived from multiple patient cohorts that have been characterized carefully with respect to clinical features, and for which biobanked specimens are available.

In selected cases, molecular-based allergy diagnostics ('component-resolved' diagnostics) has already been achieved for some allergic conditions, allowing the precise identification of the set of allergens and epitopes against which that patient has sensitivity.

There is a great need for more simplified and routinely useful point-of-care *in vitro* diagnostic techniques for type IV allergic conditions such as contact allergy or allergic drug reactions.

Allergy therapy

With regard to therapy, it was found that although there is a rich pharmacotherapeutic and immunotherapeutic arsenal, allergic diseases in many patients still remain undertreated and poorly controlled. There is a truly unmet need for better therapies for patients with severe disease. An increasing prevalence of diseases characterized by eosinophils (e.g., eosinophilic esophagitis and gastroenteritis, and the hypereosinophilic syndrome) represents a growing challenge for clinical management.

Except allergen-specific immunotherapy (ASIT), there is a shortage of curative approaches. ASIT, which generates specific immune tolerance to allergens, has only been established for a limited number of allergic diseases and only for some allergens; there is a wide area for future development with regard to skin allergy and food allergy. Another large unmet clinical need is for effective approaches to induce tolerance to drugs or contact allergens. Finally, one of the major symptoms of allergic diseases, namely itch, currently can only be poorly treated.

The further improvement of ASIT is hampered by regulatory hurdles at national (including USA) and European regulatory agencies. The development of additional target-oriented biologics that are effective for treating allergic diseases is of utmost importance. The possibility of combination therapies should be studied, even though establishing appropriate regulatory and economic settings to encourage the development and clinical testing of such approaches will be challenging.

The group recommended gaining access to data from previous studies that to date remain hidden in files of regulatory agencies or companies. In order to develop new immunotherapeutic options, an orphan drug approach, and an extension of the biosimilars concept, might be helpful in overcoming regulatory hurdles.

Allergen-specific immunotherapy and allergy diagnostics (including pharmacogenomics as applied to drug allergies) represent excellent examples of moving toward the goal of patient personalized, stratified medicine. The pharmaceutical industry and industry in general (e.g., the food industry) should become more involved in tackling and solving many problems connected with allergy.

Education

Although there has been tremendous progress in many fields of research, there is still a huge gap between existing knowledge and its effective application for the benefit of affected individuals (3, 14, 15). Therefore, one working group dealt specifically with the topic of education addressing the needs and methods to approach them.

Allergic diseases are caused by environmental exposures, can affect many organs, and can afflict individuals of all ages. It is therefore appropriate to engage with many different interest groups in order to improve education in allergy (14). Besides the scientific community and allergists, other physicians who treat patients with allergic disorders, including dermatologists, ENT specialists, gynecologists, rheumatologists, and anesthesiologists, as well as general practitioners, primary care providers, and emergency medicine specialists, need to be provided with essential know-how and basic skills in managing allergic diseases. Patient advocacy groups and industry organizations also need to be engaged in this effort. The tools of education to be deployed include congresses, seminars and courses, as well as print and electronic media, including new social media.

- For physicians, allergy education must start during medical school. This will require improving the curriculum at university medical schools, particularly in the many countries which do not include allergology as a medical specialty (2, 7).

- Allied health personnel and other professionals (e.g., nurses, pharmacists, nutritionists, psychologists, teachers, and nursery attendants) should also be engaged. Indeed, consideration should be given to the development of new professional careers for allied health personnel, such as 'allergy nurse', 'allergy nutritionist/dietitian', or 'allergy social worker' (for visiting families at home).
- To reach the general public and those making decisions regarding health policy and in the areas affecting the allergen content in indoor and outdoor environment, there should be effective and ongoing cooperation with patient organizations. This requires effective coordination of the resources and information that is made available to patient advocacy groups, which should be provided in language that is understandable by interested lay people, as well as cooperation with such groups in the development of campaigns to increase awareness about allergies among policy makers, the health care and insurance industries, and the general public.
- Patients and their families need more information about allergies than what typically is available in the allergist's office. Therefore, educational programs such as 'asthma schools', 'eczema schools', or 'anaphylaxis schools' have been developed in Germany and other countries and should be further promulgated. Similar educational programs should be developed and made available for those with other allergic diseases.
- In all educational activities, it should be recognized that not all physicians are good teachers (16); they have to be trained in order to provide adequate education. Therefore, specific 'train-the-trainer' seminars should be organized in order to provide a high degree of effectiveness, standardization, and quality control in educational activities in allergy. In all of these activities, the special needs of patients, families, and caregivers in emerging countries have to be considered to a much greater extent than is now the case.

Conclusion

In summary, allergic disorders now affect approximately one billion people worldwide, and both our understanding of disease origin and the development of truly curative therapies have proved to be challenging and elusive goals. Moreover, we know little or nothing about how to prevent the development of allergic diseases. Yet the tools that can now be deployed to solve these problems have never been more powerful. This gives the group hope that, with appropriate and sustained allocation of resources and persistent coordinated effort among allergists and other healthcare professionals and scientists, patients and their advocacy groups, and policy makers and governmental agencies, the problem of allergy ultimately will be solved.

Conflicts of interest

All authors have no conflicts of interest to declare.

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