A conversation on allergy

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PERSPECTIVE

OPEN

A conversation on allergy: recognizing the past and looking to the future

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Abstract

Allergy is an ever-evolving group of disorders, which includes asthma, atopic dermatitis, rhinitis and food allergies and that currently affects over 1 billion people worldwide. This group of disorders has exploded in incidence since around the start of the 20th century, implying that genetics is not solely responsible for its development but that environmental factors have an important role. Here, Fabio Luciani and Jonathan Coquet, in their role as editors at *Immunology & Cell Biology*, asked nine prominent researchers in the field of allergy to define the term 'allergy', discuss the role of genetics and the environment, nominate the most important discoveries of the past decade and describe the best strategies to combat allergy at the population level going forward.

Erik Melén conducts epidemiological studies on the development of respiratory and allergic diseases.
Bart Lambrecht is interested in understanding innate and adaptive mechanisms that drive the progression of allergic disease.
Clare Lloyd studies pulmonary immunity across the life span.
Marc Rothenberg is interested in uncovering the mechanisms of allergic inflammation with a focus on eosinophilic diseases.
Kenji Kabashima's core interest is in the pathogenesis and treatment of atopic dermatitis.
Carole Ober leads studies on the genetics and epigenetics of asthma.
Martijn Nawijn studies allergic responses especially in the context of the lung.
Thomas Platts-Mills conducts studies into how allergens can drive different forms of allergic inflammation and disease.
Erika von Mutius is the coordinator of the farm studies ALEX, EFRAIM, GABRIEL, PASTURE and a PI of the Amish–Hutterite comparison.

1. WHAT IS ALLERGY?

The definition of allergy has changed over the last century and will probably continue to evolve with time. When hypersensitivities increased in frequency in the second half of the 19th century, there came a quest to understand the mechanism behind these reactions. A breakthrough came in 1921 when Prausnitz and Kustner[1] established that immediate hypersensitivity could be transferred from blood serum of an allergic individual into the skin of a nonallergic individual—spawning the so-called Prausnitz–Küstner (PK) test. It was this phenomenon that both Kimishige and Teruko Ishizaka in the United States, and Johansson and Bennich in Sweden were studying, which led to the discovery of immunoglobulin E (IgE) and the development of assays for allergen-specific IgE detection between 1965 and 1967.[2–5] These discoveries remain the cornerstone of what we currently consider to be the 'typical' allergic immune response—a rapid inflammatory event mediated by IgE.

Since then, our understanding of the allergic immune response and allergic disease has continued to evolve. Cell-mediated immune responses involving communication between dendritic cells, T cells and innate lymphoid cells induce the production of so-called type 2 cytokines including interleukin (IL)-4, IL-5 and IL-13.[6] These can not only amplify the production of IgE by B cells but also drive distinct allergic pathologies including itch, eosinophilia, smooth muscle cell thickening/contractility, mucus production and epithelial hyperplasia[7] by various mechanisms. Increasingly, the physical disruption of epithelial barriers at the skin, throat, airways and intestines is thought to play an important role in allergen sensitization and allergic disease.[8]

At this point in time, we can say that allergic immune responses appear to be caused by a disruption in epithelial barrier integrity and are marked by type 2 immune responses (both cell-mediated and humoral) to substances that would often be considered nonhazardous (Figure 1). Allergic disease occurs when this response becomes uncontrolled.

2. ALLERGY IS CAUSED BY A COMBINATION OF GENETIC AND LIFESTYLE/ENVIRONMENTAL FACTORS. ARE THESE BOTH SUFFICIENTLY ACKNOWLEDGED AS PLAYING AN IMPORTANT ROLE?

Simply put, both genetic and environmental factors play a clear role, but seldom are the two analyzed side-by-side.

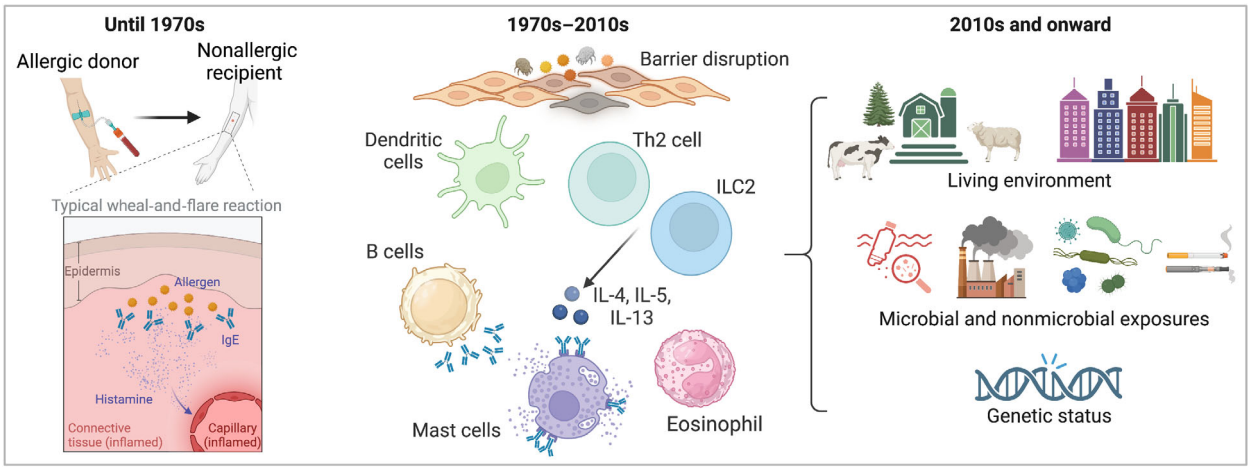

Figure 1. Understanding of allergic disease over time. From work conducted in the late 19th century and up until the 1970s, it became clear that the allergic response to allergens such as ragweed pollen was mediated by soluble mediators including antibodies of the subclass immunoglobulin E (IgE), which could be isolated from the blood of allergic patients. Since around the 1970s, the cellular components of the allergic immune response have been deciphered. We have come to appreciate that allergic disease often involves the disruption of epithelial barriers and a coordinated innate and adaptive immune response which is centered on the production of type 2 cytokines by CD4 T cells and innate lymphoid cells (ILCs), and the inflammatory activity of innate cells including eosinophils and mast cells. In that time, we have also come to appreciate that environmental factors play an important role in driving allergic disease. Now, and looking toward the future, the field needs to better understand precisely how lifestyle and environmental factors impact on allergic immune responses on the backdrop of a detailed genetic understanding of the human population. IL, interleukin; Th2, T helper type 2. Created with BioRender.com.

Large genome-wide association studies have uncovered single-nucleotide polymorphisms (SNPs) in coding and noncoding regions of many genes, which on their own have small effect sizes on allergic disease.[9] However, these SNPs are often tied to specific biological processes such as barrier integrity, T-cell function and cytokine production, which implies that these few pathways are central to the allergic disease process. Moreover, **Martin Nawijn** observes that '*genetic factors associated with different allergic diseases have a very high degree of overlap*,[10] *which indicates that the altered biological response to the allergen driven by the genetic susceptibility is largely the same between different atopic disorders: these diseases share a common cellular and molecular mechanism*'.

When it comes to environmental factors, **Erika von Mutius** states that '*there are environments which very significantly protect from development of allergies in genetically similar populations. For example, investigations of traditional farm and other rural areas in Poland*,[11] *Karelia*,[12] *China*,[13] *South Africa*[14] *and the Amish versus Hutterites*[15] *comparison in the US, have revealed that a traditional farm environment protects from the development of allergy*.[16,17] *However, I have not seen any population-based study in which skin prick test rates go below 7% (equally in serum-based assays for the detection of allergen-specific IgE). I therefore assume that there is a genetic contribution, which cannot be overcome by environmental determinants*.'.

Thus, there are clear effects of genetics and of environment in published literature. What is missing are robust demonstrations of how genetic susceptibilities confer allergic disease in specific environments—so-called gene-by-environment (G×E) interactions—that may be applicable to the broader population. Allele frequency variation across ethnic groups, confounding factors in different study settings and challenges to demonstrate functional (biological) effects in complex traits such as allergy make G×E interactions difficult to study.[18]

Erik Melén offers the following: '*We have yet to define and identify combinations of genetic and lifestyle factors that jointly drive disease development and this has been more challenging than many of us thought. There seems to be no G×E interaction examples that are general or that (so far) may be used to effectively identify people at risk of developing allergy*.[19] *Using epidemiology frameworks, we may apply Rothman's causal models to understand this complex interplay, where a sufficient cause of disease is defined as "a complete causal mechanism" that "inevitably produces disease*.[20]*" Allergy would be a prime example of this theory where a "sufficient cause" is not a single, unique factor, but a minimum set of factors or events that, if present in a given individual, will produce the disease. The "sufficient cause" will be different depending on genetics, environmental context and timing (i.e. GxExtime*[21]*) – in its extreme forms unique to each and every individual*.'.

Thus, understanding how genetic susceptibilities impact on our responses to allergens, microbial exposures, cigarette smoke and pollutants and how the timing of exposures in our lifetimes can have protective or detrimental outcomes still requires exploration (Figure 1).

3. WHAT ASPECTS OF THE GENETICS OF ALLERGY REQUIRE MORE RESEARCH AND EMPHASIS?

Martijn Nawijn and Erika von Mutius both make the point that not all allergies are well studied. Research on asthma, rhinitis and atopic dermatitis dominate the scientific literature, but venom and food allergy, and anaphylaxis have not been studied in the same detail. Genetic analysis of rare allergic disorders, including life-threatening anaphylaxis, may reveal that these responses are caused by rare genetic variants.

To **Martijn Nawijn**, '*the most challenging aspect at this moment is to translate the genetics of allergy into a detailed understanding of the biological changes that are the consequence of the genetic susceptibility to the disease, and that are expressed in response to environmental factors triggering disease onset. Novel single-cell and multi-omic techniques, as well as the computational frameworks to analyze such datasets have been developed over the last decade, and the initial results of studies in small groups of patients pioneering this field are already very promising*.[22–28] *Well-powered studies using these methods will transform our knowledge of the disease process and strengthen our capacity to intervene at the inception of allergic disease, provide novel targets for curative treatment and support the transition to precision medicine for allergic diseases*.'.

Precision medicine was exactly where **Erik Melén and Marc Rothenberg** saw great potential going forward. Polygenic risk scores could identify individuals at high risk of developing specific allergies, while promising examples from the allergy literature demonstrate that transcriptomics signatures from nasal brushings or peripheral blood correlate with biological treatment response in asthma[29] or oral immunotherapy response in severe peanut allergy.[30] These applications are just beginning to emerge in the literature and more comprehensive studies are needed.

Bart Lambrecht and Carole Ober emphasized that genetic information could prove more informative if it was given a temporal context. Genetic polymorphisms may only confer allergic risk at certain times of life and it is important to understand the genetics of organ development, for instance in the lung, where growth factors are important for the development of the local

macrophage pool[31,32] and where waves of type 2 immune cell influx have been noted.[33] Is the longevity of such waves genetically encoded and does the length of these waves confer greater or lesser susceptibility for the establishment of allergic immunity?

Kenji Kabashima made the point that a deeper understanding of how genetic polymorphisms in barrier genes leads to disease still requires investigation. He points to the fact that mutations in Filaggrin (*FLG*) can lead to atopic dermatitis (characterized by abnormal skin inflammation) and ichthyosis vulgaris (characterized by dry, rough and scaly skin but without evident skin inflammation). Although these conditions can coexist in some individuals, how mutation of the same gene (i.e. *FLG*) gives rise to two distinct diseases remains unclear.

Lastly, **Clare Lloyd** observes that asthma is initially more common in boys but reverses after puberty when the prevalence and severity of symptoms becomes higher in women.[34] Moreover, changes in asthma symptoms in women coincide with times of hormonal change such as puberty, pregnancy and menopause,[35] implicating sex hormones in pathogenesis. In support of this, estrogens and androgens have been shown to modulate key immune processes, such as type 2 cytokine pathways.[36]

4. WHAT ASPECTS OF ENVIRONMENTAL FACTORS THAT CONTRIBUTE TO ALLERGY REQUIRE MORE RESEARCH AND EMPHASIS? IS THE IMPACT OF OUR MICROBIAL ENVIRONMENT, POLLUTION AND OTHER LIFESTYLE FACTORS EMPHASIZED ENOUGH?

Increasingly, research in our field is taking into account how our microbial and nonmicrobial environment may contribute to the development of allergic disease (Figure 1).

G×E interactions

There is a pressing need to understand how genetic polymorphisms affect our responses to infections, pollution or dietary factors. For instance, exposure to farm dust and endotoxin has been proposed to desensitize the airway epithelium to inflammatory stimuli, and a loss-of-function polymorphism in *TNFAIP3* (encoding the A20 protein) was associated with increased asthma risk in children that grew up on farms.[37] Likewise, polymorphisms in genes regulating innate immunity and metabolism[38] could contribute to how we respond to pollution and dietary factors, respectively. As many genetic associations have been made over the past two decades, uncovering the precise environments in which these polymorphisms result in allergic disease is now of utmost importance.

Microbes—The good, the bad and everything in between

Our microbial environment has a clear impact on allergy susceptibility, and yet, remains one of the most enigmatic areas of our field. Notwithstanding many studies that have associated the microbial environment with allergic sensitization and disease,[39] there is still an urgent need to determine the precise microbes that may exacerbate allergic disease, and those that may protect us from allergy.

Intervention studies with well-defined microbes are required. One example is a recent study monitoring immune modulation in infants supplemented with *Bifidobacterium infantis*,[40] which reduced T helper type 2 and T helper type 17 cytokine levels in circulation. Long-term follow-ups that assess allergy prevalence into adolescence and adulthood are desperately needed in such trials.

The relative roles of the lung, skin and gut microbiota are also unclear in different allergic conditions. Certain respiratory infections including respiratory syncytial virus, *Haemophilus influenzae, Streptococcus pneumoniae* may increase the likelihood of developing asthma,[41] but does the lung contain a commensal microbiota that may exert regulatory effects on inflammation? Similarly, at the skin barrier where *Staphylococcus aureus* is associated with atopic dermatitis, is *S. aureus* the cause or consequence of atopic dermatitis, and do skin commensals exist that could reduce the development of atopic dermatitis[42,43]? When it comes to the intestinal microbiota, is this most relevant when it comes to ingested antigens, or can it have large consequences on systemic immunity? Would it be capable of overriding the functions of lung-specific microbes (in asthma) or the skin-specific microbiota (in atopic dermatitis)?

We should also strive to better understand the composition of viruses, phages and fungi (and not just of bacteria) that colonize the human body. For all the improvements in genome sequencing and alignment of nonmammalian genetic material over the last decades, the classification of microbes from other kingdoms remains an important challenge.

Understanding the impacts of pollution

We need to come to a better understanding of pollutants in our environment that have detrimental effects in the context of allergy. What is a pollutant? Inhalable particulate matter (PM) measurements are often used to

stratify pollutants into particles of different sizes (i.e. $PM_{2.5}$ and PM_{10} for particles less than 2.5 and 10 μM in size, respectively). However, the molecular composition of these particles varies and could impact on whether they cause allergic immune responses and lead to disease. Recently, improved urban air quality was shown to improve lung function growth from childhood to adulthood.[44] Further investigations are needed to evaluate the potential health benefits of improved air quality on allergic diseases.

We are what we eat

Pinpointing the constituents of the most beneficial diets for avoiding allergy—whether its raw cow's milk, breast milk or other foods—and coming to a general understanding of the molecular characteristics and timing of consumption that makes food beneficial are important.

Addressing the impacts of food processing, especially for milk and wheat, is important. An example lies in the high-temperature processing and homogenization of milk, which has weaponized fat droplets to particles of approximately 200 nM in size, covered in Bos d 4, Bos d 5 and Bos d 8 and altered the allergenicity of milk.[45–47] Changes in the properties of fat particles in milk may be directly relevant to the dramatic increase in eosinophilic esophagitis among children who drink homogenized milk.[48,49]

Changes in lifestyle can have profound effects on our susceptibility for allergic diseases

Increasing our understanding of humankind's impact on the environment and how this can drive changes in allergy phenotypes is vital. An example of this is the rise in severe allergic responses to galactose-alpha-1,3 galactose (alpha-gal), a common constituent of products from nonprimate animals including beef and pork.[50,51] Sensitization to alpha-gal was shown to occur through tick bites, which are thought to have been carried by migrating deer populations. The migration of deer may have been due to the enactment of leash laws for dogs, a reduction in hunters and the movement of deer into urban areas.[52] This is only one example of how our lifestyle/behavior can alter our environment and influence the incidence of an allergic disease.

Understanding the health impact of climate change, with a focus on allergic diseases, is an area in need of attention.[53] Lengthening of the pollen season, extreme weather conditions and changes in humidity are examples of climate change issues that are impacting allergic diseases. Mitigation of these factors and curtailing climate change are important issues for the field.[54,55]

Exposures in the neonatal period are increasingly considered to be of particular importance when it comes to triggering allergic disease. Among these exposures, use of antibiotics and acid-suppressive medications in the perinatal period (e.g. maternal as well as infant exposure) are major risk factors for subsequent development of allergic diseases.[56,57]

Thus, both microbial and nonmicrobial environmental factors as well as lifestyle changes remain highly relevant fields of research to pursue when it comes to understanding allergic diseases.

5. WHAT ROLE DO YOU SEE FOR NONGENETIC BUT HERITABLE TRAITS (I.E. CROSS-GENERATIONAL TRAINED IMMUNITY MEDIATED BY INHERITED EPIGENETIC CHANGES IN GENE EXPRESSION) IN ALLERGIC DISEASE AND IS THIS GIVEN ENOUGH EMPHASIS?

Most experts consider nongenetic heritable traits as having a major impact in driving allergic disease. However, there is a lack of convincing studies in the human population that illustrate this point clearly. A recent study of male mice challenged with endotoxin showed that one dose of lipopolysaccharide could impact on immune responses two generations later,[58] inferring that endotoxin challenge induced changes in sperm that were heritable. In the human population, the epigenetic status of the nasal epithelium and blood is different in allergic *versus* nonallergic individuals.[59–61] It is evident that children born to mothers that smoked during pregnancy have several genomic loci with altered methylation patterns, but whether this can be inherited in subsequent generations remains unclear. Smoking in teenage boys has also been proposed to impact on sperm condition and alter the risk of producing allergic offspring.[62] With cigarette smoking having come into and out of the human population and with rates of vaping now rapidly increasing, there are at least opportunities to address the impact of smoking or inhaled tobacco on heritable nongenetic traits, but these studies will have to be well controlled to provide meaningful results.

6. HOW DO YOU SEE THE ROLES OF ANIMAL MODELS AND CLINICAL STUDIES IN ALLERGY RESEARCH? WOULD YOU LIKE TO SEE MORE EFFORTS MADE IN EITHER REALM?

Animal models go hand-in-hand with clinical studies but they could be optimized and combined with other approaches. Mice have proven to be valuable in

providing mechanistic insights into clinical observations, allowing us to develop various models of allergy that have been informative for analyzing type 2 immune responses and understanding the mechanism of action for the current batch of biologics that have entered the clinic. They are also useful for analyzing putative cell–cell interactions and have emphasized a role for type 2 innate lymphoid cells, where studies in humans would have struggled.

Several experts emphasized that animal models should be used to go where human studies cannot. To that end, they should be used for testing combinations of environmental factors, and could be used to a greater extent to incorporate genetic risk alleles[63,64]—this is an area of research that is still lacking. Until now, humanized mice have primarily been used to analyze the response to novel biologics, but they could also be used to understand basic biology of human allergy. One could envisage humanized mouse strategies where peripheral blood mononuclear cells (or $CD34^+$ cells) from patients with risk alleles (affecting the hematopoietic compartment) could be transplanted into mice, thereby allowing for analysis of human SNPs on the allergic immune response.

The need for organoids or tissue explant systems in allergy research was also emphasized. Mixed lineage organoid cultures to determine the impacts of allergens and pollutants on various cell types would be highly appealing. Moreover, lung organoids derived from patients carrying SNPs in *IL33* for example, or skin explants from patients with *FLG* mutations provide a way of studying G×E interactions in a well-controlled manner.

Clinical studies also hold much greater potential now than they once did. Technological advances have made multi-omics analyses more common. Combining genetic information with gene expression, response to therapy and so forth means that valuable mechanistic insights can also be extracted from well-conducted clinical studies.[65]

7. WHAT ARE THE MOST INTERESTING ADVANCES IN ALLERGY RESEARCH OVER THE PAST DECADE?

A number of meaningful advances have been made in the field of allergy research over the past decade, which have revolutionized the way we think about allergy and the treatment options for patients. These are summarized in Figure 2.

Oral tolerance comes to the fore

Thomas Platts-Mills, Erik Melén and Martijn Nawijn highlighted the success of early food introduction in the prevention of allergy. In light of the fact that food avoidance was the primary strategy to deal with food allergy for a large period, it took courage to conduct a clinical trial explicitly testing the impact of early food introduction, but that is exactly what researchers from the LEAP Study Team did to great effect.[66] That study showed that early introduction of peanut into the diet could prevent the development of severe allergic reactions in high-risk infants and these results have now been expanded to other solid foods with impressive results.[67,68] In addition, immune therapies to various allergens including pollens, dust mites and pet danders have become more commonplace and effective.[65]

Biologics that target type 2 cytokines are highly efficacious in allergic disease settings

The development of therapeutics that target molecules other than IgE has been a major breakthrough according to **Erik Melén**. Omalizumab (a monoclonal targeting IgE) was first approved for use in 2003 and demonstrated efficacy in moderate–severe asthmatics.[69–71] However, over the past decade, a new wave of biologics targeting the cytokines IL-4, IL-13, IL-5, IL-33, thymic stromal lymphopoietin (TSLP), IL-31 and/or their receptors have heralded a new age in the treatment of diseases including asthma, atopic dermatitis, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis and other diseases.[6,72,73] In line with the efficacy of several new biologics, we have come to a greater appreciation of endotypes of allergy, which greatly inform patient treatment options. Patients are no longer stratified only on the basis of IgE, but on the expression type 2 cytokines, levels of eosinophils, presence of airway inflammation (fractional exhaled nitric oxide) and on specific allergen reactivities.[74,75] The use of this information now as a predictive tool for response to therapeutics brings us closer to personalized therapy approaches.

Identifying the cellular players involved in allergy

Over the past few decades, we have come to understand the allergic immune response in its totality, in particular the cell–cell interactions and the contribution of innate and adaptive lymphocytes. Technological advances, for instance, in our ability to purify and analyze single cells, have given us a greater appreciation of B-cell evolution over time,[76] says **Bart Lambrecht**.

Marc Rothenberg nominated the finding that eosinophils are effector cells in a range of allergic diseases and the success of therapeutics targeting eosinophils as a major step forward in our understanding of allergy.[57] Moreover, the fact that many of these biologics targeting

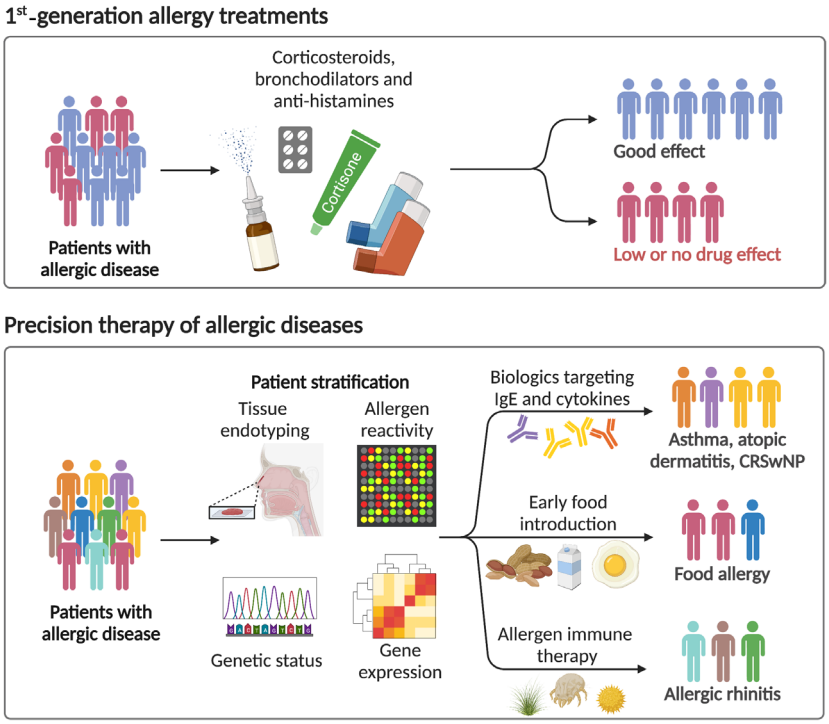

Figure 2. Moving toward personalized therapies of patients with allergic diseases. Antihistamines, corticosteroids and bronchodilators have long been used to treat patients with allergic disease, including asthma, hay fever and atopic dermatitis, and these remain frontline therapies today. Over the last two decades, a more targeted approach to the treatment of allergic diseases has begun to emerge. Allergen diagnostic arrays have improved immensely, while patient stratification on the basis of tissue endotyping, genetic status and whole genome expression has allowed for more precise insights into the patient population. This has led to the tailored use of biologics targeting immunoglobulin E (IgE), several cytokines and their receptors including interleukin (IL)-4, IL-13, IL-5, IL-33, IL-31 and thymic stromal lymphopoietin (TSLP) in several settings including moderate–severe asthma, atopic dermatitis and chronic rhinosinusitis with nasal polyps. Targeted allergen immune therapies have become commonplace for patients sensitive to pollens, dust mites and pet danders, while we have come to appreciate that early food introduction in infants from 3 to 6 months can build tolerance to foods with allergenic properties including peanut, milk and egg and reduce the incidence of food allergy including severe anaphylactic reactions. CRSwNP, chronic rhinosinusitis with nasal polyps. Created with BioRender.com.

type 2 immune responses are safe to use in humans over extended periods could not necessarily have been predicted.

Traditional living practices offer us protection from allergies

The confirmation of the protective effects of farm living continues to provide insights into the mechanism by which allergy develops. **Carole Ober, Clare Lloyd and Marc Rothenberg** all remind us of the seminal studies by von Mutius and colleagues[17] demonstrating protective effects of traditional farm living and more recent results from Stein and colleagues,[15] where they compared the prevalence of asthma and allergies in Amish and Hutterite populations, two genetically similar groups with similar lifestyles that deviate only in respect to their farming practices. This study found that inhalation of extracts from dust collected from Amish households (but not Hutterite) was sufficient to inhibit airway reactivity and eosinophilia in a mouse model of ovalbumin-induced allergic asthma, pointing to greater microbial exposures in Amish households. This is corroborated by other studies which have shown a protective effect of dust from cattle barns and of microorganisms such as *Acinetobacter lwoffii* in mouse models of airway hyperresponsiveness.[37,77]

Epithelial barrier integrity is a key piece in the allergy puzzle

Kenji Kabashima highlighted how disruption of the epithelia barrier is now considered a key factor in the development of allergic diseases. Following on from observations of loss-of-function mutations of the *FLG* gene in atopic dermatitis in the 2000s,[78] germline *FLG* mutations were also implicated in nonskin allergies including asthma, which implicated the skin barrier as a

point of susceptibility for systemic allergic responses. Other associations in genes typically expressed by epithelial cells including *IL33* were also made in the setting of asthma,[79] while **Marc Rothenberg** highlighted another important gene *CAPN14*, a protease expressed by epithelial cells of the esophagus. Variants in *CAPN14* were found in patients with eosinophilic esophagitis and transcription of *CAPN14* was found to be regulated by IL-13, highlighting that type 2 immune responses may elicit tissue-specific inflammatory responses dependent on underlying genetic susceptibilities.[80]

8. WITH ALLERGY PREDICTED TO AFFECT 4 BILLION PEOPLE BY 2050, HOW CAN WE PREVENT THE RISE IN ALLERGIES GLOBALLY? WHAT ARE THE CRITICAL QUESTIONS THAT NEED TO BE ADDRESSED NOW?

Treatment of patients with allergy

We are now in a position where we have evaluated a new raft of very promising biologics, which have greatly improved quality of life in patients with a broad range of allergies. However, a clear unmet need going forward is the need to find a cure beyond allergen immunotherapy, because in essentially all patients with manifest disease where therapy is withdrawn, patients do relapse. Completely new therapeutic targets are needed and existing drugs could be repurposed to target nonresponding patient populations. Effective patient stratification and early detection of clinical endotypes will also ensure that patients can be treated with the most effective drugs at the earliest possible time. These interventions may lead to curative therapies of allergy, even once it has taken hold. A good example comes from the autoimmune condition type 1 diabetes, where a monoclonal antibody targeting T cells was shown to significantly delay the progression of disease in children.[81]

Preventing the onset of allergy

Perhaps the ultimate gains can be made in preventing allergy in the first place. Achieving beneficial immune modulation early in life will require substantial investment from public and private health systems. The Finnish Allergy program has taught us that allergy prevention is possible through a multifaceted approach—by promoting biodiversity, strengthening tolerance (e.g. by oral immunotherapy) and reducing harmful exposures. Using the Finnish approach, food/allergen avoidance is only implemented if absolutely necessary as they look to maximize exposures that may benefit the human population.[82,83] The need to identify protective and harmful factors still exists and human exposure to these agents ideally needs to be tested in epidemiological and intervention studies. Preventing passive smoking, improving air quality and increasing our diversity of food consumption will likely prove important. Controlling barrier function at an early age will also likely play a role, and intervention studies with agents that can improve barrier health in early life are still needed. Vaccination strategies to allergens could even be deployed, especially in light of recent advancements in technologies for vaccine manufacturing and delivery, which limit production time, cost and side effects. For allergy prevention to prove successful on the global scale, it will require not only extensive collaboration, but also for these studies to be executed in both developed and developing nations.

Toward a holistic understanding of allergy

Ultimately, fundamental challenges still exist in understanding allergic immune responses and allergic disease. If history has taught us something, it is that dogmas in our field have the potential to hold us back. One potential example is the case of IgG4—this subclass of antibody is often proposed as an anti-inflammatory antibody in allergen immunotherapy, but high levels of allergen-specific IgG4 in patients with eosinophilic esophagitis suggest that this class of antibodies may play other roles.[49] Thus, we should understand the history of allergic disease but remain open to new features of allergic disorders in the future. The relationship between changes in lifestyle and different forms of allergy will need to be clearly dissected if we want to find a cure and better preventative approaches. Lastly, the impact of humans on the planet's climate and pollution level is an incontrovertible factor that will determine the prevalence and severity of allergy over the coming decades.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Erik Melén: Resources; writing – original draft; writing – review and editing. **Bart N Lambrecht:** Writing – original draft; writing – review and editing. **Clare M Lloyd:** Writing –

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