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REVIEW ARTICLE

Navigating the evolving landscape of atopic dermatitis: Challenges and future opportunities: The 4th Davos declaration

Claudia Traidl-Hoffmann[1,2,3] | Jamie Afghani[1] | Cezmi A. Akdis[3,4] | Mübecel Akdis[4] | Handan Aydin[5] | Katja Bärenfaller[4] | Heidrun Behrendt[6] | Thomas Bieber[3,7] | Paul Bigliardi[8] | Mei Bigliardi-Qi[8] | Charlotte Menné Bonefeld[9] | Stefanie Bösch[10,11] | Marie Charlotte Brüggen[3,10,11] | Sebastian Diemert[12] | Hans-Werner Duchna[3,13] | Martina Fähndrich[14] | Danielle Fehr[3,10,11] | Marc Fellmann[15] | Remo Frei[3,16,17] | Lena H. Garvey[18,19] | Raschid Gharbo[20] | Mehmet Gökkaya[1,2] | Karin Grando[3,10,11] | Carole Guillet[10,11] | Erman Guler[21] | Jan Gutermuth[22] | Nadine Herrmann[23] | Dirk Jan Hijnen[24] | Claudia Hülpüsch[1,2,3] | Alan D. Irvine[25] | Erika Jensen-Jarolim[26,27] | Heidi H. Kong[28] | Hillel Koren[29] | Claudia C. V. Lang[3,9,10] | Roger Lauener[30] | Laura Maintz[23] | Pierre-Yves Mantel[3] | Emanuel Maverakis[31] | Matthias Möhrenschlager[13] | Svenja Müller[23] | Kari Nadeau[32] | Avidan U. Neumann[1,2] | Liam O'Mahony[33,34] | Fahafahantsoa Rapelanoro Rabenja[35] | Harald Renz[36] | Claudio Rhyner[3] | Ernst Rietschel[3] | Johannes Ring[37] | Caroline Roduit[16,30] | Mari Sasaki[16] | Mirjam Schenk[3,38] | Jens Schröder[39] | Dagmar Simon[40] | Hans-Uwe Simon[41,42] | Milena Sokolowska[3,4] | Sonja Ständer[43] | Martin Steinhoff[44,45,46,47,48,49,50] | Doris Straub Piccirillo[3] | Alain Taïeb[51] | Roberto Takaoka[52] | Martin Tapparo[53] | Henrique Teixeira[22] | Jacob Pontoppidan Thyssen[54] | Stephan Traidl[55,56] | Miriam Uhlmann[3] | Willem van de Veen[4] | Marianne van Hage[57] | Christian Virchow[58] | Andreas Wollenberg[59,60,61] | Mitamura Yasutaka[4] | Alexander Zink[62,63] | Peter Schmid-Grendelmeier[3,9,10]

Abbreviations: AA, alopecia areata; AD, atopic dermatitis; AGS, galactose-α1,3-galactose (α-Gal) syndrome; AMPs, antimicrobial peptides; AS, ankylosing spondylitis; CGRP, calcitonin gene-related peptide; CIDAMPs, Cationic Intrinsically Disordered Antimicrobial Peptides; CNS, central nervous system; CRSWNP, chronic rhinosinusitis with nasal polyps; EE, eosinophilic esophagitis; ETFAD, European Task Force on Atopic Dermatitis; EH, eczema herpeticum; FLG2, filaggrin-2; GAAD, Global Atlas on Atopic Dermatitis; GAF, the 4th Global Allergy Forum; HBD2, human beta-defensin 2; HRNR, Hornerin; HSV, herpes simplex virus; IEC, International Eczema Council; IL, interleukin; ILC, Innate lymphoid cells; JAKi, janus kinase inhibitors; LCEs, late cornified envelope proteins; MOOCs, Massive Open Online Courses; Nr-SpA, non-radiographic ulcerative colitis; PACAP, pituitary adenylate cyclase-activating polypeptide; PN, prurigo nodularis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, axial spondyloarthritis; TARC, thymus and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin; VT, venous thromboembolism; WHO, World Health Organization.

For affiliations refer to page 2618.

Correspondence
Claudia Traidl-Hoffmann, Institute of Environmental Medicine and Integrative Health, Faculty of Medicine, University of Augsburg, Augsburg, Germany.
Email: claudia.traidl-hoffmann@med.uni-augsburg.de

Abstract

The 4th Davos Declaration was developed during the Global Allergy Forum in Davos which aimed to elevate the care of patients with atopic dermatitis (AD) by uniting experts and stakeholders. The forum addressed the high prevalence of AD, with a strategic focus on advancing research, treatment, and management to meet the evolving challenges in the field. This multidisciplinary forum brought together top leaders from research, clinical practice, policy, and patient advocacy to discuss the critical aspects of AD, including neuroimmunology, environmental factors, comorbidities, and breakthroughs in prevention, diagnosis, and treatment. The discussions were geared towards fostering a collaborative approach to integrate these advancements into practical, patient-centric care. The forum underlined the mounting burden of AD, attributing it to significant environmental and lifestyle changes. It acknowledged the progress in understanding AD and in developing targeted therapies but recognized a gap in translating these innovations into clinical practice. Emphasis was placed on the need for enhanced awareness, education, and stakeholder engagement to address this gap effectively and to consider environmental and lifestyle factors in a comprehensive disease management strategy. The 4th Davos Declaration marks a significant milestone in the journey to improve care for people with AD. By promoting a holistic approach that combines research, education, and clinical application, the Forum sets a roadmap for stakeholders to collaborate to improve patient outcomes in AD, reflecting a commitment to adapt and respond to the dynamic challenges of AD in a changing world.

KEYWORDS
allergy treament, atopic dermatitis, barrier, environment, hygiene hypothesis

1 | INTRODUCTION

Atopic diseases such as atopic dermatitis (AD), allergic rhinitis, asthma and food allergy are common and debilitating conditions that affect people of all ages. They are considered to represent one of the most prevalent non-communicable disease spectrums worldwide and are frequently under-recognized by primary care professionals.[1–3] The resulting inadequate treatment poses unnecessary suffering for patients, especially in lower-income groups who often may not have access to adequate treatments and a worse prognosis due to increased severity and chronicity.[4] Atopic diseases reduce the patients' quality of life and pose substantial socioeconomic burdens on both society and the individual. AD is one of the most prevalent atopic diseases. The first manifestations of AD usually appear early in life and often precede other allergic diseases. Therefore, AD is considered the gateway to other allergic diseases. Currently, there is no cure, but the increasing numbers of innovative and targeted therapies hold promise for achieving disease control, including in patients with recalcitrant disease.[5,6] To address these concerns, the 4th Global Allergy Forum (GAF) was held, with a focus on AD. The forum covered a wide range of topics, including education and issues related to neuroimmunology, immunology, environmental factors, comorbidities, prevention, diagnosis, and treatment. The forum brought together experts from various specialties to discuss the latest research and advancements in the field and identify gaps or unmet medical needs. The key messages of the GAF were that atopic diseases are increasingly prevalent and are becoming a greater public health problem because broad environmental changes, including climate change, pollution, physio-chemical exposures, lifestyle, and psychosocial factors, are increasingly shown to act as drivers of these common diseases.[7,8] Simultaneously, our knowledge of atopic diseases has expanded dramatically such that we now have new targeted therapies based on improved insight into the pathogenesis and concrete approaches for prevention and disease modification.[9] This growing knowledge contrasts with the reduced focus on the successful implementation of these new and effective forms of therapy into clinical practice. In addition to extending our understanding of the pathophysiology of atopic diseases and developing therapeutic and preventative strategies, there was consensus that greater awareness, education, and translational research on implementation are needed. The forum also highlighted the importance of addressing the underlying causes of atopic diseases, such as passive environmental factors (e.g., air pollution, chemicals in food and

water, etc.) and active lifestyle choices to effectively manage or better prevent disease.

Overall, the GAF was an invaluable opportunity for experts and researchers to convene and discuss the latest developments and challenges in the field of atopic diseases. This platform allows for the sharing of knowledge and ideas and for identifying high-yield areas for further research and is crucial for advancing the diagnosis, treatment, and management of atopic diseases. The ultimate goal is to improve the health and resilience of people who face these challenges in a changing world.

After each GAF, a Davos Declaration is developed to disseminate knowledge and information on the topics discussed during the GAF. Previously, Declarations covered, including but not limited to, the need for interdisciplinary research on allergy and AD development,[1] prevention strategies for allergic diseases,[2] and the building of patient registries as the underpinning for precision medicine.[3] For this Declaration the latest research on the environmental, immunological, and neurological influences on AD development was highlighted, and new strategies for education, prevention, and global- and individual-centered care were discussed. The main messages and identified gaps in AD and allergic diseases from the 2022 GAF are summarized below:

2 | EPITHELIAL BARRIER MAINTENANCE AND DISTURBANCES IN ATOPIC DISEASES

2.1 | Definition of the epithelial barrier

The epithelial barrier is one of the first interfaces between humans and their external environment and is a necessary adaptation for terrestrial life.[10,11] Epithelial tissue has several functions, including (1) Barrier, (2) Secretion, (3) Excretion, (4) Absorption, (5) Filtration, (6) Diffusion, and (7) Sensing. For over two decades, the interactions between the epithelial barrier and the immune system have been investigated.[12] Skin barrier-related genes and their proteins, such as filaggrin, play a pivotal role in the formation of the cornified envelope in the stratum corneum. Mutations in the filaggrin gene and low copy numbers of filaggrin which lead to lower protein expression have been identified in patients with AD.[13] In addition, filaggrin's organic acid breakdown products contribute to the acidic skin pH, which is important for the skin barrier, with rises in skin pH observed in filaggrin-mutant AD.[14] An extensive epithelial barrier hypothesis has been proposed to explain the sharp increase in many chronic noncommunicable inflammatory diseases including AD in the last 60 years.[15] It proposes that environmental exposure to certain substances (e.g., detergents, food emulsifiers) causes defective, or "leaky," epithelial barriers, contributing to allergies and other chronic diseases. As an early event, the impairment of the epithelial barrier results in the release of alarmins, followed by microbial alterations and potential translocation of the commensal bacteria and pathogenic or bacterial products to deeper tissues.[11,15]

2.2 | The role of the skin barrier in the pathogenesis of AD

Recent environmental changes have now exposed the skin barrier to man-made exogenous stressors, with which the skin is functionally unsuited to cope. These exposures occurred primarily in the second half of the 20th century in industrialized regions but have expanded globally as a result of climate change and global industrialization. This daily exposure to a variety of toxins and chemicals can lead to a dysfunctional skin barrier, which is highly relevant to allergic diseases, especially AD. Many studies have demonstrated epidemiological evidence linking the development of AD to direct detergent exposure,[15–17] and important changes in the epidermal lipid structure are observed in healthy infants before onset of AD.[18] Barrier alteration may also occur following domestic exposure to "hard water", notably in individuals with filaggrin gene mutations[19] pointing to an important gene–environment interaction.

2.3 | Skin immunity: Innate and adaptive responses and trained immunity

AD is dominated by a Th2 immune response in the skin, with additional yet varying contributions by the Th1, Th17, and Th22 immune pathways, as previously reviewed (Figure 1).[20–22] Activated Th2 cells release cytokines, mainly Interleukin (IL)-4 and IL-13, into the skin. These cytokines contribute to skin barrier dysfunction by suppressing the expression of barrier proteins, such as filaggrin.[23–25] More recently, there is growing evidence that IL-13 may play a more prominent role than IL-4 in the pathogenesis of AD with suggestions that IL-13 is the key driver for AD pathology.[26] Both cytokines, IL-4 and IL-13, use the Type 2 IL-4 alpha receptor. Based on prior datasets showing increased IL-13 gene expression in AD skin, the expression of IL-13 was negatively correlated with skin barrier function genes, and blocking IL-13 with tralokinumab reversed IL-13-induced reduction of skin barrier-related genes expression in vitro (Figure 3).[25] Blocking IL-4 and IL-13 signaling has been shown to improve the clinical signs of AD, including skin barrier function.[27–30] Early interventions to maintain the skin barrier may be essential to prevent epicutaneous antigen presentation and subsequent development of other allergic diseases, such as food allergy.[31,32] However, when treatment is interrupted, the disease frequently relapses, suggesting the presence of memory cells in the skin and other pathogenic innate and adaptive immune mechanisms. Single-cell RNA-seq analyses of AD skin revealed detailed cell types and their activity[33,34] and showed the persistence of Th2A cells, mature dendritic cells, and cytotoxic cells that persist even after 1 year of treatment.[33] In addition, the presence of innate lymphoid cells (ILC) and the inflammatory or innate memory of the epithelial stem cells in the skin raises the concept of a potential role for these cells in the persistence of the inflammatory lesions in AD.[35,36] For example, inflammatory genes in these epithelial progenitor cells were activated more easily via secondary

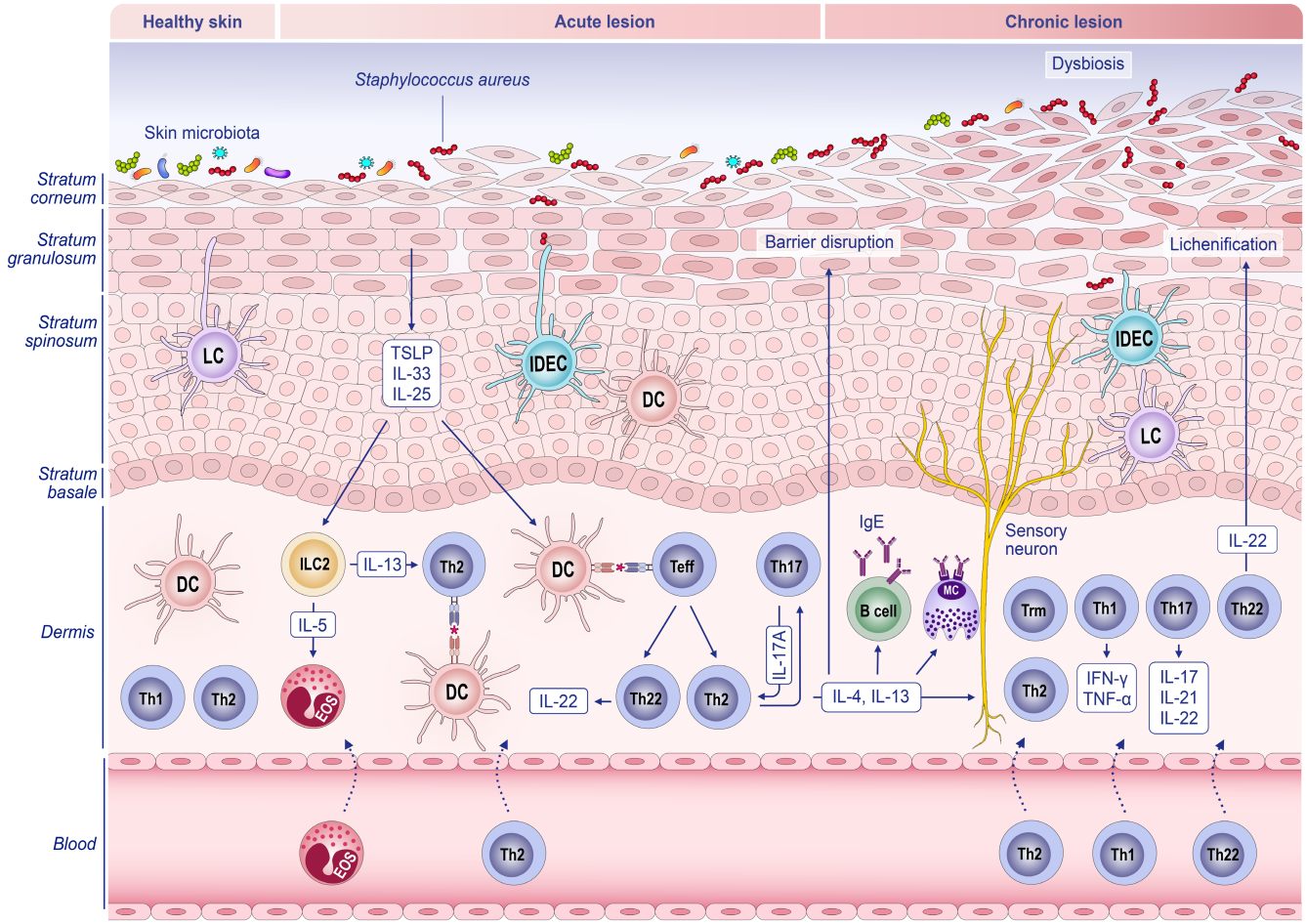

FIGURE 1 Pathogenesis and mechanisms of atopic dermatitis (AD). Skin barrier disruption and Th2/Th22-deviated immune reactions are central abnormalities in AD. The barrier-disrupted epidermis releases abundant IL-33 and thymic stromal lymphopoietin (TSLP), which activate dendritic cells and innate lymphoid cells (ILC), and then trigger the Th2 immune response. Th2/Th22 deviation is then further accelerated during disease progression. Th1 and Th17 inflammation can be found in the chronic phase of AD. In addition, Th2 cytokines (IL-4 and IL-13) stimulate B cells to produce IgE antibodies against allergens. IgE binds on the surface of mast cells (MC) and sensitizes them. Th2 cytokines such as IL-13 and IL.-31 promotes itch, while IL-5 induces eosinophil production and activation.

and unrelated stimuli due to epigenetic and metabolic changes leading to the alterations in chromatin accessibility.[37]

2.4 | Antimicrobial defenses in the skin

Constitutively produced and induced upon infection and skin injury, antimicrobial peptides (AMPs) represent the first line of defense to protect the skin from microbes. Differential expression of keratinocyte-derived AMPs, such as human beta-defensin 2 (HBD-2), HBD-3, LL-37, RNase7, and psoriasin, in AD skin as compared to healthy individuals and psoriasis patients are thought to contribute to the association of *Staphylococcus aureus* (*S. aureus*) and herpes simplex viral infections in AD.[38–44] The stratum corneum is also a source of "Cationic Intrinsically Disordered Antimicrobial Peptides" (CIDAMPs).[45] Major CIDAMP sources are hornerin (HRNR), filaggrin-2 (FLG2), late cornified envelope proteins (LCEs),[46] and the spacer regions of filaggrin. Whereas CIDAMPs express potent bactericidal activity at acidic pH, mainly towards gram-negative bacteria, palmitoylated CIDAMPs are highly potent *S. aureus*-cidal AMPs. CIDAMPs kill bacteria, like aminoglycosides, by targeting ribosomal proteins.[46] *S. aureus* secretes extracellular proteases, such as V8, or "SspA", which cleave extracellular proteins to impair the skin barrier and potentially mediate itch.[47] Studies have demonstrated that HBD-2 prevents V8-mediated damage.[48]

2.5 | Skin metabolism

Proper cell function depends on the efficient use of various metabolic pathways and on the availability of glucose, amino acids, lipids, minerals, and oxygen,[49] each of which are disrupted in AD and previously reviewed.[50] Inflammation in AD lesions is characterized by keratinocyte hyperproliferation and the expansion of inflammatory cells which suggests specific metabolic reprogramming of the skin.

AD patients show increased levels of circulating lactate which indicates a metabolic shift toward the anaerobic glycolysis pathway.[51] As indicated by gene expression signatures, the glycolysis pathway is also differentially altered in AD lesions as compared to lesions in discoid lupus erythematosus.[52] On the other hand, oxidative phosphorylation characterizes non-lesional skin in AD compared to healthy control. Lipid metabolism also plays an important role in the pathogenesis of AD.[53] Anti-IL-4/IL-13 treatment, that is, dupilumab, treatment can change the metabolome of AD lesions with clinical responders demonstrating pathway enrichment in glycerophospholipid metabolism and the TCA cycle.[54] These metabolism markers could be integral to resolving AD; for example, gut-derived short-chain fatty acids can improve the integrity of the epidermal barrier, early allergen sensitization, and disease development in AD mouse models.[55]

2.6 | The sensory and adaptive roles of the skin barrier

The crosstalk between type 2 skin inflammation, neuroimmune dysfunction, and skin barrier dysfunction are prominent features of human AD pathobiology and eventually lead to chronic itch in AD.[56] During cutaneous neurogenic inflammation observed in both chronic pruritus and AD, somatosensory afferent nerve fibers are activated by itch-inducing mediators which are released by a variety of different cells in the skin, including damaged keratinocytes and immune cells such as T-cells, dendritic cells, basophils, mast cells, eosinophils, and ILC2. Many cytokines and pathways are involved in skin inflammation and itch, in particular type 2 cytokines including IL-4, IL-13, and IL-31, and the alarmins IL-33 and thymic stromal lymphopoietin (TSLP) (Figure 1). IL-4, IL-13, and IL-31 contribute to the persistence of itch by directly interacting with sensory neurons to sensitize them and induce itchiness.[45,57] IL-33 is elevated in AD and chronic pruritus, with signaling from the IL-33 receptor on sensory neurons being necessary for inducing itch.[46,58] Recently, Keren et al. reported that humanized mice[48,59] showed characteristic neuro-immunological abnormalities such as β2-adrenergic receptor downregulation with barrier dysfunction. The presence of chemical contaminants in epithelial tissue is associated with hypersensitivity, chronic inflammation, and oxidative stress, each of which leads to barrier defects in the epithelial tissues and affects the central nervous system.

3 | ENVIRONMENTAL CHANGES AS A DRIVING FORCE OF ATOPIC DISEASES

Understanding and combating atopic diseases requires a deeper consideration of the exposome, which is defined as one's exposures over a lifetime and how those exposures relate to one's health. The concerning rise in atopic diseases is strongly linked to environmental exposures on a background of genetic susceptibilities.[60] Increases in temperature, drought, wildfires, humidity, and pollution lead to higher outdoor exposures to pollen, molds, parasites, smoke, and insects, as well as secondary changes in the composition of the indoor exposome.[61] Air pollution—as a component of the exposome—contributes to changes in the global climate and vice versa and exacerbates allergic diseases, particularly asthma and AD.[62] Thus, the components of the exposome as well as the timing of these exposures whether early in childhood or later in adulthood are critical to studying and reducing the prevalence of atopic diseases.[63] Infant immune development is strongly influenced by host biology and the environment. The "hygiene hypothesis" suggests that reduced microbial exposure in industrialized countries impairs immune development. Global studies correlate early-life microbiota with atopy, but the exact mechanisms are still being explored.[48,64]

With warming climates, new allergens, for example, ticks and ragweed, are being introduced to previously less exposed regions. The Darwinian "survival of the fittest" theory portrays how invasive species outcompete the rich, diverse local fauna and flora, thereby massively changing the exposome.[65,66] The loss of biodiversity in the macro- and microenvironment is associated with an increase in atopic diseases.[64] An illustrative example of the effects of environmental changes on allergic diseases is the increase in the tick population which corresponded with the first tick bite-transmitted allergic disease, the galactose-α1,3-galactose (α-Gal) syndrome (AGS), commonly called "red meat allergy".[67] Patients with AGS have IgE antibodies to the carbohydrate α-Gal, which is transmitted by tick bites, and suffer from urticaria to life-threatening anaphylaxis after ingesting the carbohydrate α-Gal which is found in mammalian (red) meat or mammalian products.[68–70] The highly allergenic ragweed pollen (*Ambrosia artemisiifolia*) also reflects the effect of environmental changes as well as globalization on allergic diseases. Ragweed, an invasive flowering plant native to North America, has successfully expanded its presence across Europe and in particular within warmer climates, and is a source of concern for the increase of allergic diseases with warming temperatures.[71–75]

3.1 | Protective environmental factors

In parallel with climate changes, naturally protective nutritional and environmental factors that counteract the development of allergies are also endangered in an increasingly urbanized world. People living in more rural areas are incorporating features of urban lifestyles. Industrialization in farming and food processing has been important for expanding food supplies, and the establishment of requirements for hygienic processes has reduced potential contamination and the risk of infections. However, the so-called "farm effect" that comprises various environmental and microbial exposures has been linked to lower rates of allergic diseases.[76] Food processing is linked to higher immunogenicity and allergenicity of proteins such as those found in milk.[77] Understanding how industrialization contributes to atopic diseases and how biodiversity is linked to atopic diseases is vital for developing possible preventive or therapeutic modalities[78] or nutritional interventions.[79]

3.2 | Microbial aspects

The intricate relationship between the exposome and the host—particularly the cause-and-effect relationship between the microbiome and AD—remains complex and incompletely defined. One such connection between microbes and AD is skin pH: skin pH is elevated in AD[80] and the abundance of *S. aureus* in AD is correlated with a rise in skin pH.[81] The challenge in elucidating causality is that human microbiome studies tend to examine associations in which skin microbiome changes are described alongside AD progression and treatment efficacy yet typically do not provide evidence of causality. Of note, studies have shown that *S. aureus* can elicit skin inflammation thus highlighting the complexity of the relationship between microbes and AD.[82] In an infant cohort, reduced diversity of the skin microbiome at 2 months of age was predictive of subsequent development of AD in early childhood.[83] Further longitudinal human studies with standardized skin microbiome protocols should be conducted, addressing (a) a deeper understanding of the skin microbiome and (b) its potential use for personalized medicine in the future.

4 | CONCEPT OF IMMUNOLOGICAL MARCH ALONG THE COURSE OF AD

4.1 | Physiological development of the immune system versus immunological march in AD

The immune system is a dynamic construct that is constantly exposed and reacting to a variety of external and internal signals. During one's lifetime, even before birth, the immune system undergoes physiological development with an early-life education. This is followed by a robust, balanced immunity which includes an age-dependent appearance of various cell types, expression and function of pattern recognition receptors on antigen-presenting cells, and immunological responses classified as T helper cell and regulatory T responses based on specific cytokine profiles (Figure 2 and reviewed in[84]). In contrast to this physiological development and age-related changes in immunity, immunological differences have been described during the course of AD, starting with the activation of the local innate immune system in the skin and followed by a Th2 dominant adaptive immune response. In fact, the increased epidermal levels of thymus and activation-regulated chemokine (TARC) in healthy infants predict the later onset of AD.[85] Of note, distinct Th1, Th17, and Th22 responses of varied intensities, centered around an initial core Th2 response, have been observed in studies performed in children, adolescents, and adults suffering from AD. The age-dependent increase of IFN-γ/Th1 in healthy children and adults (0–40 years) is absent or mostly obscured by the Th2 dominance in AD children.[86] While IL-13 and TARC are highly elevated in AD patients as compared to controls in all age groups, a steady increase of IL-6, IL-17A, and IL-22 with increasing age was observed in AD patients, whereas controls had constant or even decreased levels of these cytokines at ages less than 60-years-old.[87] Thus, these series of immune deviations observed across different age groups in AD – termed the "immunological march"—clearly differ from physiological immune development.

A major gap in understanding the immunological march in AD exists because the majority of the data has been drawn from the cross-sectional studies of specific age groups that reflect certain characteristics of AD. To understand both the physiological immuno-development and the pathological deviations of the immunological march in AD patients, future longitudinal studies in patients are essential.

The term "atopic march" describes the development of AD followed by the clinical onset of other Th2-related atopic comorbidities such as allergic asthma, allergic rhinitis, food allergy, and eosinophilic esophagitis (EE) in distinct subgroups of patients.[88] However, necessary information on the detailed dynamics of the immunological march, its players, and a clear mechanistic link to the clinical trajectories of AD, including atopic march, is still missing. While epicutaneous sensitization leading to Th2-comorbidities has been reported, the other mechanisms are still enigmatic.[89] One of the gaps that need to be addressed is the unclear role of IgE in AD, whereas the role of IgE is well documented in other Th2 comorbidities. The role of the Th2-induced class switch of B cells to IgE production and the impact of IgE-specificity remains to be elucidated. Unsatisfactory results of IgE-targeted therapeutic approaches, such as omalizumab, in AD, show the need for a deeper understanding and the subsequent potential of precision medicine.[90] Furthermore, the immunological mechanisms associated with spontaneous remission or late-onset AD remain to be understood. Recent epidemiologic studies demonstrated that childhood-onset AD had higher odds of having asthma, food allergy, and multiple atopic co-morbidities, yet lower odds of allergic rhinitis, than adult-onset AD.[91,92] Taken together, our understanding of the clinical link to the immunological march is still scarce. Several animal models of AD and other atopic diseases may allow insights into certain aspects of the underlying pathomechanisms.[93,94] However, to understand the complexity of a constantly developing and dynamic atopic diathesis, novel animal models are urgently needed. Studies in dog breeds (e.g., Westie, Beagle, or Boxer) that are genetically prone to develop AD, live in similar conditions as humans, and, thus, share a comparable exposome and lifestyle may in many aspects provide additional information on the development of AD.[95] Therefore, communication and collaboration between veterinarians and human basic scientists should be expanded.

4.1.1 | Intervention strategies for the restoration of the physiological immuno-development

Under physiological conditions, the development of the immune system is actively influenced by diet and gut-microbial signals, both of which shape the immune response to its "normal" state, that is, default development. On the other hand, the immunological mechanisms occurring in the skin, such as an impaired epidermal barrier and activation of the innate immune system, may lead to chronic

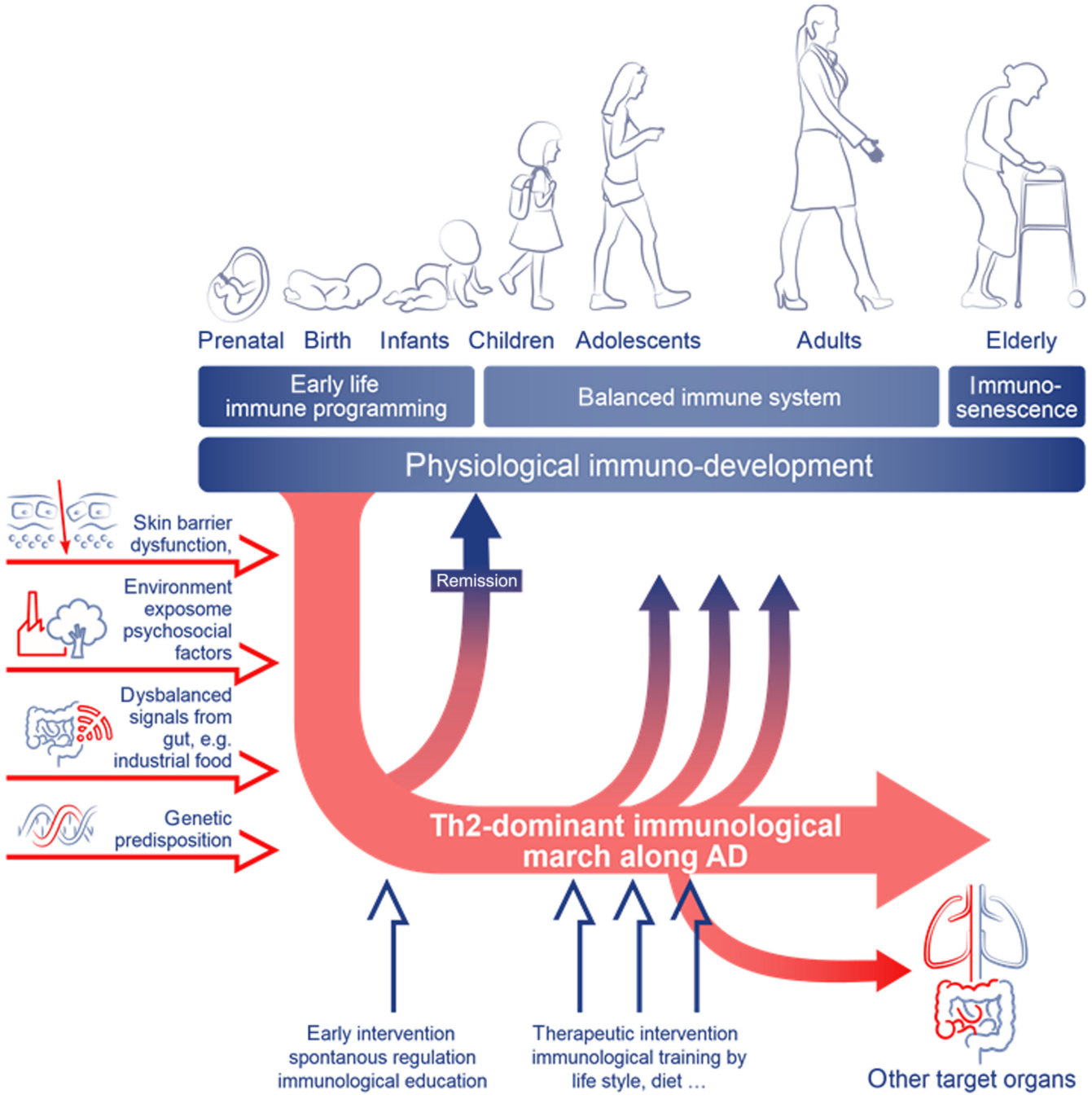

FIGURE 2 Potential opportunities to modulate physiological immuno-development. Evolutionary aspects of physiological immune development in humans include early antigen exposure in utero, birth, and early life; each of which programs a balanced immune reactivity. This phase is usually followed by a fully balanced immune system over young and adult life that then becomes increasingly unbalanced and less efficient in old age due to immune senescence. Non-physiological processes, like urbanization, overpopulation, climate change, and environmental pollution, may interfere with this ideal concept by igniting a Th2-dominated march toward atopic dermatitis (AD). This immunological march can be facilitated by imbalanced signals from the gut and skin barrier. Genetic predisposition and exposome entry may both play a role and also render skin-barrier disruption as well as the Th2-associated inflammatory situation. Progressive AD may secondarily foster comorbidities at other organ sites than the skin, for instance, atherosclerosis and depression. Early intervention or immune education within the "programming"-phase may lead to complete remission and physiological immune development. At later time points, repetitive interventions—such as, changes in lifestyle, daily skin care, and dietary management—may be necessary to reach or almost reach a physiological immune condition. In persisting AD, a basic management strategy shall be continued, but with additional therapeutic interventions to control the chronic inflammation.

inflammation and thus changing a physiological path of the immunological march. This knowledge provides unique opportunities for distinct intervention strategies: (i) by providing natural immune signals early in life (possibly during pregnancy) that booster its physiological development, (ii) by restoring the epidermal barrier function and reducing epicutaneous sensitization, (iii) by pharmacologic

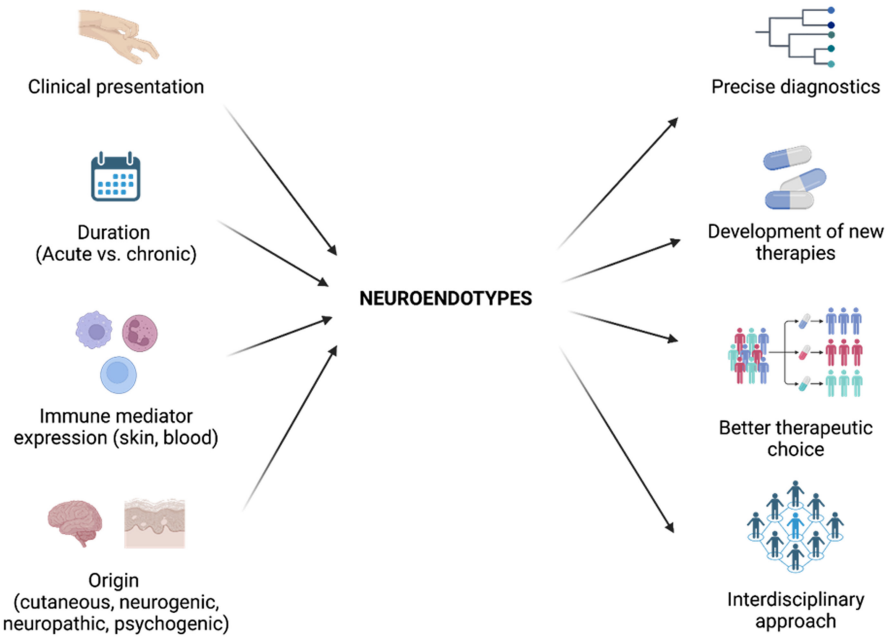

FIGURE 3 Neuroendotypes of atopic dermatitis (AD). Itch is a universal symptom in AD, and several factors stratify the development and symptoms of itch across AD patients, suggesting that there are various neuroendotypes of itch in AD. By classifying a patient's neuroendotype, a precision medicine approach can be taken that can improve patient outcomes. The first step towards this requires more precise diagnostics and interdisciplinary work, alongside the development of new and neuroendotype-targeted therapies.

intervention, for example, treating skin inflammation early and intensively, or by a combination of those three. However, whether these measures are effective may depend on proper timing which still remains to be defined. For example, in adults, the positive effects from changing the environmental factors are usually not sustained, and a continuous behavior modification, for example, repeated exposure to microbiome-derived signals, may be necessary to retain the effect. Adapting the patients' life-style towards an atopic-protective one through diets, increased activity, and smoking cessation should be considered as therapeutic measure in the management of AD.[96,97] Education of this should be included as part of patient care.

It is not known if there is a specific time-period in early life in which environmental or therapeutic interventions would have long-term benefits. A mother's diet during pregnancy can influence the child's risk of developing AD, suggesting that prenatal exposures are important.[98,99] Also, exposure of the neonate to the maternal vaginal microbiome may reduce the risk for AD. Taken together, there is increasing evidence of opportunities to positively intervene early in life and educate the immune system in a way that has long-term effects which prevent the immunological march and its clinical correlate, the atopic march.

5 | NEUROIMMUNOLOGY, SYSTEMIC INFLAMMATION, AND COMORBIDITIES

In the realm of AD research, the study of neuroimmunology is increasingly recognized for its significance in elucidating the mechanisms by which systemic inflammation can influence neuroimmunological responses within the body, thereby underscoring the intricate bidirectional communication between the immune system and the nervous system in this dermatological disease.

5.1 | Pruritus–from neuroimmune to psychosomatic aspects

Itch, the unpleasant sensation leading to the desire to scratch, is the predominant symptom and a hallmark of AD.[100] Those suffering from AD identify itch and the visible presence of eczema, particularly on the face, as one of the most burdensome aspects of the disease with its presence frequently resulting in feelings of stigmatization among patients. The itch sensation is often present all day and disturbs sleep and regular life, including but not limited to, work capacity, school performance, social life, and relationships[101] and these patients are afflicted with a vicious cycle of itching, scratching and inflammation. The mechanisms of itch are still not fully understood. Of the many factors influencing itch (Figure 3), the interplay among the nervous system (including the brain), the immune system, and the skin (e.g., mast cells) is likely key. Activation of sensory nerves transmits signals to the central nervous system (CNS); the CNS, in response, may modulate the skin's physiology by the release of hormones and the upregulation of neuropeptides and receptors in the nerves, a phenomenon described as the skin-brain axis.[102] Since both itch and pain engage the same pathways, distinct cytokines appear to drive these clinically different sensations.[103] Of note, sensory nerves involved in itch also induce a response by releasing neuropeptides such as calcitonin gene-related peptide (CGRP), pituitary adenylate cyclase-activating polypeptide (PACAP), and substance P, which is termed neurogenic inflammation.[104,105] The complex pathophysiology of itch is orchestrated not just by nerves but also by a close bidirectional interaction of nerves with immune cells, such as T-cells, eosinophils, basophils, and mast cells, contributing to neuroinflammation.[106] Various mediators released by immune cells can directly act on nerves. These include histamine,[107,108] tryptase, leukotrienes,[109,110] neuropeptides,[111,112] cytokines (e.g., IL-4, IL-5, IL-13,

IL-31),[26,113–116] and alarmins (e.g., TSLP[117]). The blockade of IL-4 receptor alpha and IL-31 receptor alpha as well as inhibition of JAK1/2 lead to the control of itch and have an important role in the sensation of itch. Furthermore, endogenous opioids and their receptors located on central and peripheral nerves and various skin cells may contribute to pruritus and changes in the skin barrier.[118]

The role of the nervous system and the psyche of itch should not be underestimated. Imaging studies of the brain have clearly shown activation of a variety of CNS areas including some of the limbic system during itch sensations.[119] In somatoform pruritus, psychosocial factors contribute to the induction of itch. Verbal suggestions or instructions have a potent impact on the perception of itch.[120,121] On the other hand, pruritus can induce or enhance the development of psychosomatic reactions such as anxiety or depression.[122] Several studies have shown an association between AD and psychiatric comorbidities.[123,124]

A concept that is heavily debated is the degree to which pruritic diseases such as AD can be seen as diseases with systemic inflammation[34,125] acting not only on the nervous system, but also on other organs such as the heart, lung, or gut. In AD, for instance, certain patient groups have an increased risk of cardiovascular diseases.[126–128] It can be assumed that sleep disturbances and reduced physical activity may enhance the risk of cardiovascular diseases in AD. Interestingly, the previously reported dose–response relationship between the severity of AD and the risk of cardiovascular diseases[126] points towards a more prominent systemic inflammation in severe AD, albeit the absolute risk is minimal.

Inflammatory mediators of pruritus can be found in skin diseases as well as in gastrointestinal[129] and lung diseases[130] and may underline the importance of studying comorbidities in pruritic diseases. Of note, sneezing and coughing in response to nasal and airway irritation, respectively, have been described as similar corresponding responses by these other organs as the scratching response to itch in the skin. Those reactions may originate as host-protective behavioral responses.[131]

Regarding environmental factors, different trigger factors of itch such as allergens and microbes have been identified. Sensory neurons can detect molecular ligands of bacteria, especially seen for *S. aureus*, and influence the sensation of itch and pain.[47,132] Beside the skin microbiome, the gut microbiome may contribute to pruritus (via a gut-skin and/or gut-brain axis). However, specific mechanisms have not yet been identified.

6 | THERAPEUTIC, EDUCATIONAL, AND GLOBAL ECONOMIC ASPECTS

6.1 | New treatments have revolutionized AD management

In the last few years, targeted treatments for AD have advanced dramatically. The biological agents dupilumab (anti-IL-4Rα), tralokinumab (anti-IL-13), and lebrikizumab (anti-IL-13) along with the Janus kinase inhibitors (JAKi) baricitinib, upadacitinib and

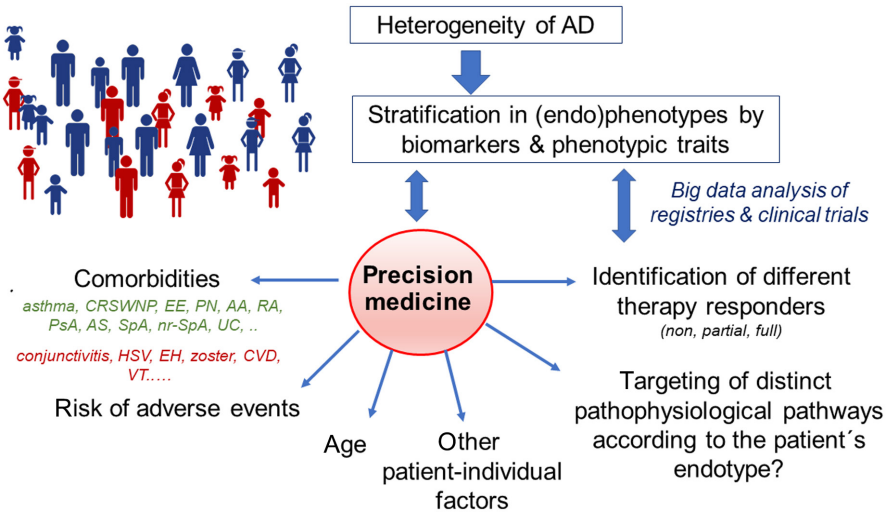

FIGURE 4 The aspects that should be considered in a precision medicine approach for the treatment of atopic dermatitis (AD). Because AD is a highly heterogeneous disease, a precision medicine approach is a more suitable treatment strategy. In selecting targeted therapy, one should consider comorbidities, risk of adverse events, age, and other factors. A biomarker method for the stratification of different endotypes and phenotypes is urgently needed. One approach to facilitate the identification of different therapy responders is to perform a combined data analysis of current AD registries and clinical trials. Certain comorbidities have approved indications in addition to AD for distinct targeted systemic therapies (green) including dupilumab for asthma, prurigo nodularis (PN), chronic rhinosinusitis with nasal polyps (CRSWNP), eosinophilic esophagitis (EE); baricitinib for alopecia areata (AA) and rheumatoid arthritis (RA); upadacitinib for RA, psoriatic arthritis (PsA), ankylosing spondylitis (AS), axial spondyloarthritis (SpA), and non-radiographic ulcerative colitis (nr-SpA).[134,136] In addition, AD patients can be susceptible to other diseases with an increased risk of adverse events to distinct therapies (red). This includes, but is not limited to susceptibility to conjunctivitis, herpes simplex virus (HSV), eczema herpeticum (EH), zoster, venous thromboembolism (VT), or comorbidities including cardiovascular diseases.

abrocitinib have been approved with indication for systemic therapy in moderate-to-severe AD in Europe.[5,133–137] Because of these potential additional applications of these therapies, consideration of comorbidities is crucial for selecting the proper treatment alongside other aspects such as short- and long-term efficacy, safety profile, etc.[5,88,133,134,138,139] (Figure 4). Ongoing clinical trials have shown further possible applications for these agents as well as even more possible treatments.[5,133,134]

Despite these advances and the high prevalence of AD, significant global, economic, and educational inequalities in the treatment of AD still remain.[140] To ensure that every AD patient receives optimal treatment, patients, healthcare providers, and the pharmaceutical industry must work together to advance science and therapeutic management.

6.2 | Global consensus on individual treatment goals

One of the biggest challenges in the treatment of AD is the lack of global consensus on defining individual treatment goals and assessing the severity of the disease, including sensory and psychosocial symptoms.[141,142] AD is a clinically heterogeneous disease with a large range of clinical phenotypes and underlying endotypes.[92,96,143–147] These AD subtypes are suggested by the variability in treatment responses including the onset, speed, and duration of response; side effect profiles (e.g., ocular involvement)[134,136]; and biomarker responses[24,148–151] such as improved responses of subgroups with higher baseline levels of certain biomarkers (e.g., periostin).[147–149,152–158] Moreover, AD in different ethnic backgrounds and climates (e.g. tropics) is characterized by different underlying pathomechanisms, for example, Th2-dominated inflammation in patients of European descent or the additional Th17 component in AD patients of Asian and African descent, which requires adapted therapeutic approaches.[145,158,159] Future directions for this research include studying how AD varies pathologically across various ethnicities, as well as the role played by the patients' environments. This would encourage the development of more efficient and cost-effective diagnostics.[5,148]

Importantly, a global consensus is needed on the definition of appropriate targets for AD treatment, disease severity assessments, and who should receive systemic therapy. Many have attempted to define such including the European Task Force on Atopic Dermatitis (ETFAD) and International Eczema Council (IEC).[141,160] Increased levels of severity-associated biomarkers, which suggest a systemic impact of skin inflammation, have been observed in a significant number of patients with low to moderate AD.[147]

The new European Guidelines already address a more personalized implementation of systemic therapy beyond the hierarchical cut-offs of objective severity scores.[134,136,155] These guidelines suggest the implementation of both clinician- and patient-reported outcome measures in accordance with the Harmonizing Outcome Measures for Eczema Initiative.[134,136,155] In addition, they recommend systemic therapy in case of functional or social indications, as defined as an insufficient response to "appropriately conducted topical therapy" or the inability to participate in daily life due to insufficiently controlled disease despite being "under an adequate treatment regimen".[134]

6.3 | Management and efficient treatment of AD as a preventive tool for AD progression and atopic march—toward disease modification

The new availability of highly effective treatment options may create a potential window of opportunity for disease prevention or alteration of progression in the early stages of AD.[161] Early sufficient treatment with topical therapy and additional targeted systemic treatment potentially could suppress disease severity and reduce the number of flares, while inducing long-term remission of AD symptoms and reducing the risk of developing type-2 comorbidities.[161]

With the widespread use of systemic treatment and improved disease control, several questions regarding the practical aspects of disease management have emerged such as the definition of "remission" and "disease modification" in the context of AD, the required duration of systemic treatment in well-controlled AD, the stability of response under dosage tapering or prolonged dosage intervals, the potential combining of systemic therapies, and the definition of patients with insufficient response to available therapies (summarized in Figure 5). Additionally, it can be expected that multiple challenges will emerge. These issues include the treatment of patients with complicated medical profiles, for example, patients who are pregnant or have metastatic malignancies, and practical issues involving mounting healthcare costs due to high drug prices not covered through insurance.

Well-designed prospective trials that test various combinations of therapies to attain therapeutic remission and the compilation of both clinical and laboratory data from patient registries and academic studies are needed to help address these questions. In addition, concerns about cost-effectiveness must be balanced with the consequences of a reduced quality of life, restricted work capability, and negatively impacted life expectancy.

6.4 | Global aspects of AD management

It should be noted that current, modern systemic therapies like JAKi[5,162] are not available or are limited in many regions worldwide. In many regions, simple treatments such as emollients or topical steroids are considered luxury products and are thus out of reach. Lack of competent or trained medical practitioners and poor medical infrastructure are additional hurdles. This situation may change now that the WHO has begun to integrate common skin diseases into its global health strategy.[163]

The Guidelines should provide clear, practical, and realistic recommendations that optimize all available therapies and support

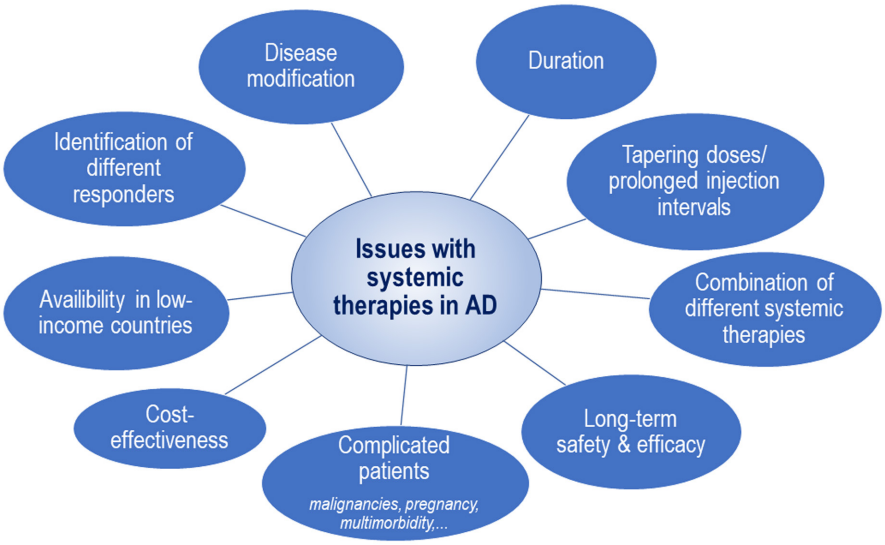

FIGURE 5 Issues to be further addressed regarding systemic therapies in atopic dermatitis (AD).

shared decision-making. In addition, the opportunities for further research into the prevention of AD and the modification of the disease are of eminent importance. Aspects regarding climate change and planetary health[164] should also be included.

6.5 | Education programs are powerful tools in the toolkit for managing AD

A global plan for patient education incorporating online information and digital tools might improve the care of AD patients even in underserved areas.[165] A lack of education on topical therapies has resulted in widespread weaknesses in the management of AD. Many patients are unaware of the full range of treatment options available, and healthcare providers may not have the knowledge or resources to provide optimal care. These issues highlight the need for greater awareness, education, and resources for AD patients and healthcare providers and the need for collaboration of all involved to develop effective educational activities and programs.[166] Education gaps, among both patients and healthcare professionals regarding optimal AD management should be addressed through targeted education interventions.[167,168] The education in AD management should consider the family as an integral factor in holistic care and the AD patient's age. Effective education optimally includes the delivery of information and an experience in which all parties (giver and recipient) are invested, motivated, and engaged, and then behavioral changes can be observed at the end. With the launch of the Global Atlas on Atopic Dermatitis (GAAD) program, an attempt to broaden education has been made and ideally may result in more widespread awareness and knowledge of AD globally.[165]

Evidence-based, holistic, and cutting-edge educational methods should be prioritized. The needs assessments via "GAP analyses" are also an essential prerequisite. Findings from modern teaching studies and resultant interactive methods, such as "blended learning", and "flipped classroom", and innovative approaches such as "design thinking", should be incorporated to impart the knowledge and skills to teach as efficiently as possible.[169] By selecting adequate education methods, motivation for change and better allergy competence can be achieved, leading also to altered behavior and improved performance and patient outcomes (see Figure 6).

Evidence-based educational principles, interprofessional learning, social aspects of learning, cultural differences, digital educational tools, and cost-effectiveness should be incorporated, leading to a true commitment to change.[170] For improved AD self-management with reduced distress, higher quality of life, and improved long-term cost-effectiveness of AD care, patients can benefit enormously from well-trained healthcare professionals and a patient learning program that is standardized to provide comprehensive education and flexible to meet individual needs, based on mindful and empathic approaches.

The community should establish an interprofessional group, consisting of physicians, nurses, dieticians, psychologists, and patients, to identify areas for educational research in AD, using the most successful practices determined from other chronic disease areas, for example, diabetes and wound care. Furthermore, accommodating different learning styles and preferences would enhance the effectiveness of these educational experiences. There should also be a move to Massive Open Online Courses (MOOCs).[171,172]

6.6 | Digital medicine in allergic diseases: harnessing wearables, AI, and exposome monitoring for enhanced therapeutic management and prevention

Advances in digital medicine provide a unique opportunity to contribute to both the systematic investigations of the exposome and the therapeutic management of allergic diseases, including education, personalized reminders, and monitoring of patient-reported outcomes.[173] We propose that technological advances can play a role in improving the management of AD. Tools such as "wearables" and artificial

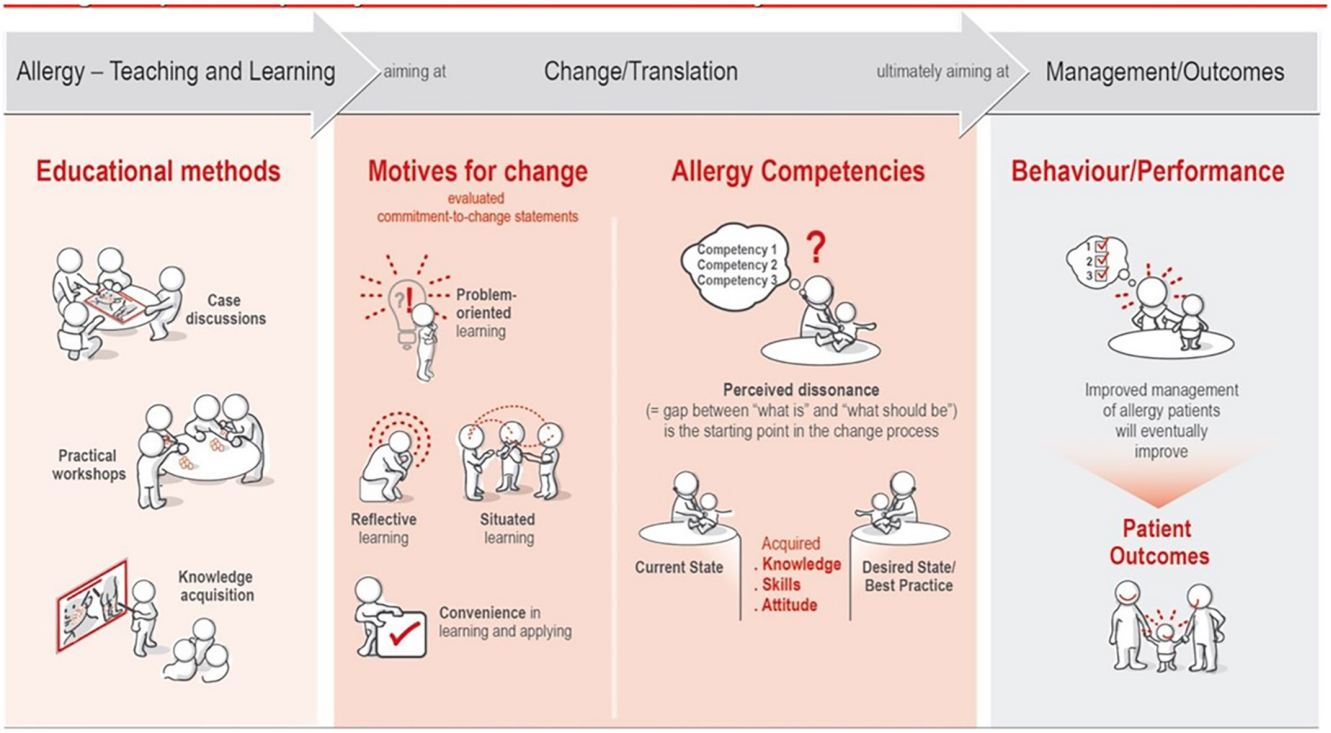

FIGURE 6 Design for effective continuing professional development: A path to facilitate the translation of acquired competencies into clinical daily practice. The focus is on teaching and learning methods that illuminate motives for change so that physicians and healthcare providers can develop and further their allergy competencies. The ultimate goal is to bring about positive behavior and performance changes among healthcare professionals, leading to better patient management and outcomes.

intelligence methods might be used to help measure and interpret changes in one's environment.[174] This could be used for individualized prevention, for example, by alerting an individual with asthma or AD in a region with elevated levels of air pollution which could lead to disease exacerbations.[61] The potential value in monitoring the exposome through the use of apps to provide rich data for research, prediction of disease development, therapeutic management, education, and prevention purposes must also be balanced with the privacy risk. The international panel highlighted the importance of securely protecting personal data given the large potential range of applications in the field of digital medicine concerning the management of comprehensive therapy in chronic inflammatory allergic diseases.

7 | FUTURE DIRECTIONS: ADDRESSING IDENTIFIED GAPS AND NEEDS

7.1 | Epithelial barrier and environmental factors

Investigating how environmental factors such as climate change, genetic predispositions, and changes in the skin microbiome influence the weakening of the epithelial barrier in AD, and assessing the need for multidimensional analysis of these factors, is crucial for developing preventative strategies, personalized therapies, and understanding geographical variations in AD incidence.

- *Impact of climate change*: What is the specific impact of climate change-related factors (e.g., increasing temperatures, humidity changes, exposure to new allergens, and altered pollen patterns) on the exacerbation or development of AD?
- *Genetic versus environmental factors*: To what extent do genetic predispositions versus environmental factors contribute to the weakening of the epithelial barrier in AD?
- *Skin Microbiome Dynamics*: How do changes in the skin microbiome, influenced by environmental factors, contribute to the disruption of the epithelial barrier in AD?
- *Longitudinal studies on environmental changes*: What are the long-term, combined effects of ongoing environmental changes (like urbanization, lifestyle changes, and dietary shifts) on the prevalence and severity of AD?
- *Need for*: Multidimensional analysis of the exposome and the reactome in time and space including longitudinal studies and registries on an international level is needed.
- *Interaction between skin barrier and immune system*: How do changes in the skin barrier, influenced by environmental factors, interact with the immune system, and how does this interaction contribute to systemic inflammation and the development of further comorbidities?
- *Preventive strategies*: Can modifications in environmental exposure (like reducing exposure to pollutants or allergens) prevent impairment of the epithelial barrier and prevent or mitigate AD?

- *Geographical variations in AD incidence*: Are there geographical trends in AD incidence that correlate with specific environmental or climate factors?
- *Therapeutic approaches targeting the barrier*: What are the most effective therapeutic approaches to strengthen the epithelial barrier in AD, considering environmental and microbiome influences?
- *Personalized microbiome-based therapies*: How can individual variations in the skin microbiome be leveraged to develop personalized treatment strategies for AD?

7.2 | Atopic march, immunological march, and neuroimmunology

There is a need for a comprehensive understanding of the multifaceted factors influencing the progression of AD to other atopic diseases, encompassing immunological, molecular, psychoimmunological, and environmental aspects, including the roles of skin barrier dysfunction and microbiome-immune interactions

- *Progression from AD to other atopic diseases*: What are the key immunological and molecular mechanisms driving the progression from AD to other atopic diseases, such as asthma or allergic rhinitis?
- *Early-life factors in atopic march*: How do early-life exposures and genetic predispositions contribute to the initiation of the atopic march starting with AD?
- *Role of skin barrier dysfunction*: How does skin barrier dysfunction in AD influence systemic immune responses and facilitate the progression of the atopic march?
- *Psycho-immunological factors in AD progression*: What role do psycho-immunological factors play in the progression from AD to subsequent stages of the atopic march?
- *Characterize immunosenescence in AD*: What is the role of immunosenescence especially in adult- and late-onset AD versus healthy individuals?
- *Biomarkers predictive of atopic march progression*: Are there identifiable biomarkers in early AD that can predict the likelihood of progression along the atopic march?
- *Impact of early intervention in AD*: How does early intervention in AD alter the course of the atopic march, particularly in terms of immunological and psycho-immunological outcomes?
- *Interaction between the microbiome and immune system in atopic march*: How does the interaction between the skin and gut microbiome and the immune system influence the progression of the atopic march?
- *Psychological stress and AD progression*: How does psychological stress in individuals with AD contribute to the immunological changes associated with the atopic march?
- *Influence of environmental factors on atopic march*: How do environmental factors, such as pollutants and allergens, impact the transition from AD to other atopic diseases?
- *Preventive strategies targeting the atopic march*: What preventive strategies can be employed in the early stages of AD to halt or slow down the progression of the atopic march?
- *Leverage knowledge for prevention*: How can interventions, for example, selective substitution of microbes, diet, and pharmacological approaches, impact the immunological march and how can the switch to a physiological immuno-development be systematically evaluated?
- *Development of more effective management strategies for AD, particularly in addressing the mechanisms of itch and reducing the associated patient stigmatization*: Understanding of the intricate interaction between the nervous system (including the brain), the immune system, and the skin.
- *Neuronal signaling*: How can an enhanced understanding of neuroimmune circuits and neuronal signaling contribute to optimizing strategies for controlling the pathological mechanisms in AD, including inflammation, barrier dysfunction, and pruritus?

7.3 | Education and prevention

Effective management of AD requires multimodal education and advocacy campaigns, timely interventions considering individual differences, and collaborative efforts among key organizations to enhance treatment compliance, raise disease awareness, and develop precise, stage-specific therapy

- *Primary to tertiary prevention*: What impact would a multimodal education and awareness campaign, targeting patients, their families, politicians, policymakers, medical doctors, nurses, and other care providers, have on improving the understanding of current therapeutic options for a specific condition, and how might such educational programs for patients enhance compliance with their therapies, thereby leading to better clinical outcomes?
- *Effect of outreach campaigns*: How can advocacy efforts for AD patients, in collaboration with patient organizations, effectively raise awareness about the severe impact of itch, sleep loss, and other mental health aspects on the quality of life (QoL) in the context of AD, and what strategies would be most effective in addressing these challenges?
- *Interventions over the lifespan*: Considering the evidence that early interventions can prevent allergies, how do the timing and nature of these interventions, especially during early life and pregnancy, compare to adult interventions in effectively preventing or altering the course of AD?
- *Optimized therapeutic approaches*: How can the therapeutic approaches be optimized according to disease stage along with the immunological march of AD, and is there a potential for a precision medicine approach according to stages of the immunological march?
- *Ethnic and sex-related differences*: Are there individual differences, such as ethnic and sex-related differences, that need

to be considered when developing treatment and prevention strategies?

- *Collaboration of societies*: It is recommended that organizations such as the International Society for Atopic Dermatitis, International Eczema Council, and HOME initiative collaborate in research, education, and advocacy efforts for patients with AD.
- *Education for both the caregivers and the patient level* should be implemented, because it is a highly effective tool to improve the awareness and management of AD.

7.4 | Identified gaps in diagnosis and therapy

These research goals are crucial for improving the quality of healthcare globally, ensuring equitable treatment for patients worldwide, and recognizing the diverse ways in which diseases can manifest and affect individuals differently.

- *Identifying variations*: Research on how different countries and cultures define and treat the same disease, particularly focusing on how they consider sensory and psychosocial symptoms in their treatment goals.
- *Analyzing the impact of diverse definitions*: Evaluating the impact of these varying definitions and treatment approaches on patient outcomes. This includes understanding how different perceptions of disease severity can influence treatment effectiveness and patient satisfaction.
- *Developing global standards*: Working towards creating a more standardized, globally accepted set of guidelines for defining and treating the disease. This would involve incorporating a broad range of perspectives and ensuring that these guidelines are adaptable to different cultural contexts.
- *Enhancing patient-centered care*: Ensuring that these global standards are flexible enough to be tailored to individual patient needs, particularly in addressing sensory and psychosocial aspects, which may be more subjective and vary greatly among individuals.
- *Cross-cultural collaboration and education*: Promoting cross-cultural collaboration among healthcare professionals to share knowledge and best practices, and educating them about the importance of considering cultural differences in treatment approaches.

AUTHOR CONTRIBUTIONS

T.H.C., P.S.G., T.B., H.H.K., E.J.J., J.A., N.H., and M.Y. wrote the text in part. Figures were provided by M.Y., N.H., L.M., P.S.G., M.U., and D.S.P.. All authors reviewed the manuscript and gave consent to the manuscript.

AFFILIATIONS

[1]Institute of Environmental Medicine and Integrative Health, Faculty of Medicine, University of Augsburg, Augsburg, Germany
[2]Institute of Environmental Medicine, Helmholtz Zentrum München, Augsburg, Germany
[3]Christine Kühne-Center for Allergy Research and Education (CK-CARE), Medicine Campus, Davos, Switzerland
[4]Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Zurich, Switzerland
[5]AbbVie Inc., North Chicago, Illinois, USA
[6]Center for Allergy and Environment (ZAUM), Technische Universität München, Germany
[7]Davos Biosciences, Davos, Switzerland
[8]University of Minnesota, Minneapolis, Minnesota, USA
[9]Department of Immunology and Microbiology, The LEO Foundation Skin Immunology Research Center, University of Copenhagen, Copenhagen, Denmark
[10]Department of Dermatology, Allergy Unit, University Hospital of Zürich, Zürich, Switzerland
[11]Faculty of Medicine, University of Zürich, Zürich, Switzerland
[12]Almirall Hermal GmbH, Reinbek, Germany
[13]Hochgebirgsklinik Davos, Davos, Switzerland
[14]LEO Pharmaceutical Products Sarath Ltd, Zürich, Switzerland
[15]Pfizer Switzerland AG, Zürich, Switzerland
[16]Department of Pediatrics, Division of Respiratory Medicine and Allergology, Bern University Hospital, Bern, Switzerland
[17]Department of BioMedical Research (DBMR), University of Bern, Bern, Switzerland
[18]Department of Dermatology and Allergy, Allergy Clinic, Copenhagen University Hospital–Herlev and Gentofte, Copenhagen, Denmark
[19]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
[20]Psychosomatic Department, Hochgebirgsklinik, Davos, Switzerland
[21]Pfizer, Istanbul, Turkey
[22]Universitair Ziekenhuis, Brussel, Belgium
[23]Department of Dermatology and Allergy, University Hospital Bonn, Bonn, Germany
[24]Diakonessenhuis Utrecht Zeist Doorn Locatie Utrecht, Erasmus MC, University Medical Center Utrecht, Utrecht, Netherlands
[25]Department of Clinical Medicine, Trinity College Dublin, Dublin, Ireland
[26]Center of Pathophysiology, Infectiology and Immunology, Institute of Pathophysiology and Allergy Research, Medical University of Vienna, Vienna, Austria
[27]The interuniversity Messerli Research Institute, University of Veterinary Medicine Vienna, Medical University Vienna and University Vienna, Vienna, Austria
[28]Dermatology Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA
[29]Environmental Health, LLC, Durham, North Carolina, USA
[30]Ostschweizer Kinderspital St. Gallen, St.Gallen, Switzerland
[31]Department of Dermatology, University of California Davis, Sacramento, California, USA
[32]Stanford University School of Medicine, Stanford, California, USA
[33]APC Microbiome Ireland, University College Cork, Cork, Ireland
[34]Department of Medicine and School of Microbiology, University College Cork, Cork, Ireland
[35]Faculty of Médicine, Antananarivo, Madagascar
[36]Institute of Laboratory Medicine, Philipps University, Marburg, Germany
[37]Klinik und Poliklinik für Dermatologie und Allergologie am Biederstein, Technische Universität München, Munich, Germany
[38]Institute of Tissue Medicine and Pathology, University of Bern, Bern, Switzerland
[39]Klinik für Dermatologie, Venerologie und Allergologie, Universitätsklinikum Schleswig-Holstein (UK-SH), Kiel, Germany
[40]Department of Dermatology, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[41]Institute of Pharmacology, University of Bern, Bern, Switzerland
[42]Institute of Biochemistry, Brandenburg Medical School, Neuruppin, Germany
[43]Center for Chronic Pruritus and Department of Dermatology, University Hospital Münster, Münster, Germany
[44]Department of Dermatology and Venereology, Hamad Medical Corporation, Doha, Qatar
[45]Translational Research Institute, Academic Health System, Hamad Medical Corporation, Doha, Qatar

[46]Dermatology Institute, Academic Health System, Hamad Medical Corporation, Doha, Qatar
[47]School of Medicine, Weill Cornell Medicine-Qatar, Ar-Rayyan, Qatar
[48]College of Medicine, Qatar University, Doha, Qatar
[49]College of Health and Life Sciences, Hamad Bin Khalifa University, Doha, Qatar
[50]Department of Dermatology, Weill Cornell Medicine, New York, New York, USA
[51]INSERM 1312, University of Bordeaux, Bordeaux, France
[52]Department of Dermatology, Faculdade de Medicina, Hospital das Clínicas, Universidade de São Paulo, São Paulo, São Paulo, Brazil
[53]Bencard Allergie GmbH München, Munich, Germany
[54]Department of Dermatology and Venerology, Bispebjerg Hospital, University of Copenhagen, Copenhagen, Denmark
[55]Department of Dermatology and Allergy, Hannover Medical School, Hannover, Germany
[56]Cluster of Excellence RESIST (EXC 2155), Hannover Medical School, Hannover, Germany
[57]Department of Medicine Solna, Division of Immunology and Allergy, Karolinska Institute and Karolinska University Hospital Stockholm, Solna, Sweden
[58]Department of Pneumology, Intensive Care Medicine, Center for Internal Medicine, Universitätsmedizin Rostock, Rostock, Germany
[59]Department of Dermatology and Allergy, Ludwig-Maximilian-University, Munich, Germany
[60]Department of Dermatology and Allergy, University Hospital Augsburg, Augsburg, Germany
[61]Comprehensive Center of Inflammation Medicine, University Hospital Schleswig Holstein Campus Luebeck, Lubeck, Germany
[62]Department of Dermatology and Allergy, School of Medicine, Technical University of Munich, Munich, Germany
[63]Department of Medicine Solna, Division of Dermatology and Venereology, Karolinska Institutet, Stockholm, Sweden

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ORCID

Claudia Traidl-Hoffmann https://orcid.org/0000-0001-5085-5179
Cezmi A. Akdis https://orcid.org/0000-0001-8020-019X
Mübecel Akdis https://orcid.org/0000-0003-0554-9943
Katja Bärenfaller https://orcid.org/0000-0002-1904-9440
Charlotte Menné Bonefeld https://orcid.org/0000-0002-0523-6229
Marie Charlotte Brüggen https://orcid.org/0000-0002-8607-6254
Danielle Fehr https://orcid.org/0000-0001-6361-3662
Lena H. Garvey https://orcid.org/0000-0002-7777-4501
Nadine Herrmann https://orcid.org/0000-0003-4924-2281
Dirk Jan Hijnen https://orcid.org/0000-0003-3379-3425
Alan D. Irvine https://orcid.org/0000-0002-9048-2044
Erika Jensen-Jarolim https://orcid.org/0000-0003-4019-5765
Laura Maintz https://orcid.org/0000-0001-6053-1530
Svenja Müller https://orcid.org/0000-0002-2118-959X
Kari Nadeau https://orcid.org/0000-0002-2146-2955
Liam O'Mahony https://orcid.org/0000-0003-4705-3583
Harald Renz https://orcid.org/0000-0003-0602-7215
Caroline Roduit https://orcid.org/0000-0002-5988-0570
Mari Sasaki https://orcid.org/0000-0003-1590-3838
Dagmar Simon https://orcid.org/0000-0001-8965-9407
Milena Sokolowska https://orcid.org/0000-0001-9710-6685
Jacob Pontoppidan Thyssen https://orcid.org/0000-0003-3770-1743
Stephan Traidl https://orcid.org/0000-0003-4806-599X
Marianne van Hage https://orcid.org/0000-0003-3091-1596
Christian Virchow https://orcid.org/0000-0003-4291-1956
Mitamura Yasutaka https://orcid.org/0000-0001-6389-9285
Alexander Zink https://orcid.org/0000-0001-9313-6588
Peter Schmid-Grendelmeier https://orcid.org/0000-0003-3215-3370

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