

Interviews

In this interview series, EMJ speaks with leading voices across allergy, immunology, and environmental health, including pioneers in immune tolerance, exposome research, childhood food allergy prevention, viral immunology, and health equity. Together, they explore how advances in barrier biology, epidemiology, precision medicine, AI, and public health policy are reshaping our understanding of allergic disease and driving the field towards prevention-focused, personalised care.

Featuring: Cezmi Akdis, Isabella Annesi-Maesano, Jennifer Koplin, Mitchell H. Grayson, and Ruchi Gupta



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Q1 You originally trained in infectious diseases and clinical microbiology before specialising in allergy and immunology. What drew you into the field of allergy and immune regulation, and at what point did you realise this would become your life's work?

Something that often crystallises this passion for me is watching clinical phenomena (seasonal allergies, asthma, autoimmunity) unfold through the lens of immune regulation. You see how small miscommunications among cells and signals can lead to big, tangible experiences in patients' lives.

My thesis was on immune tolerance and immune activation in miliary tuberculosis. It was based on the identification of lymphocyte subsets (CD4, CD8, CD16, and CD25 monoclonal antibodies) in my experiments via confocal microscopy, which was before the introduction of flow cytometry into laboratories.

We had demonstrated how the immune system shuts down and goes into a silent phase in miliary tuberculosis, which is in parallel with diminished tuberculin skin test reactivity (cellular immunity). It also demonstrated the development of regulatory T cells (Treg) for tuberculosis tolerance in this last stage of the disease.

It was a great motivation to realise that immune regulation is a symphony of checks and balances in allergies, autoimmunity, chronic infections, tumours, and pregnancy, partially from our own experiments. It's not just about attacking pathogens, but about teaching the immune system when to pause, when to tolerate, and when to escalate. That orchestration is exquisitely elegant and endlessly complex.

Better understanding is a practical superpower. Each discovery about Tregs, cytokine networks, innate sensing, or epithelial barrier function translates into

“It's not just about attacking pathogens, but about teaching the immune system when to pause, when to tolerate, and when to escalate”

new therapies, diagnostics, and strategies to prevent, mitigate, and treat diseases.

Q2 Over the past 3 decades, you've witnessed and helped shape major conceptual shifts in allergy and clinical immunology. What do you consider the most transformative change in our understanding of allergic disease since the 1990s?

If I were to distil it to a single thread: the shift from viewing allergy as a predominantly effector-driven, IgE-centric problem to seeing it as a dysregulation of immune tolerance, shaped by barrier integrity and epithelial-immune crosstalk, has been the most transformative. This perspective unifies pathophysiology across tissues, explains why exposures matter differently across individuals, and directly informs therapies that aim to restore regulatory balance and tolerance.

Early models emphasised Th2-skewed responses as the drivers of allergy. The last 2 decades revealed that regulatory networks, especially Tregs, regulatory B cells (Breg), and tolerogenic dendritic cells, actively shape, restrain, or fail to restrain

allergic inflammation. This reframes allergy as a failure (or insufficiency) of regulatory control rather than a pure overactive effector response. The use of checkpoint blockers for cancer treatment based on these ideas was extremely important.

Discoveries highlighting the epithelium's active role (airway and skin barriers) and its sensing of environmental cues positioned barrier integrity and innate sensing as central to atopy. Epithelial-derived cytokines (e.g., thymic stromal lymphopoietin [TSLP], IL-25, IL-33) became key initiators of downstream adaptive responses, linking environmental exposures with immune regulation.

The understanding that there is an immense capacity of the innate immune response in almost every cell of the body to fight pathogens and tolerate non-pathogens that evolved together has increased, with a better understanding of adaptive immune responses of T and B cells.

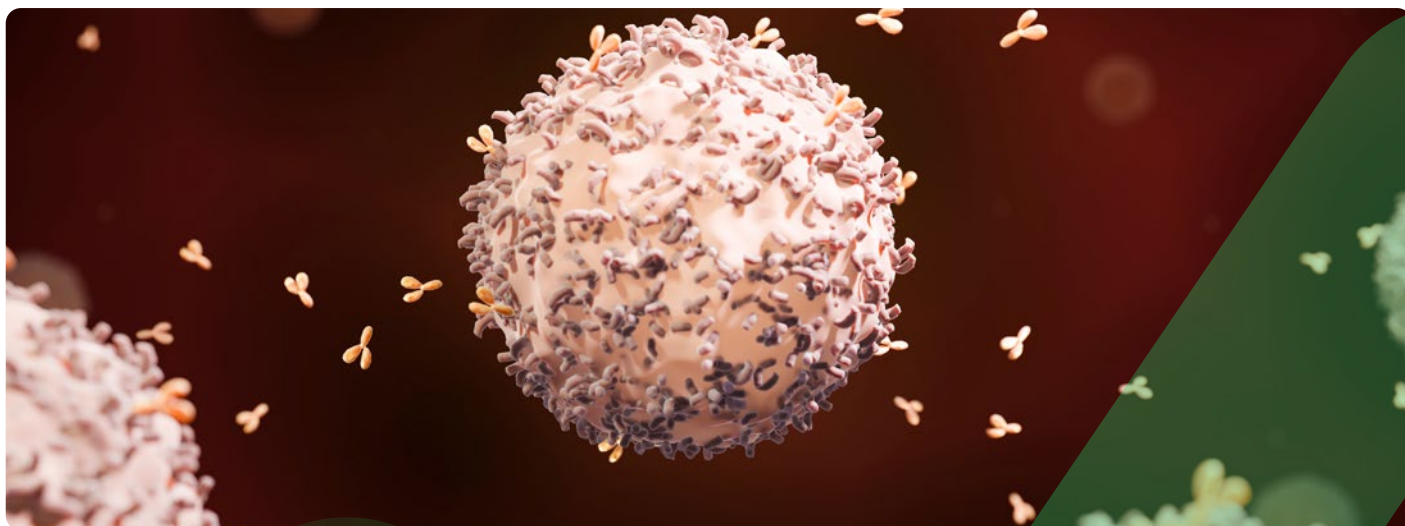
Understanding regulatory pathways and epithelial-immune crosstalk paved the way for therapies that actually modify the disease course, not just treat symptoms. Biologics targeting IgE, IL-4/IL-13 axes, TSLP, and

other regulatory checkpoints have transformed severe allergic diseases from chronic, life-impacting conditions into manageable ones for many patients.

The field moved beyond one-size-fits-all phenotypes to endotypes defined by underlying mechanisms (e.g., non-IgE-mediated triggers, barrier defects, regulatory dysfunction). This reframing supports more precise diagnostics and targeted therapies.

Q3 Your early work was pivotal in defining human Tregs and Bregs and mechanisms of immune tolerance. Looking back, how did those discoveries influence your later thinking about chronic inflammatory diseases more broadly?

Our early work showed that immune responses can be checked and redirected rather than simply suppressed. The studies mentioned in my thesis and performed in the Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland, in 1995 were quite important to show the plasticity of human Th1 and Th2 cells. This sets the stage for viewing chronic inflammatory diseases not just as hyperactive effector reactions, but



as problems of regulatory balance, where tolerance mechanisms fail or become dysregulated.

The discovery of human Tregs, Bregs, and allergen tolerance provided a scaffolding that reframed chronic inflammatory diseases as disorders of regulatory balance and barrier-immune dialogue. This has driven a shift from symptom control towards restoration of immune homeostasis across a spectrum of conditions. This perspective naturally extends beyond classic allergy to autoimmunity, chronic infections, and inflammatory conditions, where re-establishing tolerance can be therapeutic.

In contrast, cancer and the treatment of chronic infections required the breaking of established antigen-specific immune tolerance. By characterising human Tregs and Bregs, we highlighted that multiple immune compartments collaborate to maintain homeostasis. In chronic inflammation, the breakdown often involves a cascade of regulatory derangements: Tregs, Bregs, dendritic cells, and barrier-epithelial signalling all contribute. This holistic view encourages strategies that restore the entire regulatory ecosystem, rather than targeting a single cytokine or cell type in isolation.

Q4 You are widely associated with the development of the epithelial barrier theory. What were the key clinical or experimental observations that convinced you that barrier dysfunction could be a unifying mechanism across allergic, autoimmune, and even metabolic diseases?

Our epithelial barrier-centric view posits that barrier dysfunction at the epithelial interfaces of skin,

airways, and the gut acts as a primary gateway to dysregulated immunity. Our paper on eczema mechanisms and skin barrier, and the following papers on asthma and chronic rhinosinusitis, showed that defects in the epithelial barrier allow greater environmental allergen and microbe penetration, transforming a local breach into broader immune activation via epithelial-derived cues that shape overall immune system responses.

A paper from 2006 argued that maintaining barrier integrity (keep away), reducing ongoing stimuli and decreasing the inflammatory burden by draining the inflammation out of the tissues (wash away), and re-educating the immune system toward tolerance (suppress, based on our immune tolerance studies) together prevent or redirect chronic inflammation.

Taken together, these works present barrier dysfunction and epithelial-immune crosstalk as a unifying mechanism underpinning allergic, autoimmune, and metabolic inflammatory diseases, shaping strategies that prioritise barrier health and regulatory restoration across tissues.

Q5 A central component of your work links environmental exposures, such as pollutants, detergents, and food additives, to epithelial damage. From a mechanistic standpoint, what do you see as the most critical pathways by which modern environmental factors disrupt barrier integrity and drive immune dysregulation?

Environmental exposures, such as pollutants, detergents, micro and nanoplastics, and food additives, act as barrier disruptors at skin, airway, and gut interfaces. Mechanistically, they impair epithelial barrier

components (barrier lipids and tight junctions), increasing permeability and allergen/microbial ingress. Damaged epithelia release alarmins (TSLP, IL-25, IL-33) that skew dendritic cells and promote Type 2-biased responses while activating innate lymphoid cells and pro-inflammatory circuits. This epithelial-immune crosstalk, augmented by oxidative stress and redox signalling, shapes downstream immune responses and inflammation.

Chronic oxidative stress and loss of the capacity of mitochondria in the cells is one of the most important ageing and tissue-destructive factors in response to toxic substance exposure. Other mechanisms of toxicity have been identified as mitochondrial stress, endoplasmic reticulum stress, protein folding defects, DNA repair defects, cell death, and recovery mechanisms called autophagy and mitophagy.

Barrier disruption also fosters dysbiosis, reducing tolerogenic microbial signals and enhancing pro-inflammatory cues. Opportunistic pathogen colonisation in the surface tissues and loss of commensals is another main event taking place. Diet and metabolites further modulate barrier resilience, epigenetic programmes, and developmental timing, imprinting a long-term inflammation and barrier leakiness.

Therapeutic modalities that are currently developed include avoiding or decreasing the exposure dose of these toxic substances, barrier restoration (ceramides and lipid-rich emollients that occlude, hydrate and actively rebuild lamellar lipids), targeting epithelial alarmins (TSLP, IL-33), and microbiome-supportive strategies to sustain tolerance. In our understanding, these pathways

unify allergic, autoimmune, and metabolic inflammation through a shared barrier-immune axis.

Q6 You have long advocated for disease 'endotyping' and precision medicine approaches in asthma and other allergic conditions. How do you envision integrating barrier biology, microbiome data, and immune profiling into a clinically usable framework for personalised care?

A practical, clinically usable precision framework would integrate barrier biology, microbiome context, and immune profiling into a modular decision-support approach that guides diagnosis, prognosis, and therapy across airway and skin allergic diseases, with explicit inclusion of the epithelial barrier as a major factor in diseases in the European Academy of Allergy and Clinical Immunology (EAACI) nomenclature paper.

Baseline barrier assessment would use standardised, non-invasive tests, such as electric impedance spectroscopy for skin barrier function tests or gut/permeability markers for the gut and airways, to classify patients as defective/leaky, hyperreactive, or robust.

Recognising the leaky endotype, characterised by increased permeability, enhanced alarmin release, and heightened sensitisation risk, would directly steer towards barrier repair and tolerogenic strategies.

Parallel microbiome analysis (taxonomic, functional metagenomics, and metabolomics) would reveal dysbiosis patterns linked to barrier vulnerability, informing risk scores and guiding microbiome-modulating therapies.

Immune-endotype profiling (Treg/Breg function, IL-4/IL-13/TSLP signatures, and innate lymphoid cell activity) would define mechanistic subtypes with distinct therapeutic implications.

Decision tools would synthesise these data into treatment recommendations, from barrier restoration and epithelial alarmin targeting to biologics and microbiome approaches, while dynamic monitoring reclasses endotypes over time, ensuring therapy remains aligned with the patient's evolving biology.

Q7 Looking ahead 10–20 years, do you believe the greatest advances in allergy and immunology will come from biologic therapies, environmental prevention strategies, barrier repair approaches, or from an entirely new paradigm we have yet to define?

The most important of all is environmental prevention of the exposome, which focuses on reducing harmful exposures that shape long-term health across life stages.

The approach spots toxic substances, such as air pollutants, pesticides, industrial chemicals, heavy metals, detergents, rinse aids, food additives, micro and nanoplastics, and endocrine disruptors, in everyday environments such as homes, schools, workplaces, and urban landscapes, aiming to minimise cumulative burden. Micro and nanoplastic pollution will be one of the biggest threats to nature and humanity in the coming decades.

Key strategies include: 1) emission reductions and cleaner production to lower ambient pollution; 2) robust indoor air quality standards,

reducing volatile organic compounds, particulates, mould, and fumigants; 3) safer consumer products through green chemistry, substituting hazardous ingredients with benign alternatives and improving labelling and consumer awareness; 4) safeguarding water and food supplies by monitoring additives, contaminants, reducing contamination events, and promoting safe agricultural practices; 5) urban planning that expands green spaces, reduces heat islands, and facilitates active transport, thereby lowering exposure to pollutants and promoting resilience; and 6) vulnerable-population protections (pregnant women, children, migrants, the elderly) via targeted advisories, surveillance, and access to protective resources.

An exposome framework integrates real-time monitoring, biomarker data, and longitudinal health outcomes to tailor interventions and policy. Ultimately, prevention relies on cross-sector collaboration, transparent risk communication, and investment in safer environments that support lifelong health.