Paradigms and perspectives

Highlights from the 2025 Symposium of the Collegium Internationale Allergologicum

Thomas Bieber, MD, PhD,[a] Bruce S. Bochner, MD,[b] Joshua A. Boyce, MD,[c] Kenji Kabashima, MD, PhD,[d] Nora Barrett, MD,[c] John W. Holloway, PhD,[e] Kenji Izuhara, MD, PhD,[f] Maria Jenmalm, PhD,[g] Monica Kraft, MD,[h] Ronit Sagi-Eisenberg, PhD,[i] Roma Sehmi, PhD,[j] Sally E. Wenzel, MD,[k] and Donata Vercelli, MD,[l] on behalf of the Collegium Internationale Allergologicum. *Davos Switzerland; Chicago, Ill; Boston, Mass; Kyoto, Japan; Southampton, United Kingdom; Saga, Japan; Linköping, Sweden; New York, NY; Tel Aviv, Israel; Hamilton, Ontario, Canada; Pittsburgh, Pa; and Tucson, Ariz*

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Established in the early 1950s by a group of distinguished allergologists and immunologists, the Collegium Internationale Allergologicum (CIA [https://www.ciaweb.org/]) is a numerically small but scientifically vibrant international society that pursues excellence in basic, translational, and clinical research on allergic and immunologic diseases. Every 2 years, CIA members gather in a symposium that provides an unbiased perspective about their favorite discipline; it is a meeting built almost exclusively of submitted abstracts and unpublished work, with no predetermined topics. Because of this design, each CIA symposium self-organizes and identifies compelling emerging themes that drive allergic and immunologic disease research. This summary is intended to highlight themes and concepts that emerged during the 2025 CIA symposium. Table I lists presentations that illustrated these concepts.

MAST CELLS: NEVER A DULL MOMENT

The footprint of mast cells in inflammation is expanding well beyond traditional IgE-mediated allergy.[1] Mast cells are engaged by platelets in a bilateral IL-33–driven feed-forward loop that may drive IL-33–dependent immunopathology in severe asthma and aspirin-exacerbated respiratory disease (AERD). Moreover, these cells can enhance early effective immunity, but it can also promote eosinophil accumulation in respiratory syncytial virus infections. In atopic dermatitis, the cross talk between mast cells and dermal fibroblasts promotes hyperreactivity through the nuclear factor-κB and EGR1 pathways independent of IgE signaling. Finally, eczema in early life involves dysregulated fetal mast cell programming caused by stress-induced fluctuations in maternal glucocorticoids. Mast cells may even play a role in breast cancer: tumor cells activate the inhibitory function of CD300a on these cells, thereby downregulating their antitumorigenic activity.

THE RENAISSANCE OF IMMUNOLOGIC MEMORY

Memory responses—that is, the ability to recall past exposures and respond to them in ways that are sometimes protective, sometimes pathogenic—are a defining feature of the immune system.[2,3] Some work has explored classical, adaptive antigen-specific memory, focusing on a pathogenic subset of $CD4^+$ skin-resident T cells that require CXCR6-CXCL16 signaling for their *in situ* maintenance during allergic dermatitis. Other researchers have investigated a different form of memory that is innate, not antigen-specific, and relies on epigenetic mechanisms to train immune responses. Innate memory drives group 2 innate lymphoid cell responses to natural allergens but also provides enduring antiviral immunity in airways exposed to microbial farm products. Finally, work that links immunologic memory and genetic predisposition showed that convergent germline sequences across human populations encode antibodies recognizing the major peanut allergen *Arachis hypogaea* (Ara h) 2. These antibodies are commonly harmless IgG, but if isotype switching to IgE occurs, they may contribute to the high prevalence of peanut allergy.

MICROBIOTA: SOMETIMES FRIENDS, SOMETIMES FOES

The microbiome is taking center stage in allergic and immune diseases. The more we learn, the more we realize the yin and yang roles of microbiota in shaping immune responses.[4] On the one hand, the asthma-protective effects of farming were ascribed to just 9 environmental gram-positive bacterial genera that produce ligands for the human aryl hydrocarbon receptor and peroxisome proliferator–activated receptor gamma (PPAR-g). Farm exposure also promoted the production of breast milk that is microbially more diverse and richer in immune proteins. On the other hand, fecal products from 1-month-old infants at increased risk of asthma activated a novel B-cell/IL-17/neutrophil axis that promotes lung inflammation. Moreover, treatment failure in a double-blind, placebo-controlled peanut oral immunotherapy trial was associated with a specific bile acid profile, enhanced amino acid utilization, and higher copy numbers of a gene encoding a bacterial hydrolase that cleaves tripeptides containing proline residues, which is a feature of the immunogenic peanut Ara h 2. Finally, elevated levels of the immunoregulatory lipid 11,12-dihydroxyeicosatrienoic acid in mothers with allergy increased responsiveness to allergens in the offspring. These effects may have resulted from enhanced

From [a]the Christine Kühne-Center for Allergy Research and Education, Davos; [b]the Northwestern University School of Medicine, Chicago; [c]Harvard Medical School/Brigham and Women's Hospital, Boston; [d]Kyoto University Graduate School of Medicine; [e]the University of Southampton; [f]Saga Medical School; [g]Linköping University; [h]the Icahn School of Medicine at Mount Sinai, New York; [i]Tel Aviv University; [j]McMaster University, Hamilton; [k]the University of Pittsburgh; and [l]the University of Arizona College of Medicine, Tucson.

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Corresponding author: Donata Vercelli, MD, The University of Arizona, 1657 E Helen St, Tucson, AZ 85721. E-mail: donata@arizona.edu.

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TABLE I. CIA 2025: Themes, presentation titles, and authors

Theme	Presentation title	Authors
Mast cells: Never a dull moment	Platelets engage mast cells in a bilateral IL-33–driven feed-forward loop	Nishida A, Nagai J, Feng C, Zaleski K, Hastings M, Marshall S, et al
	Mast cells both enhance early effective immunity and promote eosinophil accumulation in a model of respiratory syncytial virus infection	Marshall JS, Nanjundappa RH, Liwski C, Haidl I
	Dermal fibroblast–mast cell cross talk promotes hyperreactivity in atopic dermatitis via NF-κB and EGR1 pathways	Di Nardo A, Chang Y, Alimohammadi S, Flori E, Mosca S
	Maternal stress triggers early-life eczema via fetal mast cell programming	Serhan N, Abdullah NS, Gheziel N, Loste A, Ekren R, Labit E, et al
	The context significance of CD300a on mast cells and beyond: What is its role in breast cancer? A new immune checkpoint inhibitor?	Levi-Schaffer F, Ben-Zimra M
The renaissance of immunologic memory	Pathogenic subset of $CD4^+$ skin-resident memory T cells require CXCR6-CXCL16 signaling for their *in situ* maintenance in allergic dermatitis	Kabashima K
	Epigenetic and transcriptomic mechanisms of ILC2 memory in allergic and healthy subjects	Varma R, Sripada A, Sirohi K, Alam R
	Airway treatment with Amish farm dust extracts protects against acute airway rhinovirus infection and induces enduring antiviral immune training	Hahn SM, Ezeh P, Pivniouk O, Anderson D, Banskar S, Michael AN, et al.
	Germline-encoded recognition of peanut allergens underlies structural convergent antibodies in humans	Marini-Rapoport O, Andrieux L, Keswani T, Zong G, Duchen D, Yaari G, et al
Microbiota: Sometimes friends, sometimes foes	Farm exposure protects from childhood asthma through 9 gram-positive bacterial genera	Pagani G, Loss G, Depner M, Müller C, Ru J, Strunz-Lehner C, et al
	Farm exposure is associated with human milk immune profile and microbiota	Swaney MH, Steidl OR, Tackett A, Fye S, Lee KE, IM Ong, et al
	Fecal products from 1-month-old infants at increased risk of asthma activate a novel B-cell/IL-17/neutrophil axis that promotes lung inflammation	DeVries A, Michael AN, Pivniouk O, Anderson D, Vanlinden S, Ezeh P, et al
	Gut microbial bile and amino acid metabolism associate with peanut oral immunotherapy failure	Lynch SV, Ozcam M, Lin D, Gupta CL, Gomez C, Allison Li A, et al
	Maternal 11,12-dihydroxyeicosatrienoic acid of allergic mothers increases allergen responsiveness in offspring	Cook-Mills JM, Southern AM, Bloodworth JC
Punching above one's weight: The very large effects of very rare cells	Epithelial tuft cells signal to trigeminal sensory nerves to direct allergen-elicited olfactory remodeling	Perniss A, Deng L, Wong C, Ualiyeva S, Minichetti D, Boyd AA, et al
	Tuft cells shape airway remodeling by eliciting OXGR1- and SOX9-dependent stem cell programs	Lee M, Wang X, Ye Q, Huang G, Mandanas M, Hallen NR, et al
	Metabolic control of the innate type 2 immune–tuft cell axis in the gastrointestinal tract	Huth K, Duteil C, Keiner H, Patt A, Wichmann N, Alessandrini F, et al
	Involvement of tuft cells in the pathogenesis of eosinophilic gastroenteritis	Morita H, Matsuoka R, Hayashi Y, Kubo T, Kusuda R, Motomura K, et al
At the interface between metabolism and immune responses	Asthma increases abundance and metabolic activity of myeloid and lymphoid effector cells in adipose tissue from adults with obesity	Cahill K, Mashayehki M, Tomasello A, Cartailler JP, Shrestha S, Newcomb DC
	Reduced ALDH2 in the respiratory tract causes dysregulated alcohol metabolism and respiratory reactions in AERD	Zawacki M, Huang GX, Cho L, Omilabu V, Bensko JC, Barrett NA, et al
	L-Phenylalanine orchestrates T_H2 cell fate and function in allergic inflammation	Kulkarni AJ, Rodriguez-Coira J, Stocker N, Radzikowska U, García-Cívico AJ, Delgado Dolset MI, et al
	Oxysterol regulation of mast cell hyperplasia during allergic lung inflammation	Pahima HT, Santos R, Case NA, Salloum T, Barrett NA, Dwyer DF
Novel tools for allergic disease treatment	Dual targeting of mast cells and TSLP with the bispecific antibody CDX-622	Alvarado D, Vitale L, Crocker A, Patterson C, O'Neill T, Mills-Chen L, et al
	MY006: A trispecific antibody blocking 4 allergenic epitopes for the treatment of peanut allergy	Wuillemin N, Bieli D, Arena C, Scheibling R, Gasser P, Häner R, et al

(Continued)

TABLE I. (*Continued*)

Theme	Presentation title	Authors
	Fel d 1–expressing plant-derived bioparticle as a novel treatment for cat allergy	Layhadi JA, Gutierrez LC, Keane S, Fulton W, Samson N, Wu LYD, et al
	Ara h 2–expressing cucumber mosaic virus-like particle (VLP): A new generation of hypoallergenic and tolerogenic therapeutic vaccine for peanut allergy	Shamji MH, Layhadi JA, Samson N, Shreffler WG, Oriel RC, Palmer E, et al
	The Bruton tyrosine kinase inhibitor acalabrutinib aborts ongoing acute food-induced anaphylactic reactions in humanized mice	Arce B, Vilela NM, Chichester KL, Sokol KA, Alvarez-Arango S, Iacobelli L, et al
	Targeting sodium channel (NaV) subtypes to treat allergen-induced respiratory disease	Undem BJ, Kim J

expression of epoxide hydrolase (an enzyme that synthesizes 11,12-dihydroxyeicosatrienoic acid) by lung microbiota from mice with allergy.

PUNCHING ABOVE ONE'S WEIGHT: THE VERY LARGE EFFECTS OF VERY RARE CELLS

Tuft cells have been known for a few decades, but new technologies and the identification of a master transcriptional regulator of their development have now defined these rare chemosensory epithelial cells as multifunctional mucosal sentinels that rely on taste-signaling pathways and initiate type 2 responses, primarily through IL-25 and leukotriene C_4 production. Tuft cells signal to trigeminal sensory nerves to direct allergen-elicited olfactory remodeling. A tuft cell–OXGR1–SOX9 circuit detectable in the human sinus mucosa remodels the airway after injury. In the gastrointestinal tract, a group 2 innate lymphoid cell–tuft cell feed-forward circuit relies on the L-amino oxidase IL-4–induced 1 (IL4i1) expressed by intestinal dendritic cells, which is amplified by helminth infection. IL-4–induced 1 generates tryptophan metabolites that activate the aryl hydrocarbon receptor and drive intestinal tuft cell differentiation and IL-25 production. Finally, succinate, an activator of intestinal tuft cells, induces eosinophilic inflammation in the mouse gut, and the numbers of tuft cells in the gastric tissue of patients with eosinophilic gastroenteritis are increased, pointing to a potential involvement of these cells in the pathogenesis of this disease.

AT THE INTERFACE BETWEEN METABOLISM AND IMMUNE RESPONSES

Thanks to technologic advances that enable deeper deconvolution of metabolic responses, the immunometabolism field is advancing rapidly.[5] Footprints of the metabolic control of immunity can be found almost everywhere and connect seemingly distinct conditions. In obese adults, asthma increases abundance and metabolic activity of myeloid and lymphoid effector cells in adipose tissue. In AERD, acquired alcohol dehydrogenase-2 (ALDH2) deficiency within the respiratory tract, likely due to high local levels of IL-4 and IL-13, impairs alcohol metabolism and prevents the degradation of alcohol-derived acetaldehyde, leading to mast cell activation and alcohol-induced respiratory reactions. Treatment with either dupilumab, which blocks IL-4Rα signaling, or high-dose daily aspirin, which blocks production of prostaglandin D_2, was reported to improve alcohol tolerance in patients with AERD. In allergic lung inflammation, L-phenylalanine acts as a key metabolic checkpoint orchestrating the fate and function of T_H2 cells, whereas oxysterol regulates mast cell hyperplasia by acting on its chemotactic receptor EBI2 expressed on rare circulating mast cell progenitors. Of note, cholesterol 25-hydroxylase, the enzyme that generates the EBI2 ligand, is expressed by vascular endothelial cells, allowing the EBI2–cholesterol 25-hydroxylase axis to direct mast cell progenitor recruitment to the lung during allergic inflammation.

NOVEL TOOLS FOR ALLERGIC DISEASE TREATMENT

Lively discussions focused on new therapeutic tools, of which there are many.[6-8] Antibody-based approaches are advancing. CDX-622, a humanized bispecific tetravalent antibody that targets both TSLP and stem cell factor, was shown to neutralize TSLP and deplete mast cells— effects that are potentially desirable in inflammatory diseases in which these largely nonredundant pathways play pathogenic roles. CDX-622 demonstrated a favorable safety profile, good pharmacokinetics, and evidence of mast cell reduction in nonhuman primates and healthy human participants. MY006, a trispecific antibody that blocks 4 allergenic peanut epitopes, suppressed *ex vivo* basophil and mast cell responsiveness in samples from patients of different ages with different clinical histories and different geographic origins. In a humanized mouse model of peanut allergy, a single administration of MY006 prevented anaphylaxis in response to oral gavage of peanut butter. The antibody, which is currently undergoing IND-enabling studies, is expected to require only a few subcutaneous injections per year and provide continuous protection from allergic reactions caused by accidental peanut exposure.

Novel tools for allergen immunotherapy were highlighted. *Felinus domesticus* 1–expressing plant-derived bioparticles showed potential benefits against cat allergy. Initial studies in donors with cat allergy and nonatopic donors showed that these particles have strong tolerogenic properties and enhance T_H1 cell, IL-10–positive T-cell, and regulatory B cell responses. In peanut allergy, hypoallergenic Ara h 2–expressing cucumber mosaic virus–like particles were well-tolerated and demonstrated a reduced reactogenicity profile with induction of protective blocking antibodies indicative of potential efficacy.

Interesting developments regarding food-induced anaphylaxis, a field in need of novel rescue therapies, were presented. The Bruton tyrosine kinase inhibitor acalabrutinib stopped ongoing IgE-

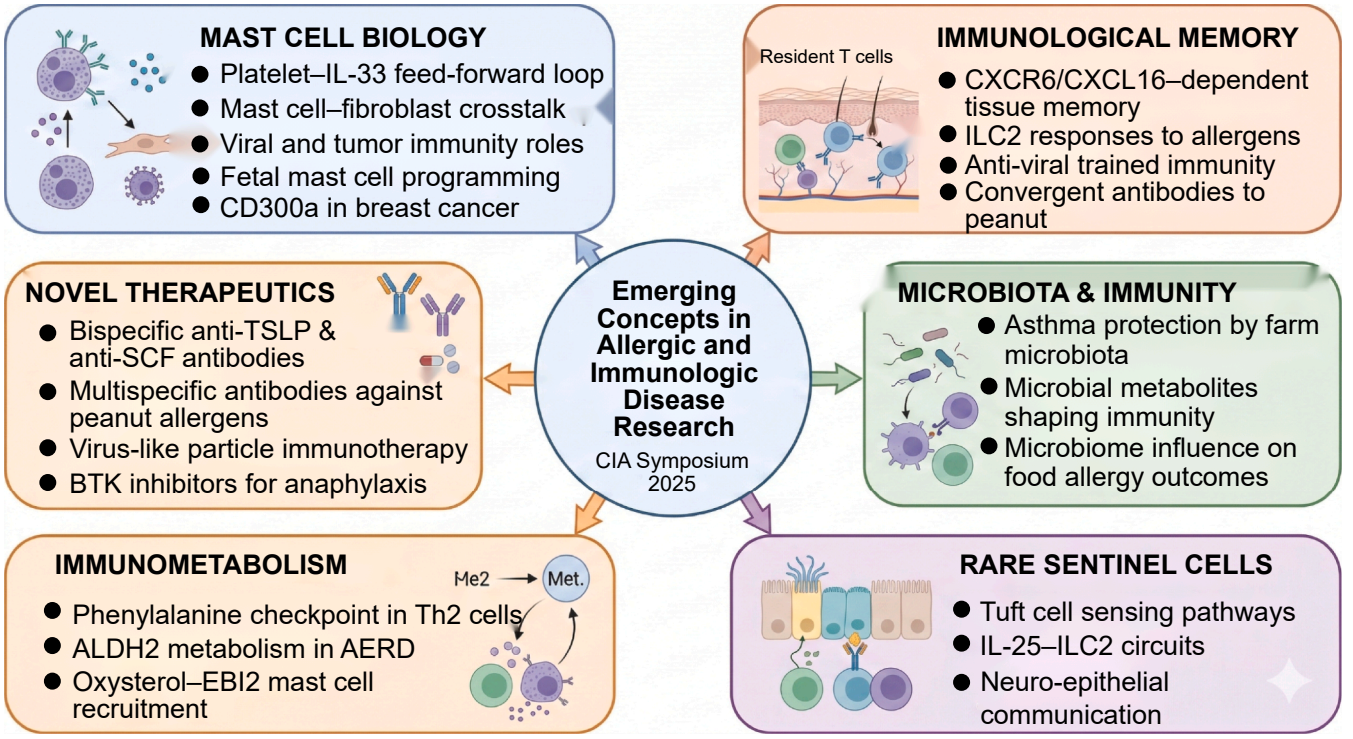

FIG 1. Emerging concepts in allergic and immunologic disease research: the 2025 CIA symposium.

mediated anaphylaxis and prevented mortality in humanized mice, suggesting that Bruton tyrosine kinase inhibitors could be effective rescue medications for treating acute anaphylaxis when given in conjunction with epinephrine. Moreover, selective blockers of specific voltage-gated sodium channels in the airway mucosa (NaV1.7, NaV1.8, Nav1.9, or a strategic combination thereof) were proposed as a safe and effective treatment for allergy-associated coughing and sneezing, as well as reflex secretions, stuffiness, and bronchoconstriction.

SUMMARY

This article highlights only a handful of the research concepts that emerged from the 2025 CIA symposium (Fig 1). The overall takeaway from the presentations is loud and clear. Basic, translational, and clinical research at the interface of allergy and immunology is thriving because of its rigor, imagination, and willingness to explore uncharted experimental territories and technologic developments. A discipline that used to be somewhat narrow in its focus is now embracing complexity and expanding its horizons, goals, and tools. If this trend continues, as it likely will, the future of allergic disease research is truly bright.

DISCLOSURE STATEMENT

Disclosure of potential conflict of interest: T. Bieber is a speaker and/or consultant for AbbVie, Almirall, AnaptysBio, Apogee, Aristea, Astria, Attovia, Belenos, Biogeneration, BioVerSys, Böhringer Ingelheim, Bristol-Myers Squibb, Bluefin, BYOME Labs, Cantargia, CellDex, Choate, Dermavant, DirigentBio, Domain Therapeutics, EMD Serono, EngImmune, Ennovate, Evommune, Forbion, Formycon, Galderma, Gilead, GSK, ImagGeneBio, Janssen, Kymab, Kymera, LEO, LG Chem, Lilly, Mabylon, MSD, Micreos, Nektar, Nextech, Novartis, Numab, Ornavi, Overtone, Pfizer, Pierre Fabre, Protagonist Tx, Samsung Bioepis, Sanofi/Regeneron, Scienta Lab, Serono, SwitchKine, TIRmed, Triveni, UCB, Union Therapeutics, UPStream Bio, WinWard, YUHAN, and Zurabio; in addition, he is founder and chairman of the board of the nonprofit biotech enterprise Davos Biosciences AG within the international Kühne-Foundation and founder and senior medical advisor of the consulting firm Bieber Dermatology Consulting. B. S. Bochner is a consultant for AllerGene AI Therapeutics, Zelig Therapeutics, and Celldex Therapeutics. J. A. Boyce is on the advisory board of Siolta Therapeutics. K. Izuhara reports grants from TORII Pharmaceutical Co, Ltd, Shino-test Co, Ltd, Maruho Co, Ltd, and Nippon Zenyaku Kogyo Co, Ltd. M. Kraft reports consulting fees and lecture payments from Sanofi, Regeneron, Chiesi, AstraZeneca, Kinaset, and Genentech; in addition, she has issued and pending patents related to surfactant protein A peptidomimetics, has leadership roles with the Association of Professors of Medicine and the Alliance for the Advancement of Internal Medicine; owns stock in RaeSedo, Inc, and serves as an UpToDate section editor for severe asthma. R. Sehmi reports research grants from the Canadian Institutes of Health Research, AstraZeneca, GlaxoSmithKline, Third Harmonics BioHaven, Inc, and Jasper Therapeutics, as well as speaker engagement and consulting fees from AstraZeneca, Sanofi, Respiplus, GlaxoSmithKline, and Areteia Therapeutics, Inc, outside the submitted work. S. E. Wenzel reports personal consulting with Chiesi, GSK, and Pfizer; has received compensation from Amgen for participation in a multicenter industry sponsored trial and from Regeneron for an investigator-initiated single-center study; and owns stock in the startup company Aer Therapeutics. D. Vercelli reports grants from Johnson & Johnson

and OM Pharma (to her institution). The rest of the authors declare that they have no relevant conflicts of interest.

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