swiss medical weekly

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www.smw.ch

Supplementum 289
ad Swiss Med Wkly 2025;155
August 21, 2025

Swiss Society of Allergology and Immunology
Abstracts of the annual meeting 2025

Lausanne (Switzerland), August 28–29, 2025

ANNUAL MEETING OF THE SWISS SOCIETY OF ALLERGOLOGY AND IMMUNOLOGY

LAUSANNE, AUGUST 28–29, 2025

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SHORT COMMUNICATION SESSION – ALLERGOLOGY

SC01

The bacterial lysate OM-85 mitigates HDM-induced allergic inflammation through the airway epithelial cell-macrophage crosstalk

A. Kouklas[1], A. Trompette[1], S. Guney[1], L. Stickley[1], A. Vaslin Chessex[2], C. von Garnier[1], C. Pasquali[2], E. Baulier[2], N. Ubags[1]

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Aims: The increase of allergic diseases in industrialized countries highlights the need for interventions restoring microbial diversity to support immune balance. Microbial-based therapies, like the bacterial lysate OM-85, show potential for immune modulation in allergic asthma. We hypothesize that intranasal OM-85 reduces HDM-induced airway inflammation by modulating alveolar epithelial cell–macrophage interactions.

Methods: Eight-week-old female BalbC/J mice received intranasal (i.n.) OM-85 (1 mg/kg in 40 µl) or vehicle every 48-72 hours, starting 5 days before and continuing through HDM sensitization and challenge (25 µg HDM every 48-72 hours for 2 weeks). Bronchoalveolar lavage (BAL) fluid was collected 96 hours post-challenge for cell counts. Lung immune cell composition and kinetics were analysed by flow cytometry, respiratory function assessed with FlexiVent™, and bulk RNA-sequencing on CD45+ and CD45- lung cells.

Results: I.n. OM-85 reduced HDM-induced AAI, decreasing BAL eosinophilia, airway mucus hypersecretion, and improving respiratory function. Type II alveolar epithelial cells (ATII) and distinct macrophage subsets, including alveolar macrophages, increased following OM-85 treatment in both control and HDM-exposed groups. GM-CSF-mediated ATII-macrophage interactions were observed. RNA-sequencing revealed OM-85-driven modulation of immune pathways, particularly those resolving inflammation.

Conclusions: Intranasal OM-85 reduces HDM-induced AAI by modulating immune and epithelial cells, promoting inflammation resolution, and enhancing lung function.

SC02

Type 1 IFNs drive trained immunity in asthma

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Trained immunity in innate immune cells provides protection against pathogens; however, its role in type 2 immune responses, such as allergy or helminth infections, remains relatively underexplored. Our previous work has identified an inflammatory macrophage memory in human asthmatics and demonstrated that intranasal exposure to house dust mite (HDM) reprograms myeloid progenitors in the bone marrow of mice, highlighting the involvement of central trained immunity in asthma. In this study, we identify type I interferons (IFNs) as key drivers of macrophage reprogramming in asthma. RNA sequencing of macrophages derived from the bone marrow or airways of HDM-exposed mice revealed the persistent, type I IFN-dependent upregulation of genes involved in extracellular matrix (ECM) remodeling—defining a hallmark of trained immunity in asthma. Supporting this finding, mice lacking hematopoietic type I IFN signaling failed to upregulate cysteinyl leukotrienes (cysLTs), which are critical mediators of type 2 inflammation. Our findings uncover a previously unrecognized role for type I IFNs in trained immunity in asthma and identify a pathway through which these mediators drive an alternative "type 2 training" program in airway macrophages.

SC03

Characterization of young children with food allergy in Northwestern Switzerland

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Background and aims: The prevalence of food allergy (FA) is raising. It is therefore important to better understand FAs and their course to improve prevention and treatment. This study describes characteristics of FA patients in Northwestern Switzerland.

Methods: This study is part of an ongoing prospective cohort study, including children <2y with newly diagnosed IgE-mediated FA. We analyzed clinical data from 64 patients enrolled between 06/2020 and 02/2022.

Results: Mean age at enrollment was 12.4 months (SD=5.18), with positive family history for atopy in 53/64 patients. Atopic dermatitis was found in most patients (N=62/64, mean SCORAD 9.37), 24/64 patient presented allergic rhinoconjunctivitis/wheezing in the follow up. 36/64 patients were allergic to a single food allergen, milk allergy (MA) being the most common FA (N=30/64), followed by egg (EA) (N=25/64), tree nut (TN) (N=24/64) and peanut allergy (PN) (N=10/64). Patients with MA/EA started a stepwise introduction using food ladders (N=30). Patients who completed food ladders showed resolution after 15.64 months (SD 2.75) for MA (N=26/30) and 13.5 months (SD 8.93) for EA (N=20/23). TN/PN allergy resolved in 10/34 patients. Oral immunotherapy was started in 14/25 patients with persisting food allergy.

Conclusion: Our cohort represents distribution of FA as previously described among children in Europe and is therefore valuable cohort for further investigations. With TN allergy as the second frequent FA, this study supports the need to focus on prevention and treatment strategies for TN allergy.

SC04

Predicting Tolerance and Intolerance in Pediatric Hazelnut Oral Food Challenges: A Cohort Analysis

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Aim: Oral food challenges (OFCs) are the gold standard for diagnosing food allergy, yet predicting outcomes remain difficult. We aimed to identify predictors of hazelnut OFC outcomes in a real-world setting.

Methods: We analyzed 166 hazelnut OFCs conducted between 07/2022 and 04/2025. Clinical and diagnostic parameters—including specific IgE (sIgE), skin prick tests, and clinician-assigned risk categories—were assessed. Predictive performance for OFC outcomes was evaluated statistically including positive predictive value (PPV) and negative predictive value (NPV). EAACI cut-offs were included.

Results: OFCs were performed for allergy exclusion (48%), threshold evaluation before oral immunotherapy (OIT; 37%), and family-requested clarification (15%). Overall, 53% tolerated the OFC, while 45% were intolerant. Notably, 11% of OIT candidates tolerated the OFC, while 10% of low-risk patients reacted. Intolerant children were older, with a median reactive dose of 300 mg protein and median oFASS-5 score of 3. The strongest predictor of intolerance was high-risk classification by experienced clinicians (PPV 90%), followed by Cor a 14-specific IgE ≥0.64 kU/L (PPV 86%). Tolerance predictors included sIgE hazelnut <0.35 kU/L (PPV 96%), Cor a 14 <0.64 kU/L (PPV 93%), and low-risk classification (PPV 90%).

Conclusion: Low hazelnut and Cor a 14 sIgE, and a low-risk profile, strongly predicted tolerance. Clinical risk assessment and Cor a 14 ≥0.64 kU/L were the best predictors of intolerance. Outliers in both directions confirm that OFCs remain indispensable.

SC05

The Impact of Obesity in Asthma and Small Airway Dysfunction: Prevalence, Clinical characteristics, and Predictors

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Aim: Obesity is a growing global health threat and a comorbidity that worsens asthma outcomes. Small Airway Dysfunction (SAD) is a significant but often overlooked contributor to asthma pathophysiology. SAD is common in obese asthmatic patients, but its relationship with BMI and role as a clinical predictor remain unclear.

Methods: A 3-year study was conducted on 660 asthmatic patients undergoing spirometry, impulse oscillometry (IOS), and FeNO tests. Patients were divided into non-obese (n=556, BMI 20–29.99 kg/m²) and obese (n=102, BMI ≥30 kg/m²) groups. Obese patients were further classified into mild (n=87, BMI 30–39.99 kg/m²) and morbid (n=15, BMI ≥40 kg/m²) obesity. SAD was defined as R5–R20 > 0.07 kPa/L/s.

Results: Obese patients had lower atopy (42.2% vs 65.3%), more nocturnal awakenings (70.6% vs 38.1%), and higher exercise-induced asthma (78.4% vs 48.2%) (Chi-square p<0.005). Exacerbations (0.64±0.701 vs 0.44±0.70) and ER visits (0.24±0.470 vs 0.08±0.273) were higher (p<0.005). IOS showed superior sensitivity compared to spirometry: SAD prevalence was higher in obese patients (90.2% vs 57.7%, p<0.05), with no correlation observed between BMI and FEF 25–75%.

Conclusions: SAD is multifactorial and strongly linked to obesity. IOS showed superior sensitivity compared to spirometry, emphasizing limitations of standard lung function tests. Early identification of SAD in obese asthmatic patients allows for better phenotyping and personalized treatments, such as extra-fine inhalers, improving asthma control, reducing exacerbation, and enhancing quality of life.

SC06

Protein profiles of children with food allergies

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Background and aim: As the prevalence of food allergy (FA) increases, new treatments such as oral immunotherapy (OIT) are being used more often, especially in young children. OIT is usually well tolerated but can lead to serious side effects like anaphylaxis or eosinophilic esophagitis. Tree/peanut allergies are less likely to outgrow than egg/milk allergies. To date, there are no objective markers to predict FA persistence or outgrowth. We investigated immune-related protein profiles in children with FA, some of whom have outgrown FA, to identify potential diagnostic markers.

Methods: We used Olink® to measure 162 proteins involved in inflammation and immune response in dried blood spots from 64 children aged under 2 years at the time of FA diagnosis. Hierarchical clustering and sparse partial least squares discriminant analysis (sPLS-DA) were used for the analysis.

Results: Clustering of the measured proteins revealed 3 distinct clusters with differences in age and total IgE, but not in FA persistence or outgrowth. Younger children had lower IgE and higher normalized protein expression (NPX) levels, while older children showed the opposite. Interestingly, children who had outgrown their FA showed higher levels of certain cytokines, including IL12b, CCL20 and IL10RB.

Conclusion: This is the first study of protein profiles in children with FA. Certain proteins, including IL12b, CCL20 and IL10RB, may help to identify patients at an early stage who are at higher risk of developing persistent FA and who may therefore benefit from an early OIT.

SHORT COMMUNICATION SESSION – CLINICAL IMMUNOLOGY & ALLERGY

SC07

Dupilumab Treatment is Associated with a Shift towards a health-associated Nasal Passage Microbiota in Diffuse Type 2 Chronic Rhinosinusitis

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Background: Nasal microbiota composition of patients with diffuse type 2 chronic rhinosinusitis with nasal polyps (CRSwNP) is altered compared to healthy individuals. Dupilumab, an anti-IL-4Rα-mab, modulates type 2 inflammation but the effect on microbiota composition in CRSwNP is unknown. The aim of this study was to investigate longitudinal effects dupilumab on the nasal passage and gastrointestinal microbiota.

Methods: Twenty-seven patients with diffuse type 2 CRSwNP treated with dupilumab 300mg subcutaneously every two weeks, 10 untreated patients with CRSwNP and 11 healthy controls were included. Nasal and stool samples were collected at day 0, 28, 90, and 180 post-treatment of the treated CRSwNP group and at day 0 and 28 of untreated CRSwNP and healthy controls. The samples were analysed using 16S rRNA gene amplicon sequencing (V3/V4).

Results: In CRSwNP patients, the most abundant genera in nasal passage microbiota were *Corynebacterium* and *Staphylococcus*. *Cutibacterium* and *Lawsonella* were less abundant in CRSwNP at baseline compared to healthy controls. Dupilumab treatment was associated with increased abundances in nasal passage of genera such as *Lawsonella, Corynebacterium and Dolosigranulum.* Microbial diversity of the gastrointestinal microbiota in CRSwNP at baseline was significantly higher than in healthy controls.

Conclusion: Dupilumab treatment was associated with a shift in the nasal passage bacterial microbiota towards that of healthy controls. These findings suggest that nasal passage microbiota composition is influenced by the underlying inflammatory endotype.

SC08

PLGA-Microsphere based T-cell vaccination against Influenza A virus

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Current influenza vaccines target the highly variable surface proteins hemagglutinin (HA) and neuraminidase (NA) of Influenza A virus (IAV), resulting in inconsistent efficacy due to antigenic drift and shift. Frequent changes necessitate annual vaccine updates, creating logistical and financial burdens. In contrast, internal proteins like matrix protein 1 (M1), viral polymerase (PA), and nucleoprotein (NP) are highly conserved. We developed a T-cell vaccine targeting epitopes of these conserved proteins to achieve heterosubtypic protection. Peptides from M1, PA, and NP, as well as full-length NP, were encapsulated with the TLR3/RIG-I ligand Riboxxim into Poly(lactic-co-glycolic acid) (PLGA) microspheres (MS). PLGA-MS offer high bioavailability, biodegradability, and an antigen depot effect. Vaccination with PLGA-MS induced a cytotoxic T-cell response that reduced lung IAV titers and mortality in mice after lethal infection. Cross-protection against distinct IAV strains was observed for both peptide and protein vaccines. However, differences in the magnitude and durability of the immune response highlighted the broader protection achieved with full-length protein vaccines. Our findings underscore the potential of PLGA-MS as a platform for T-cell–mediated influenza vaccines and reveal important distinctions between peptide- and protein-based formulations.

SC09

Type 2 inflammatory microenvironment in patients with Chronic Rhinosinusitis with Nasal Polyposis: exploring before and after 12 months of Dupilumab

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Aim: Patients with CRSwNP often experience disease recurrence despite conventional therapies. Biologics like Dupilumab have shown significant efficacy, but the underlying mechanisms of response and residual disease are not fully understood. This study explores changes in the type 2 immune microenvironment of nasal polyps before and after 12 months of Dupilumab treatment.

Methods: FFPE nasal polyps sections collected from 9 male and 4 female CRSwNP patients (mean age: 54±10 years), before and after 12 months of Dupilumab therapy, were stained with H&E and immunohistochemistry for eosinophils, mast cells (MCs), and M2-like macrophages (M2 Mφ). Immunoreactivity was quantified via computer-assisted image analysis and expressed as a percentage of the total tissue area.

Results: 12 out of 13 subjects fulfilled ≥2 EPOS/EUFOREA response criteria to biologic treatment. Eosinophil immunoreactivity significantly declined from 2.94±2.69% to 0.62±1.21% at 12 months post-treatment (p=0.009). In contrast, MCs increased (3.12±2.77% to 4.16±2.94%; p=ns), and M2 Mφ showed a slight decrease (3.92±2.51% to 2.84±2.38%; p=ns), with no significant correlations observed among the three cell types.

Conclusions: The nasal polyp microenvironment involves diverse interacting immune and non-immune cells. While eosinophils decreased, MCs and M2 Mφ persisted 12 months after Dupilumab treatment. These results suggest further investigation is needed to clarify their roles in CRSwNP pathogenesis and to understand why some patients respond poorly, possibly due to incomplete inflammatory blockade.

SC10

A Collaborative Care Model for Patients with Primary Immunodeficiency - Update on a Swiss Model with Comprehensive Genetic Characterization

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Background: Effective management of primary immunodeficiency disorders (PID) requires experienced centers, which are limited in number and funding. We present a Swiss collaborative care model synergizing specialized private practices and university centers to enhance patient care by facilitating earlier access to specialized diagnostics, comprehensive laboratory and genetic analyses, including participation in a prospective research cohort.

Methods: We report on a prospective cohort of 18 patients (median age 52 years, 8 females, mean diagnostic delay 5 years) managed through this collaborative model. All patients underwent detailed clinical phenotyping and comprehensive immunological workup. For the majority of patients (10/18), research-based whole exome sequencing (WES) was performed.

Results: Specific results of rare immune gene variants and their predicted relevance for clinic, prognosis and treatment adaptations will be presented at the meeting.

Conclusion: Rare predicted functionally relevant immune-gene variants were found in all assessed patients, informing on therapeutic adaptations in some. The integration of WES into routine care provided novel insights into underlying molecular mechanisms and supported tailored patient management. The combined expertise of peripheral clinical immunologists and university centers contributed to improved patient outcomes and a deeper molecular understanding of immunodeficiency. Patients benefit from both immediate clinical care with individualized treatment plans and inclusion in a prospective cohort for ongoing research.

SC11

Harnessing an epigenetic rewiring technique to tailor T cell differentiation for controlling colitis and tumors

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Aim: CD8⁺ T cell exhaustion limits the efficacy of immunotherapies such as PD-1 blockade, ACT, and CAR-T. This dysfunction is associated with stable epigenetic changes, including locus-specific DNA methylation. We hypothesize that targeted demethylation of exhaustion-related loci could durably restore T cell functionality. Our aim is to (1) develop a mouse model enabling locus-specific DNA demethylation, and (2) adapt this strategy to human T cells for therapeutic purposes.

Methods: We engineered a transgenic mouse expressing a demethylation machinery recruited by gRNAs to specific genomic regions. We first validated the system on induced regulatory T cells (iTregs), which are inherently unstable due to methylation-driven loss of *Foxp3*. We then applied it to candidate loci involved in T cell exhaustion.

Results: Targeted demethylation of the *Foxp3* locus in iTregs restored stable expression and suppressive function, notably improving disease control in a colitis model. The system also allowed us to identify and functionally interrogate exhaustion-associated genes in CD8⁺ T cells, by actively reversing methylation at several selected loci in vivo.

Conclusions: This approach offers a flexible platform to reshape T cell fate through precise epigenetic editing. It opens new possibilities to enhance the durability and depth of anti-tumor responses by directly targeting the epigenetic roots of exhaustion.

SC12

Targeting Type 2 Cytokines Alters Epigenetic Reprogramming of Eosinophil Progenitors in Severe Asthma

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Asthma is a chronic type 2 inflammatory condition in which both innate and adaptive immune cells drive its onset and exacerbation. However, the mechanisms and functions of allergen-induced metabolic and epigenetic reprogramming of these cells remain poorly understood. In a severe eosinophilic asthma model, we found expansion and epigenetic reprogramming of eosinophil progenitors (EoP) using single cell ATAC-Seq of hematopoietic stem and progenitor cells (HSPC).

Mice with chronic asthma induced by house dust mite and curdlan were treated intraperitoneally with anti-IL-4Ra antibody (mimicking dupilumab treatment in patients). Eosinophilic lung inflammation was analyzed by histology, differential cell count, flow cytometry, and immunofluorescence staining, while bone marrow EoP were assessed via flow cytometry. To further study EoP reprogramming, we have established long-term *ex vivo* HSPC (exHSPC) cultures that preferentially differentiate into either EoP or monocyte progenitors (MoP).

Asthmatic mice showed elevated eosinophils in bronchoalveolar lavage fluid, lung tissue, and increased EoP in the bone marrow. Anti-IL-4Ra treatment significantly reduced both airway eosinophilia and EoP expansion. However, this effect was independent of IL-4Ra expression on eosinophils, as $IL\text{-}4Ra^{fl/fl}xEpx^{Cre}$ mice showed normal airway inflammation, eosinophil development, and activation. Thus, epigenetically "trained" EoP may sustain chronic type 2 inflammation, and dupilumab indirectly targets EoP potentially by targeting IL-4Ra-expressing lymphocytes during chronic asthma.

SHORT COMMUNICATION SESSION – BASIC IMMUNOLOGY

SC13

Dysfunctional Mitochondria Promotes DNA Damage and T Cell Exhaustion in CD8+ T Cells

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T cell exhaustion is a state of T cell dysfunction with reduced proliferation capacity, cytokine production, and loss of responsiveness to immune checkpoint blockade. Growing evidence demonstrates that the global epigenetic alterations are the critical factors to drive T cell exhaustion under persistent antigen exposure. However, it is unclear how the epigenetic alteration is induced. We found tumor-infiltrating $CD8^+$ T cells (TILs) accumulated damaged mitochondria, characterized by increased mitochondrial mass but reduced mitochondrial membrane potential. The TILs with disturbed mitochondria exhibited more severe exhausted phenotype, including reduced cytokine production and upregulation of co-inhibitory receptors. We further identified that glucose deprivation, hypoxia, and tumor cell-conditioned medium can induce the accumulation of damaged mitochondria *in vitro* and drastically weakened T cell immunity *in vivo*, suggesting metabolic stress in tumors can drive T cell exhaustion. Intriguingly, ATAC-seq revealed that genes involved in DNA damage signaling were more accessible in TILs. Indeed, $PD\text{-}1^+$ $TIM\text{-}3^+$ TILs or TILs with disturbed mitochondria displayed high level of γH2AX, a marker of DNA break, and upregulated DNA damage-associated genes. Interestingly, we found DNA damage can increase PD-1, TIM-3, and TOX while decrease IFN-γ and TNF-α expression *in vitro*. The exhausted phenotype was sustained even when DNA damage was resolved. Together, our study reveals that the mitochondrial fitness and DNA damage signaling may determine the fate of T cell toward exhaustion.

SC14

Training improves antimicrobial innate immune defenses in aged mice

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Introduction: We demonstrated that trained immunity, the memory-like property of the innate immune system, protects young adult mice against a wide range of infections.

Aim: To determine whether trained immunity counteracts immunosenescence and protects aged mice from bacterial infections.

Methods: We compared young (8-12 weeks) and aged (18-24 months) mice trained using β-glucan.

Results: Training increased bone marrow hematopoietic stem cells (HSCs) and myeloid-biased progenitors, and blood monocytes and neutrophils. HSCs from trained aged mice, compared to young mice, up-regulated pathways associated with DNA repair and replication, cytokinesis, metabolism and myeloid differentiation. RNA-seq data segregated monocytes from aged and young mice, and monocytes from control and trained mice exposed to LPS. Training increased pathways associated with cell migration and inflammatory response in LPS-stimulated monocytes from aged mice. Blood from aged mice produced low levels of cytokines in response to microbial stimulation, but training restored cytokine response. Training protected aged mice from *Escherichia coli* peritonitis and *Streptococcus pneumoniae* pneumonia.

Conclusions: Cardinal signs of training, including increased myelopoiesis, cytokine response to microbial stimulation and protection against bacterial infections, were observed in aged mice. It suggests that therapies along the lines of training may be designed to enhance antimicrobial resistance in the elderly.

SC15

Tailoring T cell anti-tumor immunity in hepatocellular carcinomas by exploiting Kupffer cell-guided priming

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Although macrophages are considered as antigen-presenting cells (APCs), their roles in supporting T cell anti-tumor immunity are less appreciated as their differentiation into immunosuppressive status prevails over immune supportive differentiation in the tumor microenvironment (TME). Moreover, it remains elusive whether macrophage-driven T cell priming can lead to distinct impacts on host anti-tumor immunity compared to dendritic cell (DC)-mediated priming. Here, we find that depletion of Kupffer cells (KCs), the liver-resident macrophage population, leads to the decreased abundance and accelerated exhaustion of tumor-reactive CD8 T cells in murine hepatocellular carcinoma (HCC) models. Moreover, KCs play an instructive role on formulating anti-tumor immunity by differentially priming CD8 T cells compared to DCs. Intriguingly, KC-mediated priming resulted in a specialized differentiation program forcing unique activation status retaining high TCF1 expression and elevated effector functions in CD8 T cells, indicating KC-mediated priming can drive formation of T cells displaying stem-like effector phenotype. Moreover, monocyte-derived Kupffer cells (MoKCs), a subset that can replenish resident KC pool upon liver damages and tumor formation, also support differentiation of T cells into a status similar to that of KC-primed CD8 T cells. Overall, these findings unveil novel anti-tumoral functions of KCs against HCC via exerting *in situ* priming of CD8 T cells within the liver and further indicate the potential on applying HCC treatments by boosting KC-mediated T cell priming.

SC16

The role of Regulatory factor X 7 in B cell activation and lymphomagenesis

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Regulatory Factor X 7 (RFX7) is a transcription factor emerging as an important regulator of immunity. We previously found that it is required for maintaining natural killer (NK) cells' homeostasis by limiting their activation and metabolic rate. Interestingly, elevated metabolism is a hallmark of cancer and RFX7 mutations have been reported in Burkitt's lymphoma as well as in diffuse large B cell lymphoma (DLBCL), two B cell malignancies

originating from antigen-experienced B cells. We thus set out to study the role of RFX7 in B cell lymphomagenesis and activation. We observed that RFX7 mutations found in Burkitt's lymphoma and DLBCL cause loss of transcription factor function. Notably, *in vivo* deletion of Rfx7 in B cells accelerated pathogenesis in Bcl6- and p53 loss-driven murine lymphoma models. Accordingly, Rfx7-deficient B cells exhibited higher Myc activity and stronger activation *in vitro* and, upon immunization, mice with Rfx7-deleted B cells produced larger germinal centers (GCs) and higher plasmablast responses. This phenotype was reverted by Myc haploinsufficiency, providing partial protection from non-aggressive *p53/Rfx7*$^{-/-}$ B cell lymphoma, but not from aggressive form of the disease. Full deletion of Myc or AID, which garners genomic instability in activated B cells, protects the mice from aggressive lymphoma in the *p53/Rfx7*$^{-/-}$ double-hit model. Collectively, these data shed light on the importance of RFX7 in orchestrating B cell activation, Myc activity, as well as repressing Myc and AID-dependent lymphomagenesis.

SC17

CCDC134 controls TLR biogenesis through the ER chaperone Gp96

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Aim: Toll-like receptors (TLRs) play a central role in initiating immune responses against pathogens. While dysregulation of TLR signaling can contribute to inflammatory and autoimmune diseases, the regulatory networks controlling TLR responses remain incompletely understood. This study aimed to identify novel molecular mechanisms underlying specific TLR signaling pathways.

Methods: We performed a loss-of-function genetic screen in a reporter cell line engineered to undergo cell death upon TLR7-induced IRF5 activation and identified genes conferring resistance to IRF5-induced cell death. A subset of candidate genes was validated, and follow-up assays were performed to elucidate their molecular functions.

Results: We identified CCDC134 as an essential factor for TLR responses. CCDC134 deficiency impaired endolysosomal TLR-induced NF-κB, MAPK, and IRF5 activation, as well as downstream production of proinflammatory cytokines and type I interferons. CCDC134 was found to be an endoplasmic reticulum (ER)-resident interactor of Gp96 (HSP90B1/Grp94), a chaperone essential for the folding and trafficking of plasma membrane and endolysosomal TLRs. CCDC134 controlled Gp96 stability as its loss resulted in Gp96 hyperglycosylation and degradation via the ER-associated protein degradation (ERAD) pathway. Accordingly, CCDC134 deficiency impaired the folding, maturation, and trafficking of TLRs, resulting in blunted inflammatory responses upon stimulation.

Conclusions: CCDC134 is a key regulator of the chaperone Gp96, controlling thereby TLR biogenesis and signaling responses.

SC18

Skin TSLP acts on non-canonical DC population to promote GATA3+ Treg

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Skin represents the first line of defense against pathogens and external physical dangers. In Atopic Dermatitis (AD), a damaged skin barrier is associated with a keratinocyte-derived overproduction of Thymic Stromal Lymphopoietin (TSLP), driving the pathogenesis. Originally identified as a pro-Th2 cytokine, TSLP has been recently reported by our lab to promote via dendritic cells (DC) the generation and accumulation of GATA3-expressing regulatory T cells (GATA3^{+} Treg). In this study, we used a TSLP overexpressing AD model originally established by the lab, and also employed DC-selective knock-out mouse lines associated with gene reporter and lineage-tracing mouse tools, combined with flow cytometry, scRNAseq analyses and functional assays, to decipher TSLP-triggered DC-T cell axes. Our data revealed that TSLP drives GATA3^{+} Treg through a specific migratory DC population where the costimulatory molecule OX40L is crucially required, thus uncovering a previously unrecognised tolerogenic axis in promoting immune suppression.

SHORT COMMUNICATION SESSION – TRANSLATIONAL

SC19

Neutrophil-mediated melanoma cell killing in adjuvant antibody therapy

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Aims: The potential of neutrophils as potent effector cells can be harnessed for immunotherapies. For patients at a high risk of melanoma recurrence, post-surgery adjuvant therapy is recommended, but current approaches are variably effective and often associated with treatment-limiting side effects. Here, we propose using antibodies against a tumor-associated antigen as an alternative adjuvant therapy with an improved safety profile.

Results: We discovered an association between antitumor B-cell responses, tumor-infiltrating neutrophils, and long-term survival in patients with melanoma. We screened tumor-associated antigens and identified the melanocyte differentiation antigen tyrosinase-related protein 2 (TRP2) as a relevant target. We then identified TRP2-specific B-cell clones and recombinantly produced monoclonal antibodies against TRP2 that protected wild-type mice from tumor challenge in the absence of marked side effects, mediating tumor cell killing by neutrophils. When humanized, the discovered antibodies also recognized human TRP2 and mediated the killing of human melanoma cells.

Conclusions: Our findings identify TRP2-binding antibodies as candidates for a well-tolerated and potentially highly effective adjuvant treatment for melanoma. Tumor-specific antibodies represent a promising therapeutic modality for solid tumors with potential for rapid translation to clinical practice, particularly as an adjuvant treatment to enhance existing therapies.

SC20

Autophagy in dendritic cells impacts immunoscenecence

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Context: Aging significantly impacts the T cell compartment, leading to immunosenescence a decline in immune function associated with inflammaging. Dendritic cells (DCs) play a crucial role in this context, as their function is altered with age.

Objectives: Our study aims to analyze the contribution of autophagy, a major pathway in cellular homeostasis, to DCs function and its impact on the aged CD4 T cell compartment.

Methods: We studied a cohort of old mice (60-80 weeks) lacking autophagy in their DCs ($Atg14^{flox/flox}$ /CD11c-Cre^{+}). We monitored their survival rate, weight loss, and systemic signs of inflammaging using cytokine analysis, histological screening of peripheral organs, and an extensive immunophenotyping of the CD4 T cell compartment (single cell RNA sequencing). In parallel we monitored DCs phenotype and function and analyzed by mass spectrometry their immunopeptidome.

Results: Our results revealed a critical contribution of autophagy in DCs to inflammaging. $Atg14^{flox/flox}$ /CD11c-Cre^{+}mice show reduced survival and increased weight loss, that correlate with an enhanced inflammatory status. Single cell RNA sequencing analysis revealed a skewed distribution of CD4 T cell subsets with an imbalance in the naïve/memory ratio as well as an increase in the diversity of their TCR repertoire. This phenotype could be the consequence of the observed alterations of the immunopeptidome of autophagy-deficient DCs.

Perspectives: Ongoing analysis on the phenotype of aged DCs will reveal how autophagy impacts immunosenescence, opening new avenues for therapeutic interventions.

SC21

Targeting IFN-γ-Driven DCsion to Harness Type-2 Immunity Against Tumor Resistance

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Aim: Acquired resistance to ICB remains a major challenge in cancer therapy, often driven by tumor cell loss-of-function mutations in IFN-γ sensing that promote immune evasion and T cell dysfunction. We aimed to define how IFN-γ signaling alters T cell responses and to identify strategies to restore effective anti-tumor immunity in the context of acquired resistance.

Methods: We employed a murine melanoma model with defective IFN-γ sensing and a CAR-T cell system to mimic acquired resistance. IFN-γ was depleted genetically or via antibody treatment. scRNA-seq profiled immune landscape changes. Functional studies involved targeted deletion of IFN-γR1 and IL-4 in T cells, and selective depletion of cDCs to assess their impact on T cell function.

Results: IFN-γ-insensitive tumors accumulated excessive IFN-γ, driving $CD8^{+}$ T cell exhaustion and CAR-T therapy failure. IFN-γ blockade restored tumor-specific $CD8^{+}$ T cell responses and rejuvenated CAR-T function. scRNA-seq revealed that IFN-γ blockade reprogrammed cDC2 and induced a Th2-like $CD4^{+}$ T cell phenotype producing IL-4 and IL-13. Targeted ablation of IL-4/IL-13 increased Tcf-1^{+} progenitor $CD8^{+}$ T cell but impaired effector differentiation, while enhancing IL-4 signaling improved $CD8^{+}$ T cell effector function and tumor control.

Conclusions: Our study identifies enormous IFN-γ signaling as a key driver of immune dysfunction in acquired resistance. Targeting IFN-γ and leveraging type 2 immune responses restore $CD8^{+}$ T cell activity and improve anti-tumor response, offering a promising therapeutic strategy to overcome resistance to ICB.

SC22

Mapping Intestinal Development and Function with Spatiotemporal Analysis and Organ-on-a-Chip Models

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Understanding the development of immune, epithelial, and stromal compartments in the gut around birth allows us to elucidate age-dependent changes in tissue function and disease susceptibility. Here, we used single-cell RNA sequencing (scRNA-seq), single-cell assay for transposase-accessible chromatin with sequencing (scATAC-seq), and spatial transcriptomics to analyse 52 samples from fetuses aged 12-20 post-conceptual weeks, newborns and up to teenage years. This comprehensive approach allows for the identification of cell types and states, as well as spatial interactions during development.

Preliminary data reveal significant changes in metabolic pathways within the epithelium and alterations in immune system components, extracellular matrix organization, and metabolic pathways in fibroblasts around birth. Notably, genes involved in chemotaxis, extracellular matrix organization, and oxidative stress exhibit higher expression and chromatin accessibility postnatally.

To further investigate these findings, we are developing patient-derived organoids to perform functional studies. These organoids, integrated into an organ-on-a-chip system, will enable hypothesis testing derived from transcriptomic data and allow to investigate host-microbiota interactions in early life.

This study provides a foundational framework for understanding age-dependent changes in the gut, with potential implications for developing targeted therapies for pediatric diseases. Further functional studies using organ-on-a-chip models will allow to validate these findings and explore their clinical relevance.

SC23

Dysregulations in L-phenylalanine metabolism facilitate pro-inflammatory Th2 phenotype in severe allergy

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Changes in T cell metabolism determine their fate. Metabolic reprogramming exhibited by CD4⁺T cells in allergic diseases remains poorly understood.

Hence, we performed metabolomics of circulating memory CD4+Teff and Treg cells from healthy subjects which revealed significant enrichment in pathways and metabolites related to L-phenylalanine (Phe). Next, we studied effect of Phe on CD4+T cell energy metabolism and observed that Phe significantly enhanced memory CD4+T cell glycolysis and limited OXPHOS. Furthermore, Phe blocked memory CD4+T cell proliferation via an Interleukin-4-induced-gene 1-dependent mechanism confirmed by siRNA experiments. Energy metabolism assessment of Phe-treated Th2 cells by single cell energy metabolism profiling (SCENITH), revealed that Phe significantly increased glycolytic capacity and decreased mitochondrial dependence. In in vitro differentiated Th2 cells, Phe limited cell proliferation via IL4I1 induction, STAT6 and mTOR phosphorylation, and expression of critical type 2 factors including mTOR, IL4, IL5, IL9, and IL13 and pathogenicity marker CD161. Metabolomics and ex vivo assessment of CD4+Teff cells and serum of allergic patients revealed significantly lower intracellular abundance of Phe in circulating memory CD4+Teff cells of a subset of severe allergic patients, elevated serum Phe, and significant negative correlation between LAT1, an important Phe transporter, and serum Phe.

Altogether, these data highlight that Phe regulates Th2 cell metabolism and development of pathogenic Th2 cells and this mechanism is impaired in severe allergy.

SC24

Tumor specific regulation of T cell exhaustion can be targeted for immunotherapy

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Persistent exposure to antigen during chronic infection or cancer renders T cells dysfunctional. The molecular mechanisms regulating this state of exhaustion are thought to be common in infection and cancer, despite obvious differences in their microenvironments. We focused our studies on several transcription factors specifically involved in the regulation of T cell exhaustion in cancer. Among them, NFAT5, an NFAT family member lacking an AP-1 docking site, is highly expressed in exhausted T cells from murine and human tumors and is a central player in tumor-induced exhaustion. While NFAT5 overexpression in T cells led to increased tumor growth, NFAT5 deletion improved tumor control by promoting the accumulation of more functional tumor-specific CD8+ T cells. Conversely, NFAT5 had no effect on chronic infection-induced T cell exhaustion. Taking advantage of our NFAT5-activity reporter mice, we found tumor specific mechanisms regulating the specific role of NFAT5 in tumors. In a more translational approach, we developed NFAT5 specific inhibitors. We demonstrated that they blocked NFAT5 activity in T cells both in vitro and in vivo, without affecting organs such as the kidney or the heart, where NFAT5 activity has central roles. This blocking led to a decrease in T cell exhaustion, showing the potential of such an approach for increasing anti-tumor response.

SHORT COMMUNICATION SESSION - SYIS

SC25

The IL-9-IL-18 Axis Drives Th2 Activation in Atopic Dermatitis

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Background: T helper 2 (Th2) cells are crucial contributors to the pathogenesis of atopic dermatitis (AD) by secreting high levels of interleukin (IL-)13 and IL-22. Yet, the upstream regulators that activate Th2 cells in AD skin remain unclear. IL-18 is a putative upstream regulator of Th2 cells as it is implicated in AD pathogenesis and has the capacity to activate T cells.

Objective: To decipher the role of IL-18 in Th2 responses in blood and skin of AD patients.

Results: IL-18R$^+$ Th2 cells were enriched in blood and lesional skin of AD patients. Of all the cytokines for which Th2 cells express the receptor, only IL-9 was able to induce IL-18R via an IL-9R-JAK1/3-STAT1 signaling pathway. Functionally, stimulation of circulating Th2 cells with IL-18 induced secretion of IL-13 and IL-22, an effect that was enhanced by co-stimulation with IL-9. Mechanistically, IL-18 induced Th2 cytokines via activation of both NF-κB and AP-1 signaling in Th2 cells, and neutralization of IL-18 inhibited these cytokines in cultured explants of AD skin lesions. Finally, IL-18 protein levels correlated positively with disease severity in lesional AD skin.

Conclusion: Our data identify a novel IL-9-IL-18 axis that drives Th2 cell responses in AD and demonstrate a critical role of IL-9-mediated upregulation of the IL-18R via an IL-9R-JAK1/3-STAT1 signaling cascade. Our findings suggest that both IL-9 and IL-18 could represent upstream targets for future treatment of AD.

SC26

Vaccine-enhanced competition permits rational bacterial strain replacement in the gut

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Infections with antimicrobial resistant bacterial were responsible for almost 5 million deaths worldwide, in 2019. Therefore, alternative treatment strategies are urgently needed. Colonization of the intestinal lumen precedes invasive infection for a wide range of enteropathogenic and opportunistic pathogenic bacteria – such as *E. coli* and non-Typhoidal *Salmonella*. However, this stage is often overlooked by current vaccines.

Here we show that combining oral vaccination with engineered or selected niche-competitor strains permits pathogen exclusion and strain replacement in the mouse gut lumen. This is based on the proven ability of specific secretory IgA to generate a fitness disadvantage for a targeted bacterium, allowing a non-targeted competitor to rapidly overtake its niche. This approach can be applied both prophylactically to prevent invasion of non-typhoidal *Salmonella* strains, or therapeutically to displace an established *Escherichia coli*. Both intact adaptive immunity and metabolic niche competition are necessary for efficient vaccine-enhanced competition.

Our findings imply that mucosal antibodies have evolved to work in the context of gut microbial ecology, by influencing the outcome of competition. This has broad implications for the elimination of pathogenic and antibiotic-resistant bacterial reservoirs, mucosal vaccine design and for rational microbiota engineering. Moreover, the generation of sterilizing immunity against pathogenic bacteria raises the possibility to drive pathogen extinction.

SC27

IL-15 enhances innate lymphoid cell-mediated anti-tumor immunity in brain metastasis

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Besides classical therapeutic approaches, the modulation of tumor-responsive brain-infiltrating immune cells represents a promising strategy for improving the treatment of brain metastasis patients. This study aims to understand the understudied response of natural killer (NKs) and closely related type 1 innate lymphoid cells (ILC1s) to brain metastasis.

We employed a metastasis mouse model by intracardially injecting the breast cancer cell line EO771 into BL/6 mice. In these mice, we compared the NK and ILC1 response in the brain and the liver as a control for a functional anti-metastasis response. Using scRNA-seq and flow cytometry, we identified several populations of functional NKs and ILC1s, with a reduced diversity in the brain compared to the liver. Even though NKs modestly penetrated the brain parenchyma, NK or ILC1 depletion experiments revealed that those cells cannot control brain metastasis, but liver metastasis. Next, we treated metastasis-burdened mice with local IL-15 injections into the brain to activate NKs and ILC1s. Indeed, NK and ILC1 numbers increased upon IL-15 treatment in the brain parenchyma. Furthermore, IL-15 treatment induced the expression of residency markers in NKs, while ILC1s upregulated the expression of granzymes and perforin, indicating their activation. Consequently, IL-15-treated mice were able to control brain metastasis.

These results establish that type 1 ILCs can be potentiated to robustly control brain metastasis, suggesting that ILC-modulating immunotherapies may hold promise for treating patients with brain metastasis.

SC28

The endolysosomal SLC15A4/TASL complex activates IRF5-mediated Th1 responses needed to control Leishmania major infection and to induce colitis

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Introduction: Upon nucleic acid sensing by TLR7-9, the immune adaptor complex SLC15A4/TASL (and its murine paralogue *Gm6377*) mediates IRF5 recruitment, activation, and downstream type-I IFN and inflammatory cytokine secretion. SLC15A4/TASL deficiency protects from systemic lupus erythematosus (SLE) but also hampers antiviral response, as we recently uncovered in mice. Another key IRF5 function is the induction of Th1-polarizing cytokines. Here, we study the role of SLC15A4/TASL on Th1-dependent responses such as *Leishmania major* infection and colitis.

Methods: Double knockout *Tasl* x *Gm6377* ($TASL^{DKO}$) or SLC15A4-deficient *feeble* mice of C57BL/6J background, naturally resistant to *L. major* infection, were intradermally inoculated with *L. major* in the ear. Colitis was induced with 7 days of DSS in drinking water.

Results: Macrophages derived from $TASL^{DKO}$ and $SLC15A4^{feeble}$ mice showed a comparable impairment of IRF5 activation and IL-12 production. $TASL^{DKO}$ mice distinctively failed to control *L. major* infection, with increased lesion size, parasite burden, decreased $IFNg^{+}CD4^{+}$ T cells, impaired IgG2c switch but elevated IL-4, IL-10 and IgE production, indicating a Th2, *L. major*-permissive response. Meanwhile, $SLC15A4^{feeble}$ mice showed an intermediate phenotype. On the far side, $TASL^{DKO}$ and $SLC15A4^{feeble}$ mice were equally protected from DSS-induced colitis, displaying a reduced weight loss, colon inflammatory score and impaired Th1/17 responses.

Conclusions: We reveal a critical role of the SLC15A4/TASL complex in Th1-dependent immune responses for pathogen control and inflammatory diseases.

SC29

Innate Immune Memory and Metabolic Reprogramming in the Lower Airway Epithelium of Patients with Allergic Asthma

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Aim: Asthma exacerbations, often triggered by respiratory viral infections such as rhinovirus (RV), are linked to airway epithelial immunometabolic reprogramming. This study explores metabolic shifts in allergic asthma and their modulation by allergen immunotherapy (AIT), which correlates to reduced viral exacerbations.

Methods: Primary bronchial epithelial cells from healthy and asthmatic donors were cultured at the air-liquid interface and subjected to repetitive RV infections. Additionaly, ex vivo analyses included bronchoalveolar lavage fluid and bronchial biopsies from untreated and AIT-treated allergic asthma patients. RNA-seq, RT-qPCR, proteomics, and metabolomics were used to assess immune responses and metabolic activity, complemented by confocal microscopy and bioinformatics of public datasets.

Results: Asthmatic bronchial epithelium exhibited enhanced glycolysis and reduced oxidative phosphorylation at baseline and post-infection. Single-cell RNA-seq of type 2-inflamed epithelium revealed metabolic remodeling in ciliated and secretory cells. Repetitive RV infections induced profound metabolic and proteomic changes in asthma, activating pathways related to cell senescence, epigenetics, and mitochondrial metabolism. AIT modulated metabolic pathways, notably carbohydrate, amino acid, and oxidative stress responses, enhancing antiviral defenses.

Conclusions: Airway epithelial metabolic reprogramming contributes to asthma pathogenesis. AIT partially restores metabolic balance, potentially reducing viral exacerbations.

GUIDED POSTER TOUR THURSDAY

A05

Early-life lung microbial dysbiosis shapes immune responses and predisposes to allergic airway inflammation

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Aim: Disruptions in neonatal lung microbiota are associated with asthma susceptibility, yet their impact on immune priming and airway barrier function remains unclear. We aimed to investigate whether early-life microbial perturbations predispose neonatal lungs to heightened allergic airway inflammation.

Methods: Neonatal (14- and 21-day-old) BALB/c mice and adult (8-week-old) mice were exposed intranasally to *Streptococcus pneumoniae* (10^3–10^5 CFU) three times over five days; then received house dust mite extract (HDM) instillations every 48 h for 14 days. Microbial shifts were confirmed by 16S rRNA gene amplicon sequencing; immune cell composition and priming were characterized by flow cytometry.

Results: Early-life exposure to *S. pneumoniae* and HDM led to lung dysbiosis, increased type 2 and type 3 innate lymphoid cells (ILC2/3) and elevated memory T-cell frequencies in the lung, and enhanced eosinophilia in bronchoalveolar lavage fluid (BALF). These effects were most pronounced in 14-day-old compared to 21-day-old mice. Adult mice showed fewer innate changes but stronger Th2 cytokine responses. The observed effects were sex-specific with female mice exhibiting enhanced BALF eosinophilia and increased DC activation (CD80).

Conclusions: Early-life *S. pneumoniae* exposure profoundly alters neonatal lung microbiota and allergic airway inflammation compared with adult exposure, highlighting a critical window of susceptibility. These results represent an initial step toward delineating the mechanisms underlying early-life lung dysbiosis-mediated allergic susceptibility.

A06

Immunogenicity Assessment of Eggplant Mosaic Virus-Based Virus-Like Particle Vaccines Displaying Fel d 1 Administered Through Different Routes in Mice

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Introduction & Aim: Cat allergy, mainly triggered by the major allergen Fel d 1, can cause allergic rhinitis and asthma. A novel vaccine was developed using Eggplant Mosaic Virus (EMV) virus-like particles (VLPs) displaying Fel d 1 to induce a protective immune response. This study evaluated the immunogenicity of alternative vaccine formulations and investigated different delivery methods, including subcutaneous and intranasal administration, in a mouse model.

Design & Methods: Fel d 1 was genetically fused to the EMV VLP capsid protein, expressed in bacteria, and purified. Mice were vaccinated with VLP-Fel d 1, VLP, or Fel d 1 protein, and received homologous or heterologous immunizations. Specific antibody responses (IgG, IgG subclasses, IgA) were measured in serum and bronchoalveolar lavage fluid (BALF) by ELISA.

Results: Both homologous and heterologous vaccination strategies induced strong Fel d 1-specific IgG responses, with levels rising after booster immunization. At Day 28, IgG1, IgG2b, and IgG3 subclasses were highly elevated, whereas IgG2a responses were lower. IgA levels remained low in both serum and BALF. IgG avidity improved after boosting, especially in groups vaccinated with EMV-Fel d 1 VLPs.

Conclusion: The EMV-Fel d 1 VLP vaccine induced a strong and specific IgG response through both homologous and heterologous strategies, supporting its potential as a safe and effective immunotherapy for cat allergy. Ongoing studies will further assess the impact of vaccination route, long-term immunity, and lung histopathology.

C01

A helminth-based biologic targets eicosanoid pathways and modulates type-2 inflammation

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Eicosanoids regulate chronic inflammation, particularly in therapy-resistant airway disease. Helminth products can act as potent natural immunoregulators. We identified glutamate dehydrogenase (GDH) from the larval extract of *Heligmosomoides polygyrus bakeri* (Hpb) as an immune-modulatory factor that regulates type 2 inflammation by modulating eicosanoid metabolism.

Mice subjected to house dust mite–induced airway inflammation were intranasally treated with Hpb extract (HpbE) or helminthic GDH (heGDH). Human monocyte-derived macrophages, granulocytes, and nasal polyp tissue were treated *ex vivo* with HpbE or heGDH. Eicosanoids and cytokines were analyzed by LC-MS/MS or multiplex assays, and lung inflammation was assessed via histology, flow cytometry, and chemotaxis assays.

In macrophages, HpbE and heGDH induced an anti-inflammatory eicosanoid shift from 5-lipoxygenase to cyclooxygenase (COX) metabolites, resulting in reduced granulocyte recruitment. Mechanistically, PGE_2 induction required the N-Terminus of heGDH, which induced p300-mediated histone acetylation. In contrast, the suppression of leukotriene (LT) synthesis depended on heGDH's catalytic activity. Treatment with HpbE or heGDH or adoptive transfer of HpbE-conditioned macrophages attenuated allergic inflammation in mice via COX-2. Consistent with its anti-inflammatory effects *in vivo* and human leukocytes, heGDH decreased LTs while increased PGE_2 in human nasal polyp tissue.

These findings highlight HpbE and its immunoregulatory component -heGDH- as a promising immunomodulatory therapy for type 2 inflammatory diseases.

L01

Machine learning classification based on a 15-autoantibody profile by a fully automated multiplex microarray immunoassay for autoimmune CTD diagnosis

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Aim: Extended serological profiling may improve autoimmune connective tissue diseases (CTD) diagnosis. We evaluated the diagnostic utility of machine learning (ML) classifiers based on the 15-antibody profile by a novel, single-use, multiplexed microarray immunoassay, using its fully automated high-throughput proprietary system for simultaneous the detection of IgG antibodies directed to dsDNA, SS-A 60, TRIM21, SS-B, Sm, Sm/RNP, U1RNP, Jo-1, Scl-70, CENP-B, Chromatin, Ribosomal P, DFS70, RNAP III and CCP2.

Methods: De-identified sera from 475 patients with autoimmune CTD [127 systemic lupus erythematosus (SLE), 74 systemic sclerosis, 76 Sjögren's syndrome (SjS), 71 idiopathic inflammatory myopathies, 54 mixed CTD, 73 rheumatoid arthritis] and 652 disease controls were tested with the MosaiQ AiPlex® CTDplus (AliveDx, Switzerland) assay. Classification models were developed with the RandomForest (RF) algorithm, using all 15 antibodies or a subset. Diagnostic performance was assessed by receiver operating characteristic curve analysis.

Results: For SLE, the 15-plex RF classifier (RFC) achieved an area under the curve (AUC) of 0.92, outperforming individual markers dsDNA (0.68) and Sm (0.60). For SjS, the 15-plex RFC achieved an AUC of 0.83, versus a 3-plex RFC based on antibodies to SS-A 60, TRIM21, and SS-B (0.62). The AUCs for these markers were 0.63, 0.59, and 0.58, respectively. Similarly, 15-plex classifiers outperformed individual disease-specific markers.

Conclusions: Multiplex autoantibody testing combined with ML algorithms has the potential to improve CTD diagnosis.

L04

The cytokine-based lymphocyte transformation test (Cyto-LTT) - evaluating quality and strength of T cell reactions to drugs in vitro

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Background: The lymphocyte transformation test (LTT) is an in vitro test to detect T cell reactivity to a drug in suspected drug hypersensitivity (DH) by measuring T cell proliferation. We adapted this test by measuring 5 cytokines (IL-5, IL-13, IFNγ, granzyme B, granulysin) with a multiplex bead-assay instead of proliferation (Cyto-LTT). Previous studies have shown that this test modification led to an improved sensitivity with preserved specificity [Lochmatter P, 2008].

Methods: This retrospective analysis of 851 positive Cyto-LTT results (97 DRESS, 754 exanthems) assessed responses to amoxicillin, vancomycin, and aromatic sulfonamides. Lymphocytes were cultured with drugs for six days, cytokine secretion was quantified, with a positive response defined as a stimulation index (SI) >2 in at least two drug concentrations and two cytokines.

Results: Our key findings were (1) dose dependency: Cytokine secretion increased significantly with drug concentration ($p<0.001$). (2) reaction strength: DRESS cases showed 3-6× higher IL-5/IL-13 and 2× higher cytotoxic mediators than exanthems. 65% of DRESS vs 34% of exanthems had strong reactions (SI>75th percentile in ≥2 cytokines). (3) Drug-specific patterns: amoxicillin/vancomycin induced Th2 cytokines (IL-5/IL-13), aromatic sulfonamides triggered Th1/cytotoxic responses (IFNγ/GzB).

Conclusion: The Cyto-LTT, utilizing five selected cytokines, identifies culprit drugs, quantifies T-cell reactivity, can distinguish severe DH like DRESS from exanthems and reveals drug-specific immune patterns, improving DH diagnosis and risk stratification.

GUIDED POSTER TOUR FRIDAY

B13

IL-33-mediated fibroblast-myeloid cell crosstalk controls intestinal granuloma formation

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Formation of highly dynamic and spatially organized granulomas is a common feature of inflammation in response to tissue invading pathogens. However, the intricate interplay between immune cells and fibroblastic stromal cells during the formation of intestinal granulomas has remained largely elusive. Here, we show that the induction of the nuclear alarmin interleukin-33 (IL-33) in lamina propria fibroblasts during the granulomatous immune response to the intestinal helminth *Heligmosomoides polygyrus bakeri* (*Hpb*) favorably affects granuloma formation and worm clearance. Ablation of IL-33 in intestinal fibroblasts targeted by the Cxcl13-Cre-transgene led to impaired immune cell recruitment and protective properties of granulomas. Thereby, IL-33-mediated activation of interleukin 1 receptor like 1 (IL1RL1)-positive myeloid cells initiated the upregulation of discrete singling pathways to support macrophage attraction and fibroblast activation within granulomas. Consequently, IL-33-dependent regulatory circuits led to the induction of the eosinophil chemotactic chemokine CCL11 in granuloma-associated fibroblasts, facilitating the accumulation of eosinophils within granulomas. Collectively, these findings highlight the pivotal role of fibroblast-derived IL-33 as a key mediator in controlling local immunological processes within intestinal granulomas, providing insights into tissue-specific immunity and host defense.

B14

The TLR7/9 adaptors TASL and TASL2 mediate IRF5-dependent antiviral responses and autoimmunity.

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Aim: Endosomal nucleic acid sensing by Toll-like receptors (TLRs) is central to antimicrobial immunity and several autoimmune conditions such as systemic lupus erythematosus (SLE). The innate immune adaptor TASL mediates, via the interaction with solute carrier SLC15A4 on endolysosome, the activation of interferon regulatory factor 5 (IRF5) downstream of human TLR7, TLR8 and TLR9, but the pathophysiological functions of this axis remain unexplored.

Methods: Using the whole body knock-out mouse models we addressed *ex vivo* and *in vivo* immune responses triggered by TLR7/9 activation.

Results: Our work shows that SLC15A4 deficiency results in a selective block of TLR7/9-induced IRF5 activation, while loss of TASL leads to a strong but incomplete impairment, which depends on the cell type and TLR engaged. This residual IRF5 activity is ascribed to a previously uncharacterized paralogue, *Gm6377*, named here TASL2. Double knockout of TASL and TASL2 ($TASL^{DKO}$) phenocopies SLC15A4-deficient *feeble* mice showing comparable impairment of innate and humoral responses. Consequently, $TASL^{DKO}$ mice fail to control chronic LCMV infection, while being protected in chemically (pristane) and genetically (Fas^{lpr}) induced SLE disease models.

Conclusion: Our study thus demonstrates the critical pathophysiological role of SLC15A4 and TASL/TASL2 for TLR7/9-driven inflammatory responses, further supporting the therapeutic potential of targeting this complex in SLE and related autoimmune diseases.

B15

Hookworm infection induces long-term changes in the epithelial compartment of the lungs

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Upon lung tissue migration, hookworm larvae cause extensive host damage. Short-term, this results in pulmonary hemorrhage; long-term, mice develop emphysema resembling COPD. While many immune cells involved in repair are known to limit emphysema, mechanisms underlying its development remain unclear.

To address this, we used digital cytometry to study the impact of *Nippostrongylus brasiliensis* infection on lung structure. From 3 to at least 12 days post-infection, ciliated, alveolar type I (ATI) epithelial cells, and capillary endothelial cells were reduced in favor of alveolar type II (ATII) cells. The ATI/ATII balance is critical for lung architecture, with imbalance linked to fibrosis. We thus investigated ATII cells upon infection with *N. brasiliensis in vivo* and *in vitro* and confirmed infection's sustained impact on ATII numbers up to 40 days. Purified epithelial cells from infected mice lacked typical cobblestone morphology, were prone to death, expressed high SMA levels, and showed impaired alveolosphere formation in 3D cultures. In co-culture assays, we observed that ATII cells recognized and bound *N. brasiliensis* larvae, with binding enhanced both short and long-term (2 and 40 days post-infection) compared to naïve ATII cells. Larval recognition by epithelial cells was TGF-β and Yap/Taz dependent, suggesting a mechanosensory mechanism. Finally, stimulation of ATII cells with larvae enhanced IL-4-activated macrophage recognition, and blockade of ATII cells activation with TGF-β inhibitor during re-infection limited macrophage trapping and killing of *N. brasiliensis.*

B17

Metabolic regulation of epithelial RIG-I signaling in viral exacerbations of asthma

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Rhinovirus (RV) infection of airway epithelial cells from patients with asthma results in an abnormal engagement of retinoic-acid inducible gene I (RIG-I) into RIG-I inflammasome formation, which subsequently delays RIG-I dependent interferon responses and enhances proinflammatory signaling in asthma. The exacerbation-prone asthma has been linked with metabolic

dysfunctions, however, the metabolic regulation of antiviral responses during those pathogenic viral infections in asthma is not well understood. Therefore, bronchial epithelium from patients with asthma and healthy controls upon in vitro and in vivo RV infection were used to analyze the metabolic regulation of RIG-I-dependent signaling. Bronchial epithelium of patients with asthma upon RV infection demonstrated increased glycolytic ATP and decreased mitochondrial ATP production. We also observed a broad downregulation of mitochondrial proteins, related to the electron transport chain (ETC), TCA cycle, reactive oxygen species (ROS) removal, and mitochondrial structure in asthma. Moreover, inhibition of ETC complex I with rotenone reduced IFNB and DDX58 (RIG-I) expression while increasing the release of mature IL-1β protein upon RV infection. Conversely, blocking glycolysis with 2-deoxy-D-glucose (2-DG) reduced both viral replication and IL-1β release, demonstrating a clear metabolic regulation of RIG-I-dependent proinflammatory/antiviral responses in bronchial epithelium. In summary, abnormal metabolic reprogramming in the bronchial epithelium affects impaired RIG-I signaling and subsequent antiviral response in asthma.

B26

Deciphering the role of Hedgehog signaling in medullary reticular cells during lymph node homeostasis

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Aim: Lymph nodes (LNs) are highly compartmentalized organs structured into three major regions: B cell zone, T cell zone and medulla. Several subsets of fibroblastic reticular cells (FRCs) organize these regions, with medullary reticular cells (MedRCs) remaining the least characterized. Previous transcriptomic analysis from our lab identified Gli1 expression specifically in MedRCs. Gli1 is a key transcription factors downstream of Hedgehog signaling, a pathway known to play a role in maintenance and repair of tissue. Here, we aim to define the specialized role of Gli1⁺ MedRCs within the medullary niche.

Methods: We utilized Gli1creERT2 mouse model to fate-map cells that have signaled, or are currently signaling, through the Hedgehog signaling pathway. Using combined protein analysis, transcriptomic profiling, live lymph node slice imaging, and pharmacological inhibition using small-molecule inhibitors, we strive to characterize the importance of Hedgehog signaling in MedRCs.

Results: Fate-mapping revealed that Gli1-expressing cells are restricted to the LN medulla and are closely associated with blood and lymphatic vessels. Single-cell transcriptomic analysis of naïve LNs identified one MedRC population with a distinct Hedgehog signaling signature. To assess the functional role of Hedgehog signaling in the LN, we are conducting experiments using *in vivo* small-molecule inhibitors.

Conclusion: Our findings demonstrate that Hedgehog signaling is specifically active in LN MedRCs, positioning them as potential regulators of vascular maintenance and the surrounding immune niche.

B27

Environmental interference in the fight against respiratory Aspergillus infection

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Antifungal resistance is increasing worldwide and development of alternative therapeutic strategies for fungal infections is imperative. *Aspergillus niger* infection induces lung damage via oxalic acid secretion and accumulation of calcium oxalate cristals (CaOx). Oxalotrophic bacteria (*C. oxalaticus*) degrade CaOx and inhibit fungal growth via environmental interference. Here we provide a proof-of-concept study for the use of biocontrol bacteria against respiratory fungal infections.

Human bronchial epithelial cells (hBECs) were cultured on Air-Liquid Interface for 28 days before exposure to *A.niger* conidia, *C.oxalaticus*, or a combination for 72h. Transepithelial electrical resistance, cell morphology, pH and calcium levels were assessed *in vitro*. Immunosuppressed adult BalbC/J mice were exposed (i.n.) to *A.niger*, *C.oxalaticus*, or a combination. Immune cell influx and hyphal development were assessed after 72h in BALf and lung tissue.

Infection of hBECs with *A. niger* modified pH and Ca2+ concentrations and impaired barrier integrity. This effect was rescued by co-exposure with *C.oxalaticus*. Coadministration of *C.oxalaticus* with *A.niger* in mice led to improved clinical scoring and reduced hyphae formation compared to control (*A.niger* alone). Interestingly, smaller CaOx crystals were observed following administration of both *C.oxalaticus* and *A. niger*, compared to control.

We successfully demonstrated the potential of environmental interference as a biocontrol strategy against Aspergillus infections. Overall, this provides novel treatment avenues for respiratory fungal infections.

POSTER

The posters will be displayed throughout the congress near the industry exhibition.

A01

Case report of a 13 years old female patient with millet allergy and cross-reactions

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We present a rare case of millet allergy in a 13-year-old girl who experienced an allergic reaction, including urticaria and vomiting, after consuming a teff-based product. Teff is related to millet and common in Eritrean cuisine. Positive skin prick tests and elevated sIgE levels confirmed an allergy to both millet and teff. The sensitization in millet allergy seems to typically occur through the respiratory route via exposure to millet-containing birdseed in pet bird owners. Our patient had no history of contact with pet birds. The allergic reaction occurred a while after she prepared a dish using teff flour. This suggests that sensitization may have occurred either via the respiratory route from inhaling the flour or through the cutaneous route during food preparation in this patient with atopic dermatitis.

There are case reports about millet allergy and cross-reactivity with rice, corn and wheat. Our patient reported oral itching after consuming whole-grain wheat products. Oats, like millet, are a sweet grass, and our patient also reported oral itching when consuming oats. We could confirm a sensitization to wheat, rye, and oats. The patient was advised to avoid millet, teff, whole wheat products and oats and was equipped with emergency medication including EpiPen. This report highlights the need for the awareness of rare food allergies in clinical practice. With increasing immigration from Eritrea, the incidence of millet allergy may rise in the future. Potential cross-reactions with related grains should be considered in the diagnostic work-up and dietary management.

A02

Thinking outside the box: Unmasking nephrotic syndrome in a case of suspected non-steroidal anti-inflammatory drug hypersensitivity

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Case report: A 2-year-old boy was referred to the allergy department for recurrent eyelid and facial swelling over the past 2 years, each episode associated with febrile respiratory infections and resolving spontaneously within 2-3 days. The episodes were often temporally linked to non-steroidal anti-inflammatory drug (NSAID) use, raising suspicion of drug hypersensitivity. However, controlled oral challenges with NSAIDs were tolerated without allergic reactions. Given the atypical presentation and inconsistent NSAID exposure, further evaluation was pursued. Routine laboratory testing revealed nephrotic-range proteinuria without hematuria, leading to the diagnosis of nephrotic syndrome. Corticosteroid therapy was initiated, resulting in marked improvement and disease remission.

Discussion: NSAIDs are a common cause of drug-induced angioedema, particularly during infections. However, when the clinical presentation is atypical or the temporal relationship with drug exposure is inconsistent, alternative diagnoses must be considered. In this case, the swelling was secondary to nephrotic syndrome, a condition that can mimic allergic angioedema in its early stages. Recognizing nephrotic proteinuria is critical, as delayed diagnosis may result in serious complications.

Conclusion: This case highlights the importance of maintaining a broad differential diagnosis in patients presenting with recurrent edema. Early identification of nephrotic syndrome through simple urine testing enables prompt treatment and the prevention of long-term renal and systemic complications.

A03

A step towards standardized Clinical Remission Criteria for Chronic Rhinosinusitis with Nasal Polyps: insights from a real-life study

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Aim: The development of biologic drugs for the treatment of CRSwNP generated growing interest in defining disease remission, for which there currently is no consensus on a precise definition and no validated criteria exist. The aim of our study is to develop and validate clinical remission criteria for CRSwNP.

Methods: We conducted a retrospective study on patients with severe refractory CRSwNP, under therapy with Dupilumab. Patients were evaluated at T0 (baseline) and at 1, 3, 6, 12 and 24 months (T1, T3, T6, T12 and T24, respectively) after initiating dupilumab. We hypothesized 3 definitions of clinical remission: Definition 1 (D1): NPS 0; SNOT-22 <20. Definition 2 (D2): NPS reduction >2 points; SNOT-22 <20. Definition 3 (D3): NPS reduction >2 points; SNOT-22 reduction ≥9points. All the definitions also include no use of systemic steroids nor adjuvant surgery.

Results: 64 patients were included in the analysis at T12 and 40 at T24. The NPS was 6.3±1.48, 4.02±2.52, 2.93±2.31, 2.48±2.42, 2.24 ±2.29, 1.36±2.03 at T0, T1, T3, T6, T12 and T24. The SNOT-22 was 64.24±19.72, 37.74±20.39, 28.71±19.00, 25.35±17.12, 21.91±15.46, 16.29±13.30 at T0, T1, T3, T6, T12 and T24. Complete clinical remission (D1) is achieved by 15.6% of patients by T12. 39.1% of patients reach the more lenient clinical remission (D2) by T12. D3, resembling Dupilumab response criteria, was achieved by 70.7% by T3.

Conclusions: The introduction of biologic drugs in the treatment of CRSwNP has positively impacted the disease outcome, making remission achievable. Now clinical remission criteria need to be validated.

A04

SDRIFE-like skin rash due to paracetamol

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Aim: We present a case of a SDRIFE-like reaction 3 times after intake of paracetamol which could reproduced with oral provocation testing (OPT). The aim of this case report is to raise awareness for a rare but frequently prescribed elicitor of SDRIFE-like eruption.

Case: Our patient had 3 episodes of skin rash in association with the intake of metamizole and paracetamol. The latency of the first 2 episodes was 3 to 4 days under continued use of both drugs with skin changes lasting 2 and 1 week, respectively. The latency of the 3rd episode was 8h after the 1st dose of paracetamol with skin changes lasting for 1 week. In the further course, the patient avoided both drugs, so that no statement on tolerance could be made. Later 1g acetylsalicylic acid was taken without complications.

Methods: 10 months after the last skin reaction, we performed a skin test with paracetamol (prick, patch) and metamizole (prick, intradermal, patch) which was negative. Later an OPT with 875mg paracetamol was administered. About 20h later, symmetrical erythema manifested on the flexural sides of the forearms, thighs extending to the popliteal fossa, the inguinal area and the flanks for a duration of approx. 24 hours. Unfortunately the patient did not present to our allergy clinic. 1 week later, an OPT with 875mg metamizole was carried out without complications. 3 months later, we repeated the OPT with paracetamol, whereby after 24h a similar erythema, as observed after the first provocation, developed again.

Conclusion: It is important to be aware that SDRIFE-like rashes can be caused by paracetamol.

A07

Undressing DReSS: p-i mediated T-Cell Activation explains Pathogenesis and Clinic

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Background: Drug Reaction with eosinophilia and Systemic Symptoms (DReSS) is a severe T-cell-mediated hypersensitivity reaction with delayed onset, eosinophilia, and multi-organ involvement. This study explores the role of pharmacological interaction with immune receptors (p-i) in pathogenesis and clinical course of DReSS.

Methods: The role of p-i stimulation in DReSS was previously shown by analysis of drug specific T cell clones, molecular modeling and HLA-binding studies. Data on drug dose and tissue concentration, therapy duration, and affinity of drug binding to HLA or TCR, as well as amount of cytokine secretion in vitro (IL-5, IL-13, IFNγ, granzyme B, granulysin) are combined to explain the clinical picture of DReSS and its clinical course.

Results: DReSS progresses through four phases: (1) Silent phase (asymptomatic T-cell expansion via high-affinity p-i stimulation, often >14 days latency); (2) Acute phase (cytokine storm, cytotoxicity, eosinophilia); (3) Viraemia/autoimmunity phase with peptide reactivity; (4) Chronic phase (persistent T-cell hyperreactivity and multi-drug hypersensitivity).

p-i Drivers: High drug doses (>300 mg/day), prolonged therapy (>7 days), and strong HLA affinity (e.g., HLA-B*58:01) amplify T-cell activation. Low-affinity interactions (piperacillin, contrast media) can be compensated by excessive drug concentrations.

Conclusion: DReSS exemplifies a strong p-i-mediated immune stimulation. Risk to develop DReSS may be mitigated by considering the presence of risk-alleles (HLA), avoidance of high drug doses and long drug therapy.

A08

Allergy to the venom of the ant Manica rubida: a family affair

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Aim: Anaphylaxis from ant stings are very rare in Europe. It is most often linked to stings from Myrmica rubra or Formica rufa. Other species, such as Manica rubida and Solenopsis invicta, an invasive species in the United States and recently detected in Sicily, are feared for their venom with anaphylactic potential.

We report two cases of anaphylaxis to M. rubida to highlight the problem of ant allergy, which has been little studied and for which diagnostic and therapeutic methods are limited.

Methods: Retrospective study of two documented cases based on: anamnesis, identification of the insect by an entomologist and detection of IgE against a hymenoptera venom allergen.

Results: A mother and her daughter repeatedly experienced H.L. Muller grade I-III anaphylactic reactions to stings from red ants near their home in eastern Switzerland. In both cases, the assessment showed IgE to paper ant venom antigen 5 (rPol d5), without other specificities, notably to allergens from S. invicta, the only ant venom available for assay. None of the patients recalled being stung by paper ants. Homologues of antigen 5 are found in the venom of other hymenoptera, including ants. An ant, killed at the time of the sting by one of the patients, was identified by an entomologist as M. rubida, a species endemic to the mountainous regions of central Europe.

Conclusions: As S. invicta reaches Europe, an increase in cases of anaphylaxis to ant venom is expected. We should not forget the possibility of anaphylaxis to ant venom from stings of endemic species, for which diagnostic methods remain limited.

A09

Lanadelumab's enduring impact on HAE attack reduction and improved disease control: final results from the ENABLE Study

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Introduction: ENABLE (NCT04130191), a Phase IV, non-interventional, prospective study, assessed lanadelumab's real-world effectiveness in preventing hereditary angioedema (HAE) attacks. This abstract reports on patient-reported attack rates.

Methods: Patients aged ≥12 years with HAE at 18 sites across 7 countries initiated lanadelumab per product labeling and recorded attacks via smartphone diaries. Disease control perception was measured via the Angioedema Control Test (AECT) at baseline and at follow-ups (months 1, 2, 3, 6, 12, and annually for up to 36 months).

Results: Of 139 enrolled, 138 received lanadelumab (mean±SD age: 41.0±14.4 years; 62.3% female). Most had HAE-C1INH-Type1 (n=127). Median treatment duration was 26.6 months. Mean monthly attack rates dropped by 83.9%, from 3.88±3.43 pre-lanadelumab to 0.30±0.53 on treatment; median attack rates reduced by 96.7%, from 3.0 to 0.1 attacks/month. Most attacks (85.9%) were mild/moderate; 82.6% of patients used on-demand treatments. AECT scores improved from poorly

controlled at baseline (7.5±3.7) to well-controlled disease (≥10) within 1 month, further increasing to 14.4±2.9 by month 36. By month 1, AECT score changes exceeded the minimal clinically important difference (≥3 points). The proportion of patients achieving well-controlled disease rose from 51.9% at baseline to 88.3% and 89.7% at months 12 and 36.

Conclusions: Lanadelumab significantly reduced HAE attacks and improved disease control early, maintaining benefits through 36 months, supporting its use as first-line prophylaxis.

A10

Comparison of responsiveness to bronchodilators using the 2021 or 2005 American Thoracic Society / European Respiratory Society guidelines

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Aim: The Aim is to compare the differences between the 2005 and 2021 ERS/ATS criteria. The ERS/ATS 2021 guidelines redefined a positive bronchodilator response (BDR) in pulmonary function tests as an increase >10% of the predicted value of FEV1 or FVC, replacing the 2005 criteria of a 200 ml and 12% change from baseline. This change, which accounts for individual patient characteristics, increases specificity for detecting lung function changes and supports personalized treatment.

Methods. We conducted a bicenter retrospective study using BDR tests from the Allergology and Clinical Immunology Center in Monserrato (Cagliari, Italy) and the Asthma and Allergology Center at IRCCS Humanitas in Rozzano (Milan, Italy) between January 2020 and October 2024. BDR outcomes based on the 2005 and 2021 criteria were designated as 2005-BDR and 2021-BDR, respectively. We compared these outcomes and examined the trend of positive BDR (BDR+) in relation to the degree of airflow obstruction.

Results: Out of 1794 tests, 540 (23%) were BDR+ by one or both definitions (using FEV1 only). Specifically, 512 tests (52%) were positive by the 2005 criteria and 482 tests (48%) by the 2021 criteria. Among 81 discordant cases—positive by only one guideline—57 (70%) were positive solely according to the 2005 criteria, while 24 (30%) were positive only under the 2021 criteria.

Conclusions. The 2021 ERS/ATS criteria yield fewer positive BDRs than the 2005 criteria, suggesting a more specific and conservative definition that likely reflects clinically significant lung function changes.

A11

MY006: A Single Multispecific Anti-Peanut Antibody For The Treatment Of Peanut Allergy

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Aim: Peanut allergy prevalence has increased over the last decade to reach 2% in the general population. As the leading cause of food allergy-related fatalities, it urgently needs improved therapies.

Methods: Mabylon has developed MY006, a trispecific anti-peanut antibody engineered from patient-derived monoclonal antibodies, for prophylactic treatment of peanut allergy.

Results: MY006 possesses excellent developability and manufacturability profiles and offers a novel mode of action via allergen neutralization, overcoming limitations of current approaches. Functionally, this trispecific molecule remarkably targets four allergenic epitopes across the three major peanut allergens. *ex vivo*, MY006 prevents the binding of patients' IgE to peanut allergen and inhibits subsequent mast cell and basophil degranulation. Due to antibody half-life extension, its potency and its mode of action, MY006 is expected to provide continuous protection from allergic reactions caused by accidental peanut exposure with only two subcutaneous injections per year.

Conclusions: MY006 is predicted to offer safe, rapid, and continuous protection from peanut allergic reactions to a very broad patient population, including pediatrics and adults. Currently, MY006 is undergoing IND-enabling studies and first-in-human Phase 1 trials will be started by the end of 2025. Applying Mabylon's advanced human antibody discovery, engineering and development platform, antibodies targeting a range of food allergies are currently developed, offering a preventive treatment for poly-allergic patients in the future.

B01

Study of a potential regulator of tumor-induced T cell exhaustion

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Persistent antigen exposure in chronic infection and cancer drives CD8 T cells towards an exhausted state of differentiation. Exhausted CD8 T cells are characterized by an increased expression of coinhibitory molecules (e.g., PD-1, Tim3), dampened effector function and reduced proliferative capacity, hampering efficient solving of viral infection or cancerous cells clearance. Despite intense research on the topic, the full picture of exhaustion remains elusive.

Our laboratory focuses on understanding tumor-specific mechanisms driving CD8 T cells exhaustion. Several transcription factors have been found to enforce exhaustion (e.g., TOX, IRF4, NFAT5). We found that IRF8, an Interferon Regulatory Factor family member and homolog of IRF4, was overexpressed in exhausted tumor infiltrating lymphocytes (TILs) from murine and human tumors. Thus my project aims at investigating the role of IRF8 during tumor-induced CD8 T cell exhaustion.

First, we demonstrated a TCR-dependent upregulation of IRF8 in tumor-specific CD8 T cells. Interestingly, IRF8 expression in CD8 T cells was maintained in TILs but not in virus-specific CD8 T cells during chronic infection. We showed that IRF8 overexpression in TILs aggravated their exhausted profile in a melanoma mouse model. Inversely, TILs with CRISPR/Cas9-mediated KO of IRF8 displayed a more functional and less exhausted phenotype compared to the WT counterpart. We also confirmed these findings at the transcriptomic level by scRNAseq.

Together, our data suggest that IRF8 plays a role in regulating CD8 T cell exhaustion in the context of cancer.

B03

Arginase 1 and 2 as regulators of the B cell response

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Most vaccines confer protection against infection by induction of specific antibodies. The effectiveness of vaccines depends on the sustained production of long-lasting, high-titre antibody responses. However, recent experiences with the COVID-19 pandemic have highlighted a lack of fundamental understanding of how these vaccine-induced antibody responses can be sustained over the long term, an essential goal in the field of vaccinology. Our experiments have shown an increased expression of Arginase 2 in MBC compared to GCB, while Arginase 1 was higher in GCB cells compared to MBC. Both arginases convert L-Arginine to Urea and L-ornithine and thus compete with inducible nitric oxide synthase (iNOS or NOS2) for the L-Arginine substrate and thus can regulate the nitric oxide (NO) pathway, a known regulator of immune function again via NF-κB. This led us to generate a $CD19^{cre}Arg1^{lox}$ mouse line to study the role of Arginase 1 in B cells and GC versus plasma cell formation. We found levels of antigen-specific IgG antibody in these mice are initially similar to wild type mice after immunization with VLPs. After day 21, these mice fail to maintain high levels of antigen-specific IgG, indicating a failure to generate long-lived plasma cells as we have previously seen in complement-receptor deficient mice. In contrast, deletion of arginase 2 in B cells led to an early increase and earlier decline of antibody responses. These indicate a critical role for arginase metabolism in the antibody response and, surprisingly, a dual role of the two enzymes in the regulation antibody responses.

B04

Trained immunity drives neutrophil reprogramming providing protection against pneumococcal sepsis

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Introduction: Trained immunity reflects the capacity of the host to adapt to an initial challenge and mount an improved response to a secondary challenge. We reported that trained immunity protects mice from a wide range of bacterial infections. Neutrophils play a key role in host defences, but their role during training is poorly understood.

Aim: Determine whether neutrophils are reprogrammed during training and assess their role in protection against streptococcal pneumoniae.

Methods: Mice were challenged with PBS (control) or β-glucan (training) given intraperitoneally. After one week, mice were sacrificed to isolate bone marrow (BM) and BM neutrophils or challenged intranasally with *Streptococcus pneumoniae.*

Results: Training increased BM stem and progenitor cells as well as neutrophils in blood and lungs (P<0.001). RNAseq demonstrated that the transcriptome of trained BM neutrophils was altered with gene pathways related to effector functions significantly enriched. In agreement, trained BM neutrophils showed increased chemotaxis, phagocytosis and *S. pneumoniae*-induced IL-1β, IL-6 and G-CSF production (P<0.05). Training protected mice from lethal pneumococcal pneumonia. The protection was lost upon neutrophil depletion (0.0% versus 87.5% survival in neutrophil-depleted versus neutrophil-non-depleted trained mice, P<0.001). The adoptive transfer of trained neutrophils to naive mice increased their resistance to *S. pneumoniae* infection.

Conclusions: Neutrophils are substantially altered upon training and required in the protection against pneumococcal pneumonia.

B05

Monosodium glutamate induces oxidative stress, protein folding defects, mitochondrial dysfunction and cell death in intestinal epithelial cells

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Aim: Environmental exposures can impair epithelial barriers and contribute to disease. Here, we report the impact of monosodium glutamate (MSG), disodium guanylate (DSG), disodium inosinate (DSI) and their combined effects on intestinal epithelial cells.

Methods: Monolayer Caco-2 cells and organ-on-a-chip model were established, and cellular cytotoxicity, transepithelial electrical resistance (TEER), paracellular flux (PF), RNA-sequencing, and reactive oxygen species (ROS) detection were performed at consumer-relevant doses.

Results: MSG, DSG, DSI, and their combination caused cytotoxicity at 1%, 0.5%, 2%, and 0.5%, respectively. A one-day exposure to 1% MSG, 1% DSG or the 1% doses of combined compounds reduced TEER. After three days, 1% MSG and the combined treatment significantly increased PF, indicating compromised barrier integrity. RNA-sequencing transcriptome revealed significant differences in gene expression between the 1% MSG and the combined exposure groups compared to controls. Key pathways affected by 1% MSG included oxidative stress, unfolded protein response and mitochondrial dysfunction. Increased ROS levels after 24 hours of MSG exposure were significantly reduced with 4 mM N-acetyl-L-cysteine. Autophagy regulation and upregulation of Deptor and TORC1 signaling were also observed.

Conclusions: Food flavor enhancers induce cytotoxicity, cellular stress, and barrier damage in gut epithelial cells. These findings raise concerns about their potential role in microbial imbalance, immune dysfunction, and inflammation.

B07

Determination of the role of CD39 and the purinergic pathway in CD8+ T cell effector functions during chronic viral infection

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Persistent infections with human immunodeficiency virus (HIV), hepatitis B/C viruses, or cancer are characterized by chronic antigen exposure and/or inflammatory signals, a condition where specific $CD8^+$ cytolytic T lymphocytes (CTLs) gradually become "exhausted" and unable to eliminate these pathogens. Recent therapies aim to reactivate these exhausted T cells by using immune checkpoint inhibitors (ICIs) that block inhibitory molecules specifically upregulated on these cells. While these treatments boost immunity, they often cause severe immune-related side effects. Identifying new molecular pathways involved in T cell exhaustion could therefore provide safer alternatives to current ICI-based approaches.

Exhausted T cells have recently been found to upregulate CD39, a purine metabolizing enzyme, on their surface. Yet it is currently unknown whether this molecule is simply a marker or whether it directly contributes to T cell functional impairment.

In this project, we used *in vivo* approaches based on a mouse model of chronic viral infection, together with *in vitro* methods, to investigate the differential roles of purinergic signaling and CD39 in acute versus chronic T cell activation. Our results suggest that CD39 modulates T cell function in a cell-autonomous manner.

B08

Immunomodulatory effect of radiotherapy on the microenvironment of muscle-invasive bladder cancer

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Bladder cancer was ranked as the 4th most frequent cancer in males in America and Europe in 2022. Among all the patients, 20% is diagnosed with muscle-invasive bladder cancer (MIBC), characterized by disruption of the urothelium and invasion of the muscle layer by tumor cells. The gold standard treatment is cisplatin-based chemotherapy followed by radical cystectomy, but it confers patients a median 5-years survival of 46-63%. The use of Abs targeting the PD-1/PD-L1 axis has been approved but the response rate is only 17-23%, which highlights the urgent need to develop new therapeutic options. Radiotherapy (RT) is used in BC for bladder-sparing protocol which include very few patients who will undergo high dose RT combined with chemotherapy. However, low-dose RT has been investigated for its capacity to stimulate the TME and could be used in combination with immunotherapy.

Our project aims to detail the effects of diverse doses of RT on the TME of MIBC. We used a mouse model of MIBC that recapitulates features of the human disease, presents a suppressed TME and resistance to anti-PD-1 treatment. MIBC-bearing mice were irradiated with different doses of X-rays and the immune compartment was characterized by flow cytometry 7 days post-RT. Data showed an increase of anti-tumor immune cells, especially CD8 and CD4 T cells, and decrease of Tregs and protumoral macrophages with low dose of X-rays compared to untreated mice. The beneficial effect of RT can lead to the development of novel therapeutic solution for MIBC patients, especially combined with immunotherapy treatments.

B09

Structuring of immune system data in UniProtKB

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In the era of big data and machine learning, knowledge databases are becoming invaluable resources of structured data that can be integrated in omics pipelines and neural networks to accelerate data interpretation, generate new hypotheses and research projects.

UniProtKB knowledgebase (www.uniprot.org) is a reference resource of protein sequences and functional annotations across species of all branches of the tree of life. It integrates expert-curated structured data using ontologies and bioinformatic tools to link protein sequences to molecular functions, processes and phenotypes. Such data encompass gene-centric curation of immune system collections of antigen presentation and recognition molecules together with antigenic peptide epitopes mapped to immunology-specialized databases IMGT and IEDB.

We are currently curating the biochemistry of immune metabolites and immunogenic molecular structures aiming to provide a reference dataset relevant to immune cell activation and migration in innate and memory immune responses. Structured data of metabolic processes and protein-ligand interactions are integrated in UniProtKB, where an immune metabolite is mapped to a biochemical reaction curated in Rhea (www.rhea-db.org) based on chemical ontology of ChEBI (www.ebi.ac.uk/chebi), to enzyme, transporter or receptor binding sites based on resolved protein structures in the Protein Data Bank (PDB/PDBe), and to biological processes based on Gene Ontology (www.geneontology.org). Such structured data can be used in neural networks to contextualize raw data and infer immunogenic molecular structures involved in interspecies interactions.

B11

Programming immunity: a tetravalent mucosal nanovaccine for enhanced local and systemic antitumor response in head and neck cancer

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Introduction: Mucosal cancers, including human papillomavirus (HPV)-driven head and neck carcinomas (HNC), present unique challenges due to their anatomical and immunological complexity. While therapeutic vaccines often prioritize T cell activation, emerging evidence highlights B cells as critical mediators of antitumor immunity, though their role in mucosal tumors remains poorly understood.

Method: Here, we evaluate a tetravalent virus-like particle (VLP) nanovaccine, Qβ-HPVag, delivering HPV16 E6/E7 antigens and a TLR-9 agonist, administered intranasally in an orthotopic HPV$^+$ HNC model.

Results: We show that mucosal immunization with Qβ-HPVag significantly reduces tumor growth and enhances cytotoxic CD8$^+$ T cell infiltration and function. Crucially, B cell depletion abrogated vaccine efficacy, with vaccination promoting the expansion of tumor-infiltrating memory B cells, plasmablasts, and IgA$^+$ B cells, alongside systemic antigen-specific IgG responses.

Conclusion: These findings contrast with traditional T cell-centric paradigms, revealing that B cells coordinate localized humoral immunity and synergize with CD8$^+$ T cells to mediate tumor control. By integrating mucosal-targeted delivery with coordinated B and T cell activation, this study advances therapeutic vaccine strategies against HPV$^+$ cancers and B cells as essential targets for next-generation immunotherapies.

B12

Preclinical Potential of γδ T Cells in Novel Personalized Antigen-Directed Immunotherapy for Triple-Negative Breast Cancer

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Introduction: Triple-negative breast cancer (TNBC) is highly aggressive, with poor prognosis and limited effective treatments. Virus-like particles (VLPs)-based personalized vaccines offer a promising way to induce lasting antitumor immunity. While γδ T cells play roles in cancer, their interaction with nanoparticles is unclear. Administration route impacts efficacy: subcutaneous (*s.c.*) delivery within lymphatic watersheds targeting draining lymph nodes (dLNs), enhance local and systemic immune responses.

Method: We developed plant-derived VLPs carrying TLR ligands and validated them by cryo-EM and biochemical assays. Using imaging flow cytometry and *in vivo* studies in the 4T1 *s.c.* TNBC model, we examined γδ T cell–VLP interaction and their role in vaccine efficacy. We compared three s.c. routes: systemic, targeting tdLNs, and targeting non-tdLNs. Survival was assessed under different dosing and ICI co-treatment. CD4+, CD8+, and γδ T cells were depleted to determine their contributions.

Results: γδ T cells were expanded in dLNs and internalized VLPs post-vaccination. γδ subsets showed distinct activation. tdLN-targeted delivery, especially with ICI, gave the best outcomes. Depletion of CD4+, CD8+, or γδ T cells impaired efficacy, showing all are essential. Despite their rarity, γδ T cells were key to early tumor control.

Conclusion: Our study highlights a crucial early role for γδ T cells in VLP-based cancer vaccination. Efficacy improved with ICI co-treatment and tdLN-targeted delivery, supporting inclusion of rare immune subsets like γδ T cells in cancer immunotherapy.

B16

A novel model to study the immune response to urinary tract infection

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Urinary tract infections (UTIs) are highly prevalent, and traditional antibiotic treatments do not completely clear a UTI. The immune response is critical to the resolution of a UTI. Although animal models have given insights into the immune response to UTI, the human system is understudied, highlighting the need for human *in vitro* approaches. We aim to develop an immunocompetent human urothelial microtissue model to study the interaction between human immune cells and uropathogens.

The urothelial microtissue model is based on an established *in vitro* Transwell model of UTI, which contains a functional urothelium but lacks immune components. The model is adapted to enable immune cell migration, while urothelial integrity is confirmed by microscopy and the Transepithelial Electrical Resistance (TEER). Monocyte-derived macrophages are integrated into the model and the response to infection is analyzed by cytokine and LDH release.

A collagen matrigel coating was successfully added to create a porous barrier below the urothelium, where immune cells can be integrated. Urothelial microtissues were successfully grown, differentiated and stratified on the new substrate. In response to infection, the urothelium secretes a multitude of pro-inflammatory cytokines. Preliminary results show that macrophages can be integrated into the model, their response to infection will be studied next.

The novel immunocompetent urothelial microtissue model will provide new insights into the interplay between human immune cells and uropathogens, enabling discovery of novel pathways to combat UTI.

B18

Unveiling the Guardians: Conventional Type 1 Dendritic Cells Orchestrating Fibrosis In The Tumor Microenvironment

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In the context of chronic diseases, such as cancer, a small proportion of exhausted memory-like T progenitor cells (Tex^{prog}) is maintained, and co-localizes with in niches formed by conventional type 1 dendritic cell (cDC1) to support them. Moreover, cDC1 also assists exhausted $CD8^+$ T (Tex) populations in the early stages of tumor development. The tumor microenvironment (TME) alters cDC1 functionality to favor a more immunoregulatory state. Another critical component is the accumulation of collagen and other ECM components, produced by cancer-associated fibroblasts (CAFs), leads to fibrosis, which is linked to poor prognosis, and treatments targeting fibrogenesis are limited. Studying the role of cDC1s in tumor fibrosis offers a new therapeutic approach.

We used the Yumm1.7-OVA melanoma model to explore cDC1 capacity to control fibrosis and improve the infiltration capacity of anti-tumor $CD8^+$ T cells during the early stages of tumor development. In later stages, cDC1 functionality changes, leading to an increase in collagen deposition, a loss of motility of tumor-infiltrating lymphocytes (TILs), and an accumulation of Tex cells. Transferring functional cDC1s from splenocytes from naïve mice restores the motility of tumor-infiltrating lymphocytes and counteracts fibrogenesis.

These results demonstrate an anti-fibrotic role of cDC1s in the tumor microenvironment, a finding that has the potential to extend to chronic inflammatory diseases where disregulated fibrous contributes to the underlying pathology.

B19

Immunometabolism in single cell resolution - PrEMIuM-seq: Projectable Epitope and Metabolic Index couple Multi-omics by sequencing

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Immune cells display diverse metabolic activities closely tied to their differentiation and function. CD8 T cells, in particular, exhibit distinct metabolic profiles across cell states during acute/chronic infections and in tumors. Advances in single-cell omics have enabled detailed transcriptomic and metabolomic

analyses, yet integrating metabolic activity with transcriptomics at single-cell resolution remains a challenge, especially considering metabolism-driven epigenetic effects.

We introduce PrEMIuM-seq (Projectable Epitope and Metabolic Index Coupled Multi-Omics by Sequencing), a sequencing-based method extending the 10X Genomics single-cell platform. It uses DNA-barcoded monoclonal antibodies to capture surface epitopes, metabolic enzymes, and transcription factors. A correctable barcode library and in silico analysis improve unbiased protein detection. This allows simultaneous profiling of metabolic activity and transcriptomes at single-cell resolution.

To complement PrEMIuM-seq, we collected paired samples from same batch for traditional metabolomic/lipidomic analyses and SCENITH, a flow cytometry-based metabolic assay. Integrating these with machine learning enhances interpretation of cellular metabolism. This multi-omics framework offers a comprehensive view of how metabolic processes intersect with immune cell function.

B20

Holding glycolysis in check via arachidonate 15-lipoxygenase is required for macrophage M2 commitment in tissue repair and anti-helminth immunity.

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Type-2 cytokine-driven macrophage polarization plays a pivotal role in both tissue repair and protective immunity against helminth infections. Although several characteristic features of alternatively activated, or M2, macrophages are well established, the mechanisms by which these cells mediate anti-helminth functions remain incompletely understood. In this study, we examined the role of arachidonate 15-lipoxygenase (Alox15), a key enzyme implicated in macrophage function during metabolic disease and a defining marker of human M2 macrophages. We found that Alox15 is essential for M2 macrophages to effectively immobilize and kill helminths. Surprisingly, M2 surface marker expression remained intact in Alox15-KO cells, despite a marked impairment in their function. This dysfunction was accompanied by heightened pro-inflammatory signaling linked to dysregulated activation of glycolysis. Further investigation revealed that lipid-mediated activation of Peroxisome proliferator-activated receptor-delta (PPAR-δ), specifically via downstream products of Docosapentaenoic acid (DPA), could re-establish proper glycolytic control. These findings uncover a previously unrecognized lipid-mediated regulatory axis that is critical for the metabolic programming underpinning effective M2 macrophage polarization, and underscore the importance of assessing both functional and phenotypic markers of polarization.

B21

Ferroptosis Promotes Anti-Helminth Immunity and Is Counteracted by Helminths

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Aim: Ferroptosis is a form of regulated cell death characterized by iron-dependent lipid peroxidation. Alternatively activated macrophages (AAM) play key roles in type 2 immunity against helminth parasites, despite being highly susceptible to lipid peroxidation and ferroptotic cell death. Thus, we investigate the role of ferroptosis in type 2 immune responses against the helminth *H. polygyrus bakeri* (*Hpb*).

Methods: We utilize murine *in vivo* infection models, *ex vivo* cell cultures, immunostainings, transcriptomics, western blotting, live cell imaging and lipidomics to characterize the presence and consequences of ferroptosis during *Hpb* infection.

Results: *Hpb* infection induces ferroptotic cell death in the small intestine (SI), while administration of the ferroptosis inhibitior liproxstatin-1 attenuates cell death, lipid peroxidation and anti-helminth immunity. The increase of lipid peroxidation and cell death in the SI was abrogated in mice lacking hematopoietic transglutaminase-2 (TG2). In line, TG2 deficient AAM show reduced arachidonic acid oxidation (eicosanoids) and an increased PUFA/ MUFA ratio in membrane phospholipids. Genetic deficiency, siRNA-mediated knock-down or pharmacological inhibition of TG2 consistently suppressed ferroptosis of human or mouse macrophages. *Hpb*-secreted glutamate dehydrogenase (heGDH), in turn, suppressed AAM ferroptosis.

Conclusions: Ferroptosis contributes to parasite control, with host-derived TG2 orchestrating ferroptosis susceptibility in AAM, while heGDH impedes ferroptosis as a helminthic immune evasion strategy during type 2 immunity.

B22

Sec61 inhibition by KZR-834 downregulates MHC-I surface expression

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The heterotrimeric translocon Sec61 plays a crucial role in the endoplasmic reticulum (ER) by facilitating the transport of newly synthesized proteins into the ER and the export of misfolded proteins for proteasomal degradation, a process known as ER-associated degradation (ERAD). Peptides presented on MHC-I molecules originate from proteasomal degradation, suggesting that inhibiting Sec61 could impact MHC-I peptide presentation. Consequently, this may influence communication with other immune cells and potentially alter immune responses. Kezar Life Sciences has developed two chemically-related Sec61 inhibitors, KZR-834 and KZR-261, which have demonstrated broad anti-tumor activity in vitro and in vivo at well-tolerated doses. KZR-834 was examined here for its impact on bulk MHC-I presentation at non-toxic levels and on certain MHC-I epitopes. Flow cytometry analysis revealed a concentration-dependent decrease in MHC-I surface expression across various cancer cell lines and primary cells. The effect of KZR-834 extends to other unrelated surface proteins, indicating a broad impact on protein surface expression. Additionally, antigen presentation assays demonstrated a reduced presen-

tation of specific MHC-I epitopes. Further experiments investigated whether KZR-834 affects antigen transport from endosomes to the cytosol. Indeed, Sec61 inhibition in cross-presentation experiments with ovalbumin showed a reduction in this process. Taken together, Sec61 inhibition can reduce MHC-I direct- and cross-presentation and is an attractive tool in modulating MHC-I surface expression.

B23

IL4-Ralpha and IFN-gamma opposing signals modulate neutrophils effector functions

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Neutrophils are the most abundant immune cells in human blood and are essential in microbial defense. Recent studies show that they are transcriptionally active, responsive to external stimuli, and represent a heterogeneous population. Atopic dermatitis (AD) is a chronic inflammatory skin disease involving genetic predisposition, barrier dysfunction, microbial dysbiosis, and type-2-T-helper-cells (Th2)-predominant inflammation. While AD skin lesions are often colonized by pathogenic bacteria, neutrophils tend to be relatively limited compared to other inflammatory conditions. In mice, IL-4 has been shown to suppress neutrophil function, promote aging features, and increase susceptibility to infection.

Here, we investigated how human neutrophils adapt to opposing signals using in vitro stimulation with IL-4, IL-13, IFN-γ, and their combinations. IL-4 and IL-13 induced STAT6 phosphorylation, with IL-4 showing faster kinetics, while IFN-γ triggered STAT1 phosphorylation. Co-stimulation led to simultaneous STAT6 and STAT1 activation, although IFN-γ attenuated STAT6 signaling in IL-4-treated neutrophils. Functionally, NETosis was reduced by IL-4Rα signaling and enhanced by IFN-γ. Transcriptomic analyses further revealed that IFN-γ addition to IL-4 and IL-13 promotes expression of genes linked to neutrophil migration and chemotaxis. These findings highlight the plasticity of neutrophils and the immune-regulatory interplay between opposing cytokine signals in vitro.

B24

Mechanistic insights into the role of IL-33 signaling in the bone marrow niche in myeloproliferative neoplasms pathogenesis

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Myeloproliferative neoplasms (MPN) are a group of chronic and life-threatening blood cancers characterized by the aberrant expression and activity of inflammatory cytokines, yet their precise contribution to disease pathogenesis is unclear. MPN patients may develop bone marrow (BM) fibrosis (BMF), which is usually associated with impaired hematopoiesis. BMF strongly correlates with increased morbidity and mortality of MPN patients. However, the mechanisms underlying BMF remain poorly understood, and current MPN treatments offer only limited improvement in BMF.

MPN patients exhibit elevated levels of IL-33 in their BM, suggesting that IL-33/ST2 signaling may play a role in MPN pathogenesis. Using a mouse model of MPN with transgenic expression of the JAK2-V617F mutated allele, we found that stromal cell-derived IL-33 is important for MPN development. Sinusoidal endothelial cells show increased IL-33 expression during MPN progression. In the BM niche, IL-33 binds to its receptor ST2 on stromal cells but not JAK2-V617F+ hematopoietic stem and progenitor cells. While megakaryocytes are known to play a critical role in bone marrow fibrosis, ST2 is present on wild-type, yet not on JAK2-V617F+ megakaryocytes. Further studies are ongoing to investigate whether and how IL-33/ST2 signaling contributes to BMF in mouse and human MPN.

B28

Trained immunity induces extramedullary granulopoiesis and enhances the effector functions of splenic neutrophils

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Introduction: Trained immunity describes challenge-induced long-term functional reprogramming of hematopoietic progenitor cells and immune cells, resulting in an altered response to a secondary challenge. We have shown that training increases central granulopoiesis and neutrophilia, but whether training stimulates extramedullary granulopoiesis is unknown.

Aim: Determine whether trained immunity induces splenic granulopoiesis generating neutrophils with altered functions.

Methods: Mice challenged intraperitoneally with PBS (control) or β-glucan (training) were sacrificed after 7 days to collect spleens used in clonogenic assays and to isolate neutrophils characterized by flow cytometry and functional assays.

Results: Training induced splenomegaly and increased 4.8-fold clonogenic progenitors of granulocytes (CFU-G, $p<0.0001$) and 12.1-fold splenic neutrophils ($p<0.001$). In trained mice, splenic neutrophils expressed increased levels of Ly6G and CXCR2 that are associated with neutrophil maturation. Trained neutrophils secreted higher levels of granule molecules (MPO, MMP9, S100A8/A9) upon stimulation with microbial products and migrated more in response to CXCL1 and CXCL2 than control neutrophils ($p<0.05$).

Conclusions: Training induced in the spleen (i) extramedullary granulopoiesis, and (ii) phenotypically and functionally altered neutrophils. The molecular mechanisms underlying neutrophil reprogramming and the consequences of splenic neutrophilia on host defenses are under investigation.

B29

Central trained immunity in allergic asthma

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Asthma is a chronic airway inflammatory disease marked by dysregulated innate immune responses. Recent evidence implicates innate immune memory, or trained immunity, in asthma pathogenesis. Yet, the underlying mechanisms remains poorly understood. Here, we explore the role of central trained immunity in a murine model of severe, steroid-resistant house dust mite (HDM)-allergic asthma induced by co-administration of HDM and the β-glucan Curdlan.

Flow cytometry and histological analyses revealed that HDM/Curdlan induces eosinophilic and Th2 responses, followed by sustained neutrophilic, Th17 inflammation in the lung,

with persistent monocyte-derived alveolar macrophage (AlvM) infiltration and enhanced bone marrow myelopoiesis.

Single-cell RNA- and ATAC-seq analyses of hematopoietic stem and progenitor cells (HSPCs) demonstrated transcriptional, epigenetic, and metabolic reprogramming of myeloid HSPCs toward a pro-inflammatory state.

In parallel, SeaHorse assays and RNA-seq analysis of BMDMs showed reduced mitochondrial respiration and upregulation of pro-inflammatory genes.

Lastly, RNA-seq and ELISA analyses of AlvMs revealed a sustained pro-inflammatory phenotype characterized by increased eicosanoid production and transcriptional reprogramming similar to BMDMs.

Taken together, these results suggests that central trained immunity, characterized by myelopoiesis and HSPC reprogramming, contributes to persistent airway inflammation through the replacement of lung-resident AlvMs by "trained" bone marrow-derived cells, revealing a novel mechanism driving severe asthma.

B30

Modulation of NK cell effector functions by human-plasma devrived-IgG and recombinant IgG1-Fc hexamer

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Therapeutic immunoglobulin G (IVIG) production is constrained by the limited supply of human plasma. As an alternative, recombinant hexamers (HEX) derived from IgG1-Fc fused with the IgM µ-tailpiece have been developed. One key mechanism of IVIG involves targeting Fcγ receptors (FcγRs) to inhibit NK cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC). This study aimed to compare the effects of IVIG, HEX variants and Fc monomers on NK cell viability, metabolism, and function.

NK cell viability was tested by trypan blue exclusion; metabolic activity by resazurin-based assay; apoptosis (Annexin-V staining), activating/inhibitory NK receptors, and activation markers were analyzed by flow cytometry; cytokines release was quantified by cytometric-bead array. Direct cytotoxicity and ADCC were assessed by non-radioactive release assays using K562 or anti-CD20-coated Daudi cells as targets.

After 16h of incubation, HEX-variants masked CD16 detection by flow cytometry, whereas CD16 was still detectable following incubation with IVIG and the Fc monomer. Both IVIG and HEX induced minimal NK cell death compared to medium (<20%), with no alterations in metabolic activity. HEX was the most potent inhibitor of ADCC (90% inhibition). Furthermore, IVIG and HEX inhibited direct cytotoxicity (55% and 45% reduction, respectively). All IgG molecules, except Fc monomer, triggered the release of TNF and IFNγ by NK cells.

In conclusion, HEX inhibited NK cell effector functions indicating the potential to substitute IVIG in the treatment of auto-antibody-mediated diseases.

B31

Kinase-Dead PI3Kγ Unleashes Memory T Cells by Bypassing mTOR and Blocking Exhaustion

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The fate of CD8⁺ T cells is crucial for immunity against chronic infection, cancer, and autoimmunity. Promoting stem-like properties and reversing exhaustion are pivotal strategies to enhance adoptive cell therapy (ACT) and immune checkpoint blockade, yet the mechanisms underlying memory formation remain poorly understood. Here, in vivo CRISPR–Cas9 screening during acute LCMV infection identifies a noncanonical PI3Kγ signaling axis as a central regulator of CD8⁺ T cell fate. We show that while both PI3Kδ and PI3Kγ deficiency enhance memory formation, only PI3Kγ deficiency improves cytokine production and strengthens T cell recall responses. Using kinase-dead knock-in models, we demonstrate that PI3Kγ kinase activity is essential for T cell fate decisions. Single-cell RNA sequencing and epigenomic profiling reveal that PI3Kγ deficiency promotes memory formation through upregulation of TCF1 and Bcl-2, bypassing canonical PI3K–mTOR signaling and engaging NFAT pathways. In chronic infection, PI3Kγ-deficient T cells sustain proliferation, resist exhaustion, and enhance cytotoxicity, driving superior responses to ACT and checkpoint blockade. These findings establish the CXCR4–PI3Kγ axis as a critical switch for CD8⁺ T cell fate, offering new strategies for optimizing T cell–based immunotherapies.

C02

A Novel Caspase Activation and Recruitment Domain 11 (CARD11) Mutation in a Patient with Fever of Unknown Origin

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CARD11 is a scaffold protein essential for NF-κB, mTORC, and JNK activation following BCR/TCR engagement. Gain-of-function (GOF) mutations in CARD11 lead to constitutive NF-κB activity, B cell expansion, and T cell anergy in patients (BENTA syndrome), whereas loss-of-function (LOF) mutations result in immunodeficiency. We identified a novel CARD11 variant (K356T) by whole exome sequencing in a patient presenting fever of unknown origin and lacking typical BENTA clinical features. Our aim is to characterize the impact of this novel mutation variant on intracellular signaling.

Plasmids encoding wild-type (WT), K356T (novel), and C49Y (GOF control) CARD11 were generated. A CARD11-deficient Jurkat T-cell line expressing an NF-κB-driven GFP reporter (JPM50.6) was electroporated with WT or mutant plasmids and stimulated with anti-CD3/CD28 antibodies or phorbol 12-myristate 13-acetate plus Ionomycin. NF-κB reporter activity was assessed by flow cytometry. In parallel, phosphorylation kinetic of S6, p65, and JNK were analyzed by phospho-flow following stimulation of PBMC.

Transient expression of CARD11 novel K356T mutant in JPM50.6 induced modest constitutive NF-κB reporter activity, in contrast to the lack of activity of WT. This activity was further enhanced upon stimulation. Phospho-flow of healthy donor PBMC identified optimal stimulation times. In conclusion, we describe a novel CARD11 mutation associated with atypical clin-

ical manifestations and mild GOF activity *in vitro*. Further characterization using phospho-flow in the patient's PBMC is ongoing.

C04

FceRIneg DC3 subset accumulates in the urine of patients with nephrotic syndrome (NS) in complete remission: a potential role in the resolution of NS?

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Nephrotic syndrome (NS) is a glomerular disease characterized by increased permeability of the filtration barrier. In order to understand the underlying immune mechanism, the aim of this study is to characterize different subsets of DCs in the urine of patients with NS.

Urine and blood samples were collected from children with NS (n=7) and compared with controls (n=10). Cells were analyzed by FACS with markers identifying DC subsets, as well as T cells, NK, neutrophils and macrophages.

Flow cytometry data, analysed by PCA, allowed the discrimination of NS patients from controls in both urine and blood samples, suggesting that the FACS panel used was relevant in identifying a cellular signature of NS in this study.

Preliminary data show that, although the frequencies of CD3T-cell populations in urine are very low (<0.05% total cells), the HLA-DR population may reach up to 5% of total cells. Among the DC subtypes, the DC3 ($CD1c^+CD14^+$) population was significantly increased in the urine of NS patients compared to controls. Screening the composition of DC3 population, a higher frequency of DC3 not expressing the FceRI-receptor accumulates in the urine of patients with complete remission compared to patients in remission but still on treatment or in relapse. These results suggest that the $FceRI^{neg}$DC3 population may develop during patients' recovery and open the question of whether it is involved in the resolution of NS.

These findings demonstrate for the first time that a DC subset can be found in urine in pediatric patients with NS and may be related to the remission status.

C05

Immune modulation through targeted therapies in atopic dermatitis: what do biomarkers tell us?

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Aim: To review current evidence regarding the modulation of immunological biomarkers in atopic dermatitis (AD) following targeted therapeutic interventions.

Methods: A narrative review was conducted, focusing on clinical trials investigating the impact of biologic therapies (dupilumab, tralokinumab, lebrikizumab) and JAK inhibitors (baricitinib, upadacitinib) on type 2 cytokines, chemokines (such as TARC/CCL17), eosinophil levels, and markers of skin barrier integrity including filaggrin.

Results: Clinical data show that targeted therapies consistently lower serum concentrations of TARC/CCL17 and eosinophils [1,2], alongside reduced expression of IL-4 and IL-13 [1], which correlate with clinical improvement. In addition, IL-31 modulation has been associated with significant relief of pruritus [3]. Restoration of skin barrier function has been reported in responders, evidenced by increased filaggrin expression [4]. These findings reinforce current recommendations that highlight the relevance of biomarker monitoring in AD management [5].

Conclusions: Targeted therapies in AD not only alleviate clinical symptoms but also address underlying immune dysregulation and epithelial barrier dysfunction. Biomarkers such as TARC/CCL17 and filaggrin may support clinicians in monitoring disease activity, evaluating therapeutic response, and informing treatment selection according to individual immune profiles. Nevertheless, additional clinical trials are needed to validate these biomarkers for routine use and to better define their role within future personalized treatment strategies.

C06

Agranulocytosis with anti-neutrophil antibodies in multicentric Castleman's disease

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Aim: Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder driven by human herpesvirus-8 (HHV-8) with cytokine overproduction. We report a case of MCD with agranulocytosis due to anti-proteinase 3 (PR3) antibodies in an HHV-8 positive, HIV-negative patient.

Methods: Retrospective study documenting agranulocytosis, anti-PR3 antibodies, and histologically confirmed MCD in the context of HHV-8 positivity and HIV negativity.

Results: A 59-year-old man with hepatitis C, cirrhosis, and substance abuse presented with fever, diarrhea, and weight loss. Labs showed agranulocytosis, elevated CRP (98 mg/l), and positive ANCA with anti-PR3 antibodies (70 UI/ml). CT revealed lymphadenopathy. Biopsy confirmed HHV-8 positive MCD. PCR for HHV-8 was positive in serum, bone marrow, bronchoalveolar lavage, and lymph node. HIV testing was negative. Skin lesions were diagnosed as Kaposi's sarcoma (KS). Despite G-CSF, agranulocytosis persisted. Bone marrow biopsy showed granulocytic maturation block. Rituximab (RTX) and low-dose prednisone were given, leading to fever reduction, CRP normalization, and KS regression. Agranulocytosis persisted for 11 months, improving with the disappearance of anti-PR3 antibodies.

Conclusion: This case demonstrates a rare presentation of agranulocytosis with MCD and HHV-8 positivity. In such MCD cases, RTX with or without liposomal doxorubicin is the preferred treatment. In our case, KS regressed with RTX alone. We suggest a link between anti-PR3 antibodies and agranulocytosis, as their disappearance coincided with the resolution of the condition.

C07

Living with Systemic Lupus Erythematosus in Switzerland: Self-reported disease activity and flare status in Lupus IMPACT Survey

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SLE causes diverse clinical symptoms, leading to significant physical and psychological strain. Active disease and flares increase fatigue, pain and organ damage. Patient-reported tools such as SLAQ are vital to capture patient experiences. Here, we

evaluate self-reported disease activity and its influencing factors in Swiss SLE patients.

Patients were invited to survey via digital ads, patient organization newsletter and a letter from Swiss SLE Cohort Study. Inclusion criteria were SLE diagnosis, age 18+ and living in Switzerland. Disease activity was assessed with SLAQ total score (ranging from 0 to 47). SLAQ also covers the flares and global assessment of overall activity (ranging from 0-10).

146 mostly female and Caucasians patients with a median age of 48.5 were studied. Mostly used SLE medications were antimalarials and immunosuppressants. The mean SLAQ score was 19.35 and disease overall activity was 3.86. Moderate/severe flares were reported by 28.7% of patients. 6.7% of those without or with mild flares were not on medication. Regression analysis showed SLAQ scores significantly correlated with having flares and daily pill intake. Higher NSAID and antidepressant use and lower average treatment satisfaction across all SLAQ dimensions were noted in patients with high disease activity.

Persisting disease burden in SLE patients in Switzerland underscored by substantial disease activity, existence of flares and high usage of glucocorticoids. The study reveals an association between increased disease activity, treatment patterns and overall treatment satisfaction.

C08

Role of inflammatory biomarkers to assess immune dysregulation and guide treatment in CVID

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Background: Common variable immunodeficiency (CVID) is a heterogenous antibody deficiency syndrome characterized by increased susceptibility to infection, autoimmune manifestations, and increased risk of malignancy. CVID patients can be divided according to the presence of immune dysregulation into complicated (c) versus infection only (io)CVID. Although CVID is the most prevalent symptomatic inborn error of immunity early detection of immune dysregulation can be challenging, and delayed detection can cause irreversible organ damage.

Methods: We conducted a single-center retrospective chart review of the role of routine biomarkers in CVID patients presenting with or without immune dysregulation prior to and upon immunosuppressive treatment.

Results: 45 CVID patients were assessed including 16 ioCVID and 29 cCVID patients on (20/29) or off immunosuppressive treatment. Routine inflammatory biomarkers (CRP, WBC, CD21low, Neopterin and sIL-2R) were compared among individual patients in respect to immune dysregulation and upon immunosuppressive treatment.

Conclusion: Our study affirms the role of biomarkers as effective method in the screening of manifestation of immune dysregulation and in monitoring treatment responses in cCVID.

C09

Breaking the Shield: Anti-Interferon-Gamma Antibodies and the Spectrum of Infections – A Case Report

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Introduction: Anti-cytokine autoantibodies (ACAAb) are increasingly recognized for their impact on disease phenotypes in infections, inflammatory disorders, and autoimmune conditions. By specifically blocking cytokine signaling pathways, ACAAb can phenocopy inborn errors in the related signaling pathways.

Case report: Here we report a case of adult-onset Legionella pneumonia followed by disseminated Mycobacterium abscessus and Salmonella enterica subsp. enterica infection associated with neutralizing anti-IFN-γ antibodies. The results corroborate the disease-causing role of neutralizing anti-interferon-gamma ACCAb in disseminated non-tuberculous mycobacterial infections. To assess the neutralizing capacity of the interferon-γ-specific ACAAb, we performed flow-cytometry based STAT1 phosphorylation experiments using Jurkat T cells in the presence or absence of recombinant IFN-gamma. Reduced IFN-gamma induced STAT1 phosphorylation was measured in the presence of the serum of the patient vs. sera from control patients from a prospective cohort of patient with primary immunodeficiency.

Discussion: IFN-gamma-specific ACAAb have been described as likely molecular cause of disease for non-tuberculous mycobacteria, Varicella-Zoster virus, Talaromyces marneffei, Salmonella spp., Cryptococcus spp., Mycobacterium tuberculosis, Burkholderia spp., and Histoplasma capsulatum. It is crucial to consider the possibility of anti-interferon gamma antibody disease. A targeted laboratory analysis should be conducted to investigate this condition. The therapeutic landscape of this disease is evolving.

C10

Erasmus Syndrome: Silica Exposure as a Trigger for Scleroderma and Pulmonary Disease. A Case-Based Review.

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Erasmus syndrome is a rare, occupationally related condition characterized by the development of systemic sclerosis (SSc) in a background of silica exposure or silicosis, a preventable fibrosing lung disease caused by the inhalation of crystalline silica. Silica particles trigger inflammation such as macrophage activation, cytokine release and upregulation of cell-signaling pathways, leading to fibrosis. The main manifestations are respiratory, including dyspnea, chronic cough, and fatigue, reflecting the underlying pulmonary and systemic fibrotic processes. We report on a 37-years-old male diagnosed in 2020 with nonspecific interstitial pneumonia (NSIP) in the context of systemic sclerosis (SSc) with diffuse cutaneous involvement. The patient is seropositive for anti-topoisomerase I and anti-Ku antibodies, although the clinical significance of the latter remains unclear. He was treated with Mycophenolate mofetil, resulting in stable pulmonary function and favorable cutaneous responses. A routine chest HRCT in early 2024 revealed mediastinal and hilar

lymphadenopathies with intraparenchymal calcifications and micronodular changes in the upper lobes, unrelated to the autoimmune condition. NSIP-like alterations in the lower lobes indicated ongoing autoimmune involvement. Imaging deterioration with new findings prompted a review of the clinical history, revealing prolonged exposure to stone dust between the ages of 15 and 19, as well as ongoing exposure to ceramic dust since 2021. A lung biopsy subsequently confirmed the presence of silicotic nodules, establishing the diagnosis of Erasmus syndrome.

L02

Diagnostic performance of the ALEX2 multiplex test for soy allergy

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Aim: Multiplex specific immunoglobulin E (sIgE) testing is widely used to infer sensitisation profiles but only provides indirect evidence of potential allergies. A major concern is the incidental detection of sIgE – such as to soy – without corresponding clinical relevance. This study aimed to evaluate the diagnostic performance of the ALEX^2 multiplex assay for soy allergy and to compare it with ISAC and ImmunoCAP (IC).

Methods: We enrolled 40 patients with clinically diagnosed soy allergy and an additional 20 control subjects without soy allergy. sIgE levels to whole extracts and molecular components were measured using IC, ISAC, and ALEX^2. We calculated Spearman's correlation coefficient (ρ) and assessed diagnostic performance of ALEX^2 using dichotomised data.

Results: sIgE to Gly m 4 (ρ = 0.88) and Gly m 6 (ρ = 0.80) showed strong correlations between ALEX^2 and ISAC, with similar correlations between ALEX^2 and IC (ρ = 0.82, 0.74, 0.63 for Gly m 4, 6, and 5, respectively) and between ISAC and IC (ρ = 0.85, 0.94, 0.76). sIgE to Gly m 5 was less correlated (ρ=0.48) between ALEX^2 and ISAC. Specificity for Gly m 4, Gly m 5, and Gly m 6 was higher with ALEX^2 (65%) compared to ISAC (50%) and IC (40%), although ALEX^2 showed lower sensitivity (60% vs. 88% and 98%). Overall, the three methods yielded comparable positive likelihood ratios (1.65–1.75).

Conclusions:

ALEX^2 demonstrated diagnostic performance for soy allergens that was comparable to ISAC and IC. Notably, ALEX^2 did not generate more false-positive results than either ISAC or IC.

L03

Increased Incidence of anaphylaxis to PEGylated compounds: Potential Link to COVID-19 Vaccine-Induced Sensitization anti-PEGylated Lipid Nanoparticles

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Most biological agents contain polyethylene glycol (PEG) derivatives, which are very stable and generally considered to be non-immunogenic. However, an explosion in hypersensitivity reactions to such products have been seen recently.

Here, we evaluated 13 patients who experienced severe anaphylaxis to SonoVue®, a contrast medium for ultrasound which contains lipid particles that are stabilised with PEG-4000. A control group of 13 tolerating individuals was also analysed. Sensitization to SonoVue® was confirmed using the basophil activation test (BAT), which yielded positive results in 6 of the 13 patients, but none in the tolerant group. Notably, all patients who suffered anaphylaxis also tested positive for BATs to COVID-19 vaccines, while none in the tolerant group did. Additionally, polysorbate 80 reactivity was observed in 8 of the 13 patients, but none in the tolerant group.

For mechanistic investigation, the inhibition of the FcεRI signalling pathway significantly reduced basophil activation. Furthermore, linear PEGs were shown to reduce basophil activation by spherical PEGs *in vitro*, suggesting that linear PEGs can occupy binding sites without cross-linking FcεRI and thus do not induce basophil degranulation.

PEG sensitization may have been boosted by mRNA COVID-19 vaccines, which contain PEG. Given its presence in numerous pharmaceuticals, PEG sensitization could pose a public health concern. Further research is crucial to understand the immune response to PEG, a molecule that is neither a protein nor a carbohydrate.

L05

Analytical performance of the HEp-2 substrate Diagnostic Kit for ANA as an initial step in the evaluation of a novel Fully Automated IFA Analyzer

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«Aim» As a first step evaluating a novel fully automated IFA analyzer (LumiQ™, AliveDx, Switzerland) combined with the HEp-2 substrate Diagnostic Kit for antinuclear antibodies (ANA) (investigational device, TEST), we assessed the analytical performance of the TEST, used manually by the same operator, compared with historical IFA results of samples from individuals under suspicion of autoimmune connective tissue diseases.

«Methods» Banked, de-identified sera, previously manually characterized by a routine HEp-2 IFA were included (50 non-reactive, 57 reactive, various titers and a broad range of IFA patterns) and assessed with the TEST at a 1:80 screening dilution. Manual testing followed the manufacturer's instructions, and 1 operator performed all readings using a fluorescent microscope. Results were interpreted as reactive/non-reactive, patterns identified, and reactivity graded (1+ to 4+) at 1:80 dilution. Positive (PPA), negative (NPA) and overall percent agreement (OPA) were calculated. Pattern agreement for reactive samples was also determined.

«Results» 5 samples were excluded due to operator error. PPA was 100% (52 of 52 reactive samples, 95% CI: 93.2, 100). 46/50 samples remained non-reactive, for a NPA of 92% (95% CI: 80.8, 97.8). OPA was 96.1% (95% CI: 92.3, 99.8). Pattern agreement was 96.3% (95% CI: 87.3, 99.5), with only 2 discordant results, graded 1+.

«Conclusions» Manual preparation and reading using the TEST showed high concordance with historical Results: Future studies will assess the fully automated performance to further validate the device and platform.

AUTHOR INDEX

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doi: https: //doi.org/10.57187/s.4930
ISSN online supplement: 2504-1622

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