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Lugano (Switzerland), August 27–28, 2026

ANNUAL CONGRESS OF THE SWISS SOCIETY OF ALLERGOLOGY AND IMMUNOLOGY AND SWISS AUTOIMMUNE LIVER DISEASE MEETING

LUGANO, AUGUST 27–28, 2026

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SHORT COMMUNICATION SESSION – T CELLS AND ANTITUMOR RESPONSES

SC1

Tumor Cell–Intrinsic PDGFRβ Drives BC Progression and Immune Remodelling

H. El Ahanidi[1], M. Leblond[2], G. Zanette[2], A. Gomez Cadena[1], M. Saillard[1], K. Georgakopoulou[2], J. A. Rodríguez Calero[3], J. Pocas[4], P. Cheng[4], C. Brossier[5], K. Falamaki[6], O. Michielin[4], D. Benamran[5], P. Tsantoulis[6], P. Krebs[3], G. Verdeil[2], C. Jandus[1]

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Bladder cancer (BC) progression is driven by molecular heterogeneity and interactions in the tumor microenvironment that remain incompletely understood. To investigate the molecular drivers of BC progression we profiled BC patients' biopsies and identified a 16-genes program of progression/recurrence where PDGFRβ (Platelet-Derived Growth Factor Receptor Beta) is acting as a central node. To define its tumor-cell intrinsic role, we combined spatial proteo-transcriptomic profiling of human BC biopsies with *in vitro* functional analyses and *in vivo* therapeutic targeting using orthotopic mouse models. High PDGFRβ expression at both the transcript and protein levels correlated with increased disease aggressiveness and poor patient survival. Functionally, PDGFRβ promoted cancer cell invasion and regulated transcriptional programs associated with cell migration. Mechanistically, macrophage-derived Galectin-9 induced PDGFRβ expression through a tumor-cell intrinsic CD40-dependent axis. *In vivo*, CRISPR/Cas9 mediated PDGFRβ deletion in cancer cells reduced tumor growth and metastasis and reshaped the immune microenvironment toward an immune-hot milieu, characterized by increased infiltrations of $CD8^+$ T cells, B cells, and anti-tumoral macrophages. More importantly, pharmacological inhibition using the selective PDGFRβ inhibitor CP-673451 improved survival in orthotopic models. Our data shows that tumor cell–intrinsic PDGFRβ drives BC aggressiveness by integrating invasive transcriptional programs with immune modulation and thereby reveal a molecular target for therapy of advanced BC.

SC2

The Development of a Novel 3D Model for Studying Immune Cell Motility and Tumour Interactions in Immunotherapy Testing

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The development of chimeric antigen receptor T-cell (CAR-T) therapies has emerged as a transformative approach for the treatment of hematological malignancies and holds promise across diverse cancer types. However, progress remains constrained by key challenges, including limited infiltration into the tumour microenvironment, treatment-associated toxicities, and poor persistence of effector function driven by T-cell exhaustion resulting from persistent antigen exposure or intrinsic tonic signaling. In addition, preclinical development of novel CAR-T strategies is hindered by poor translatability between animal models and clinical outcomes. This translational gap has driven the emergence of new approach methodologies (NAMs), encompassing in vitro systems such as microfluidic platforms, organoids, and 3D culture models. In this project, we aim to develop a NAMs-based platform to visualize and characterize T-cell motility and tumour cell interaction dynamics under baseline and experimental conditions, including exposure to immunotherapeutic agents. The 3D co-culture system will enable acquisition of morphological, migratory, and interaction data via time-lapse fluorescence microscopy, with bespoke computational tools applied to quantify and classify T-cell behaviours. To validate the in vitro model, intravital microscopy will provide a physiological reference for T-cell behaviour in vivo. Collectively, this approach aims to establish a predictive platform for evaluating CAR-T cell function and supporting the development of more effective immunotherapeutic strategies.

SC3

Colorectal cancer-infiltrating bacteria promote the proliferation of CD4-CD8- Vδ2+ γδ T cells endowed with antitumor properties

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Introduction and Aim of the study: Colorectal cancer (CRC) is the second-leading cause of cancer deaths worldwide. During carcinogenesis, alteration of the gut epithelial barrier allows the translocation of gut bacteria to the tumor tissue and their interaction with immune cells. Infiltration by T cells is associated with improved survival, but their interplay with gut bacteria has not been fully investigated. We previously identified a panel of bacteria whose abundance in CRC tissues correlates with T cell infiltration. In this work, we investigated the capacity of these bacteria to induce T cell-mediated anti-tumor responses.

Design and Methods: Peripheral blood mononuclear cells from healthy donors or CRC patients were cultured with gut bacteria of interest and assessed for proliferation based on CFSE dilution. Phenotypes and functionality of proliferating T cells were assessed by FACS. CRC and adjacent normal tissue biopsies were processed to obtain single-cell suspensions. Phenotypes and signatures of tumor-infiltrating T cells were assessed by FACS and single-cell RNA-sequencing.

Results and Conclusions: Proliferating cells to bacteria mostly consisted of CD4-CD8- double negative T cells expressing Vδ2+ γδTCRs. Expanded Vδ2+ γδT cells formed immunological synapses and showed BTN3A1-independent tumor cell killing. Tumor-infiltrating Vδ2+ γδT cells are detected within CRC tissues, and their transcriptomes partially overlapped with those expanded upon bacterial stimulation from peripheral blood. Their anti-tumor potential is currently under evaluation.

SC4

DNA damage responses induced by dysfunctional mitochondria orchestrate commitment of T cell exhaustion

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T cell exhaustion is a state of T cell dysfunction, characterized by reduced proliferation capacity, cytokine production, and loss of responsiveness to immune checkpoint blockade. Growing evidence demonstrates that global epigenetic alterations are the critical events to drive T cell exhaustion under persistent antigen exposure. However, it is unclear how the epigenetic alteration is established in an irreversible manner. In murine melanoma model, we found depolarized mitochondria accumulated in tumor-infiltrating CD8+ T cells (TILs), which exhibited more severe exhausted phenotype such as reduced cytokine production and upregulation of co-inhibitory receptors, suggesting metabolic stress in tumors can drive T cell exhaustion. Further analyses revealed that the genes involved in DNA damage response (DDR) were enriched in the TILs with depolarized mitochondria. We further found that TILs accumulated dysfunctional mitochondria and acquired γ-H2AX, a marker of DNA break, expression in tumors over time. Intriguingly, DNA damage enhanced exhausted phenotype, manifesting by increased PD-1, TIM-3, and TOX while decreased IFN-γ and TNF-α expression, and the phenotype was sustained even when DNA damage was resolved. Most importantly, we found global epigenetic alterations with enhanced T cell exhaustion landscape upon DNA damage. CRISPR screen targeting DDR pathway identified a critical role of histone acetylation in DDR-driven T cell exhaustion. Together, our study reveals that mitochondrial fitness and DNA damage signaling may determine the fate of T cell toward exhaustion.

SC5

Investigating the role of the IL-4/STAT6 axis on exhausted CD8 T cell development and immunotherapy responses

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CD8+ T cell exhaustion is a major barrier to effective cancer immunotherapy. This dysfunctional state is reinforced by a fixed epigenetic program. Checkpoint inhibitors (e.g. aPD-1) efficiently reinvigorate exhausted CD8+ T cells (T_{ex}) but ultimately fails at epigenetically reprogramming these cells. Complementary strategies are therefore needed to address this limitation and improve therapy outcomes. Recent studies showed that the g_c-cytokine IL-2 partially reverses the epigenetic program of exhaustion and synergize with PD-1 blockade. Our preliminary data identifiy IL-4 as an alternative yc cytokine with enhanced capacity to expand Tex cells and reduce exhaustion features. Using the LCMV mouse model, we investigated the physiological impact of IL-4 on Tex differentiation and its interaction with PD-1-based therapy. We uncovered a predominant expression of the IL-4 receptor a-chain (IL4Ra) and constitutive STAT6 activation in progenitor exhausted T cells (Tex^{prog}), the subset most responsive to PD-1 blockade. Functional studies combining IL-4 blockade and Stat6 genetic knock-down reveal that the IL-4/Stat6 axis regulates the transition from Tex^{prog} to intermediate Tex (Tex^{int}) – an effector-like population mediating therapeutic responses – in both chronic LCMV infection and tumor models. In human and murin *in vitro* systems modelling exhaustion, we confirmed the tremendous ability of IL-4 at expanding Tex cells and reinforcing the cytotoxic program in these cells. Together, these findings highlight IL-4 as a powerful combinatorial agent to PD-1-based immunotherapies.

SC6

Divergent contribution of CDK4 and CDK6 on tailroing mitochondrial fitness and T cell function in the tumor microenvironment

K. Hajdu[1], Y. R. Yu[1], K. C. Kao[1], J. T. Low[1], S. Moller[1], Y. M. Chuang[1], M. Akrami[2], A. Zippelius[2], P. C. Ho[1]

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T cell exhaustion is a hypofunctional state characterized by impaired effector function and proliferation, ultimately limiting antitumor efficacy. We recently uncovered that tumor infiltrating lymphocytes (TILs) accumulate damaged mitochondria, which is sufficient to drive functional and epigenetic reprogramming leading to T cell exhaustion. To identify molecular targets for sustaining mitochondrial fitness in TILs, by performing an in vivo CRISPR-Cas9 screen of over 700 murine kinases. Among the guide RNA hits that enhanced mitochondrial fitness, we identified the cell-cycle regulator cyclin-dependent kinase 4 (CDK4). Notably, CDK4/6 inhibitors have been reported to promote $CD8^+$ T cell activation and memory formation, with mechanisms that remain unclear. In our screen, CDK4-deficient T cells were enriched within the population with high mitochondrial fitness, whereas CDK6-deficient cells were not, suggesting a CDK4-specific role. Using both in vitro chronic stimulation of human T cells and murine tumor models, we show that T cell-specific CDK4 knockout (KO) preserves mitochondrial integrity and effector function in the tumor microenvironment, resulting in improved tumor control. CDK4 KO leads to upregulation of PGC1a and transcriptional changes indicative of increased mitochondrial metabolism. In contrast, although CDK6 depletion enhanced cytokine production, it did not affect mitochondrial fitness or tumor progression. Collectively, these findings uncover a previously unrecognized role for CDK4 and highlight its potential as a target to enhance T cell–based therapies.

SC7

Understanding the mechanisms underlying the protumoral effects of PD-1 in T cells

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T cells able to infiltrate the tumor can reach a state of "exhaustion", characterized by reduced functionality and the expression of inhibitory receptors, such as PD-1. Blocking antibodies against this receptor are currently used in clinics, but the signalling and the signature downstream of PD-1 remains an open question. To study the tumor response and to identify potential targets involved in PD-1 signalling cascade, we generated mice lacking PD-1 in the T cells. These mice showed a slower tumor growth and an increased infiltration of $CD8^+$ T cells, in particular of T exhausted cells. ScRNA-sequencing on immune infiltrates identified pathways upregulated in absence of PD-1, allowing us to select candidates to be tested by genetic approches for their relation to the downstream mechanism of PD-1.

Our results will help gain insights into the role of PD-1 in shaping the anticancer $CD8^+$ T cell responses and pinpoint new targets for therapies.

SC8

Kupffer cell-mediated intrahepatic T cell priming diversifies T cell differentiation and anti-tumor immunity in hepatocellular carcinomas

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Kupffer cells (KCs) are liver-resident macrophages that maintain hepatic homeostasis, but their contribution in anti-tumor immunity against hepatocellular carcinoma (HCC) remains unclear. Here, we uncover that KCs are bona fide antigen-presenting cells (APCs) capable of acquiring tumor antigens and priming CD8 T cells. Compared with dendritic cells, KC-mediated priming drives a distinct trajectory coupling polyfunctional effector activity with memory-like features. Integrated single-cell transcriptomics and interactome analysis reveals a KC-specialized CD169-CD43 co-stimulatory axis that isnecessary and sufficient for this program, which monocyte-derived KCs (MoKCs) progressively acquire. Depletion studies further demonstrate that combined loss of KCs and MoKCs diminishes tumor-reactive CD8 T cells, thereby accelerates HCC progression. In human HCC, co-expression of CD169 and CD43 correlates with a KC-primed CD8 T cell signature and associates with improved survival. These findings redefine intrahepatic priming and uncover the CD169-CD43 signaling as a potential target for therapeutic engineering of durable antitumor CD8 T cells.

SHORT COMMUNICATION SESSION – INNATE IMMUNITY, INFLAMMATION, AND MORE

SC9

CD39 defines a cytotoxic tumor-associated NK cell state responsive to NKG2A blockade in lung cancer

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Despite growing interest in Natural killer (NK) cell-targeting immunotherapies for cancer treatment, the differentiation and functional states of tumor-infiltrating NK cells remain poorly understood. Using matched single-nucleus RNA and ATAC sequencing of non-small cell lung cancer (NSCLC) specimens, we resolved the transcriptional and epigenetic landscape of intratumoral NK cells. We identified two tumor-associated NK (taNK) cell subsets marked by *ITGAE* (CD103) and *ITGA1* (CD49a) that display features of tissue residency and dysfunction while preserving cytotoxic function. Trajectory and regulon analyses revealed an inflammation-driven transition from early *GZMK*$^+$ NKs toward an *ENTPD1*$^+$ (CD39$^+$) effector state characterized by interferon-stimulated gene (ISG) programs. Functional profiling established CD39$^+$ taNK as the dominant cytotoxic NK cell population with superior killing capacity that is further potentiated by NKG2A blockade. This study offers mechanistic insights into NK cell differentiation in NSCLC and establishes CD39$^+$ taNK cells as a targetable effector population for immunotherapy.

SC10

Gut microbiota shape humoral responses to mRNA vaccines through metabolic remodeling

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Introduction and aim of the study: mRNA technology has been pivotal for anti-SARS-CoV-2 vaccine development and is being explored for other infectious diseases. However, mRNA vaccines may induce variable and short-lived antibody responses. Since gut microbiota influences host immunity, we investigated its role in responsiveness to the BNT162b2 vaccine.

Design and methods: Gut microbiota impact on vaccine responsiveness was evaluated in murine models and in COVID-19-naïve healthy donors vaccinated with BNT162b2 (n = 121). Associations between bacterial taxa and antibody titers were analyzed. To assess causality, fecal microbiota transplantation (FMT) from good- and bed-responder donors was performed in naïve mice before vaccination. Mechanistic studies included metabolic pathway analysis and histone H3 acetylation assessment in germinal center B cells.

Results: Specific bacterial taxa were associated with enhanced or impaired antibody responses in mice and humans. In vaccinated donors, antibody titers correlated with defined microbial populations. Mice receiving FMT from good responders developed stronger humoral responses than mice receiving microbiota from bad responders. Enhanced responsiveness was associated with activation of specific metabolic pathways and increased histone H3 acetylation in germinal center B cells.

Conclusions: Gut microbiota composition influences responsiveness to BNT162b2 vaccination through metabolic and epigenetic modulation of B-cell function, identifying microbiota-derived signals as potential targets to improve mRNA vaccine efficacy.

SC11

Novel bone materials selectively modulate the human immune response to favor remodeling over acute inflammation

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Successful bone regeneration depends on an immune environment that balances inflammation with repair, yet conventional bone substitutes are often evaluated mainly for osteoconductivity rather than immunomodulation. We investigated the immune effects of a fibrin-based scaffold combined with calcined bovine bone particles. Human peripheral blood mononuclear cells were exposed to fibrin sealant (EVICEL), calcined bone particles, and control particles for up to 48 hours. The inflammatory secretome was analyzed by targeted proteomics using Olink inflammation and bone remodeling panels, and cellular phenotypic shifts were assessed by single-cell mass cytometry (CyTOF) at 24 and 48 hours using a 30-marker panel. Proteomic analysis revealed a regenerative shift in EVICEL and bone combinations, marked by a high OPG/TRANCE ratio that may limit bone resorption, increased VEGFA and TGF-β1, and reduced MMP-1 and MMP-10 compared with inflammatory controls. CyTOF profiling showed reduced T-cell activation, reflected by lower CD25 and CXCR3, while survival markers CD127 and CD28 were preserved. In parallel, CD14+CD16+ monocytes and CD11c+ dendritic cells were significantly sustained, coinciding with increased tissue-repair signatures including CCR4 and CXCR5 and expansion of γδ T cells. These findings show that fibrin-based matrices differentially regulate immunity to favor regeneration by suppressing nonspecific T-cell inflammation, preserving myeloid precursors, and promoting an osteogenic proteomic state characterized by high OPG/TRANCE ratios.

SC12

Large Immune Complexes Suppress Influenza Vaccine Responses via the Inhibitory Fc-Gamma Receptor IIb on Dendritic Cells

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Immune complexes (ICs) are known to enhance immune responses. Yet pre-existing antibodies can suppress rather than boost vaccine immunity, a phenomenon known as antibody-mediated immune suppression. However, the mechanism responsible for this suppression is not fully understood. In this study we passively immunize mice with the anti-hemagglutinin (HA) monoclonal antibody H36-7, 2h before vaccination with either UV-inactivated whole influenza virus or recombinant HA alone, generating large or small ICs, respectively. Responses were assessed by ELISA, ELISPOT, flow cytometry, and confocal microscopy. Pre-immunization suppressed influenza-specific antibody responses, T cell priming, and local inflammation only with large ICs but not with HA antigen alone, despite equivalent antigen quantities reaching the draining lymph node. In addition, we observed that the inhibition of the immune response in the large ICs was selectively mediated by FcγRIIb expressed on DCs, diverting antigen toward degradation and preventing T cell activation. The suppression was abrogated in FcγRIIb-knockout mice and upon Fc deglycosylation. In conclusion, IC size acts as a molecular switch controlling immune fate through FcγRIIb. This mechanism likely extends beyond influenza — in any context where ICs form, such as autoimmune diseases or chronic infections, this axis may shape whether immunity is amplified or silenced, offering a targetable pathway to tune immune responses.

SC13

Maltol and ethyl maltol disrupt epithelial barrier integrity and induce oxidative stress in human nasal organoids

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Background: Flavor additives are widely used in foods and inhalable products such as electronic cigarettes and fragrances. Maltol and ethyl maltol can reach concentrations up to 1–2%, potentially exposing the nasal epithelium to high local doses. However, their effects on epithelial barrier function remain unclear.

Methods: Primary human nasal epithelial cells were used to generate 3D nasal organoids. Cell viability, epithelial integrity, permeability, and reactive oxygen species (ROS) were assessed using MTT, FITC-dextran, and oxidative stress assays. Secreted proteins were analyzed by targeted proximity extension assay, and organoids underwent untargeted mass spectrometry.

Results: Maltol and ethyl maltol reduced cell viability at 0.03125% and 0.001%. Both impaired epithelial integrity and increased permeability at sub-use levels. They induced dose-dependent ROS, with ethyl maltol triggering rapid ROS increase within 5 min at 0.5%. Targeted proteomics showed immune modulation: maltol increased CCL20 while suppressing IL-2 and FGF-19; ethyl maltol caused broader suppression, including IL-2 and IL-10RB. Untargeted proteomics revealed that high-dose maltol increased extracellular matrix proteins (SERPINE1, PLOD2) and reduced adhesion proteins (ITGA3, ITGAV, CD109).

Conclusions: Maltol and ethyl maltol disrupt epithelial barrier integrity and induce cellular stress at sub-cytotoxic concentrations. Proteomic data indicate impaired epithelial immune and stress signaling, raising concerns about nasal epithelial health.

SC14

Clusters of GSDMD and GSDME mediate neutrophil pyroptosis in Cryopyrin Associated Periodic Syndrome (CAPS)

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The NLR family Pyrin domain containing 3 (NLRP3) inflammasome is a cytosolic multi-protein immune sensor tuned to avoid assembly at steady state. In this study, we focused on neutrophils in Cryopyrin Associated Periodic Syndrome (CAPS) patients revealing heterogeneous subtypes using CyTOF analysis of patient blood samples. In Nlrp3 mutant mice, activating *Nlrp3* mutations identified essential and non-redundant

functions for gasdermin (GSDM) D and GSDME. Combined deletion is required to eliminate IL-1b secretion, prevent pyroptosis, and mitigate autoinflammation, as revealed using western-blot and ELISA. The absence of both GSDMD and GSDME reduces Caspase-1 cleavage and pro-IL-1b processing, while knockout of GSDMD alone increases GSDME cleavage and caspase-8 cleavage. Clusters of GSDMD and GSDME pores can be visualized at the plasma membrane of activated CAPS neutrophils using a combination of atomic-forece microscopy and high-resolution confocal microscopy. These findings suggest that the coordinated actions of membrane-associated GSDMD and GSDME reinforce cytosolic NLRP3 inflammasome activation to control IL-1 secretion, lytic cell death, and autoinflammation.

SC15

Intratumoral microbiota and host genotype cooperatively shape neutrophil cytotoxic functions in colorectal cancer

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Introduction and aim of the study: The role of tumor-associated neutrophils (TANs) in colorectal cancer (CRC) remains controversial. We investigated whether intratumoral microbiota modulates TAN recruitment and antitumor activity.

Design and methods: Bacteria-induced neutrophil activation was assessed by flow cytometry using surface activation markers. TAN phenotyping was performed on freshly resected CRC and matched non-tumor tissues using large-scale flow cytometry. Clinical correlations between bacterial load, TAN density, Siglec-14 expression, and patient survival were assessed in human CRC samples.

Results: Fusobacterium nucleatum (Fn) promotes the production of neutrophil-recruiting chemokines by tumor cells and enhances neutrophil migration more efficiently than Bacteroides fragilis. Importantly, Fn, triggers neutrophils to release cytotoxic proteins showing tumoricidal activity in vitro and in xenograft models. Mechanistically, these effects are elicited upon Fn binding to sialic-acid-binding immunoglobulin-like lectin (Siglec)-14 expressed by neutrophils but are impaired upon Siglec-14 blockade or loss-of-function polymorphisms. Supporting these findings, in human CRCs, elevated Fn loads and high TAN densities correlate with improved prognosis, whereas lack of Siglec-14 expression is associated with reduced patient survival.

Conclusions: Our findings identify microbiota composition and host genetic background as critical determinants of neutrophil functional profiles, offering insights into neutrophil-targeted therapeutic strategies in CRC.

SC16

Lymph node spatial organization of B cell lymphoma modulates NK cell immunosurveillance through IL-1α.

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DLBCL is a clinically and biologically heterogeneous disease in which the TME shapes tumor progression and response to therapy. The LN is a primary site of tumor initiation and dissemination, yet how the spatial localization of lymphoma cells within distinct LN microanatomical compartments influences the local TME and antitumor immune response remains unclear. In this study, we describe how the intranodal compartmentalization of DLBCL differentially modulates the antitumor immune response. Using syngeneic Eμ-myc B-cell lymphoma mouse models, we characterized two distinct TME in the cortical and medullary regions of the LN, formed following lymphatic or hematogenous dissemination of lymphoma cells, respectively. We demonstrated through cytokine screening and transcriptomics analysis that differential TME formation can determine the inflammatory environment. This influences immune cell responses and the tumor ability to spread in the lymphatic system. Mechanistically, we found that IL-1α secreted specifically by LN macrophages within the cortical TME suppresses NK cell activity. Intravital imaging revealed that cortical NK cells exhibited directed motility, whereas medullary NK cells displayed scanning and engager behaviors. Importantly, *in vivo* cytokine neutralization restores NK cell function, limiting lymphoma progression. In summary, our study identifies LN microanatomical compartmentalization as a key determinant of immune evasion in DLBCL and position IL-1α as both a prognostic biomarker and a tractable therapeutic target for restoring NK cell-mediated immunosurveillance.

SHORT COMMUNICATION SESSION – ALLERGOLOGY AND CLINICAL IMMUNOLOGY I

SC17

Oral Sebetralstat for On-Demand Treatment of Hereditary Angioedema Attacks: Results from the Phase 3 KONFIDENT Trial

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Introduction: Sebetralstat is the first oral therapy approved for on-demand treatment of hereditary angioedema (HAE) attacks. In alignment with HAE treatment guidelines, participants in the KONFIDENT trial were instructed to treat attacks as early as possible and to consider treating all attacks, regardless of location or severity.

Methods: In KONFIDENT, participants ≥12 years old treated ≤3 attacks with 1 or 2 doses of sebetralstat 300 mg, sebetralstat 600 mg, or placebo. Primary endpoint: time to beginning of symptom relief (PGI-C rating of at least "A Little Better" for 2 time points in a row) within 12h. Key secondary endpoints: time to reduction in severity (decrease in PGI-S for 2 time points in a row) within 12h and time to complete attack resolution (PGI-S rating of "None") within 24h.

Results: 110 participants treated 264 attacks (87 with sebetralstat 300 mg, 93 with sebetralstat 600 mg, and 84 with placebo). Median time to treatment was 41 min (IQR, 6-140). Median time to beginning of symptom relief was significantly faster with sebetralstat 300 mg (1.61h [IQR, 0.78-7.04]; P <0.001) and 600 mg (1.79 [IQR, 1.02-3.79]; P = 0.001) compared with placebo (6.72h [IQR, 1.34->12]), as was reduction in severity (P = 0.0036 and P = 0.0032, respectively) and complete attack resolution (P = 0.0022 and P <0.0001, respectively). Sebetralstat had a safety profile comparable with placebo.

Conclusions: Results support use of sebetralstat as a safe and effective on-demand treatment, offering a preferred route of administration, facilitating early treatment, and providing rapid symptom relief.

SC18

Efficacy and safety of intralymphatic immunotherapy with grass allergoid and microcrystalline tyrosine: a double-blind randomised placebo-controlled trial

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Background: Intralymphatic immunotherapy (ILIT) has been investigated for two decades in small clinical trials, mostly using native allergens adsorbed to aluminium hydroxide (alum). This randomised, double-blind, placebo-controlled study evaluated the safety and efficacy of ILIT with a grass pollen allergoid formulated with microcrystalline tyrosine (MCT).

Methods: Sixty adults with grass pollen–induced allergic rhinoconjunctivitis (ARC) were randomised to receive ILIT with grass allergoid (60 ng Phl p 5; n = 31) or placebo (n = 29). Three ultrasound-guided injections (100 µl) were administered into inguinal lymph nodes at 4-week intervals in early 2022. The primary endpoint was the combined symptom and medication score (cSMS), recorded daily during the 2022 and 2023 pollen seasons. Secondary endpoints included safety, RQLQ, serology, spirometry, FeNO, and skin-prick testing (SPT). An open-label extension was conducted in 2024.

Results: ILIT was well tolerated, with no severe adverse events. Mild local reactions (wheal, erythema, swelling) occurred after 53.8% of active injections; three moderate reactions (3.2%) were reported. In the placebo group, one mild reaction occurred. No allergen-specific systemic reactions were observed. Compared with placebo, ILIT reduced cSMS by 33% in 2022 and 50% in 2023, with sustained effects. RQLQ improved by 22% and 13%, respectively.

Conclusion: ILIT with a grass pollen allergoid formulated with MCT was safe and associated with clinically relevant reductions in symptoms and medication use in grass pollen–induced ARC.

SC19

Safety and immunogenicity of heterologous RSV revaccination with mRNA-1345 after primary vaccination with protein-based vaccine

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Background: Protection after a single dose of an RSV vaccine is not lifelong, and revaccination may be needed. Homologous revaccination with mRNA-1345 at 12 or 24 months induces non-inferior immune responses compared with primary vaccination, however heterologous schedules have not been previously studied. We report immunogenicity and interim safety of mRNA-1345 revaccination ≥12 months after primary vaccination with a licensed RSV protein subunit vaccine.

Methods: Adults aged ≥60 years who had received a licensed RSV protein subunit vaccine ≥12 months before enrollment received mRNA-1345. Various safety assessments were included. Immunogenicity was assessed using neutralizing antibody (nAb) against RSV-A and RSV-B at D1 and D29 post-revaccination.

Results: 507 participants were enrolled; median interval since primary vaccination was 23 months. Injection-site pain was the most common local reaction and fatigue, myalgia, and headache the most frequent systemic reactions. nAb titres increased substantially from baseline to Day 29 for both RSV-A and RSV-B. In a post-hoc comparison of D29 post-heterologous revaccination titers with D29 post-primary vaccination (mRNA-1345), the geometric mean ratios for RSV-A and RSV-B were 0.952 (95% CI, 0.847-1.070) and 1.087 (95% CI, 0.964-1.226). GMFR and seroresponse rate were consistent with those observed following homologous revaccination with mRNA-1345 in a separate study.

Conclusion: These findings support revaccination with mRNA-1345 ≥12 months after primary vaccination with an RSV protein subunit vaccine.

Encore abstract (ESCMID 2026)

SC20

Taste Aversion and Adverse Events Equally Drive Oral Immunotherapy Discontinuation: A Real-World Multi-Allergen Analysis in Pediatric Patients

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Introduction and Aim of the Study: Oral immunotherapy (OIT) is a disease-modifying therapy for IgE-mediated food allergy, but real-world success is limited by treatment burden and early discontinuation. This study assessed rates, reasons and timing of OIT discontinuation in a real-world pediatric multi-allergen cohort.

Design and Methods: In this single-center observational study, pediatric patients starting OIT between July 2022 and March 2026 were enrolled. Reasons for discontinuation were recorded at cessation and by chart review, and classified as adverse events (AE) or non-AE factors (taste aversion, logistical barriers, anxiety/distress). Baseline characteristics were compared, and hierarchical clustering explored phenotypes in discontinuation cases.

Results: Among 407 OIT courses in 306 patients, 61 (15%) were discontinued. Rates were highest for milk and wheat and lowest for cashew and sesame. Taste aversion and AE were the leading reasons (41% each), followed by logistics (11%) and anxiety/distress (7%). AE-related discontinuation occurred earlier, whereas taste aversion predominated during maintenance and occurred across all age groups. Higher sIgE were associated with AE-related discontinuation. Cluster analysis identified three phenotypes; in a high-risk cluster, taste aversion was the main cause.

Conclusion: In this real-world multi-allergen cohort, OIT discontinuation was driven equally by AE and behavioral barriers. Taste aversion was a major determinant of adherence. Patient-centered strategies addressing immunological and practical barriers may improve OIT success.

SC21

A humanised plant lectin-antibody fusion as a broad-spectrum therapeutic against emerging respiratory viruses

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Respiratory viruses including influenza A and SARS-CoV-2 cause recurrent pandemics driven by antigenic evolution and therapeutic resistance. We exploited conserved high-mannose glycans on viral surface glycoproteins as a variant-independent target, evaluating a plant-derived lectin and its humanised lectin-antibody fusion (lectibody) combining glycan-targeting specificity with IgG1 Fc-mediated effector properties. Plant lectin binding was characterised by ELISA, enzymatic deglycosylation, and SPR. Antiviral efficacy was assessed in pseudovirus and live virus neutralisation assays. The lectibody was produced in CRISPR-engineered N. benthamiana and characterised for Fc-mediated effector functions including ADCC and complement activation. Efficacy was validated in murine influenza A and SARS-CoV-2 infection models. The plant lectin demonstrated high-affinity binding to conserved high-mannose glycans across >15 SARS-CoV-2 variants and 3 influenza A subtypes. Neutralisation potency was retained where strain-specific monoclonal antibodies failed. Intranasal administration reduced lung viral titres and conferred protection in vivo. The lectibody format extended serum half-life, preserved broad-spectrum neutralisation, and enhanced viral clearance through Fc-mediated ADCC. Plant lectin-Fc lectibodies exhibit potent, broad-spectrum antiviral activity by targeting conserved glycan structures essential for viral fitness. This platform represents a universal therapeutic strategy against current and emerging respiratory viruses.

SC22

Heat-treated egg allergens show lower basophil activation: A path toward safer oral immunotherapy

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Background: Oral immunotherapy (OIT) is a promising treatment for IgE-mediated food allergy, but safety concerns limit its use. Heat-denaturation of food allergens may reduce allergic reactions by lowering IgE binding. We examined how heat-induced structural changes in egg allergens affected basophil activation in egg-allergic patients.

Methods: Gal d 1 and 2 were heat-treated and analyzed for structural changes using SDS-PAGE, ELISA, NanoDSF, and circular dichroism. Peripheral blood samples were obtained from 42 patients with egg allergy. Sensitization status was determined, and basophils were isolated and incubated with native or heat-denatured egg allergen preparations. Basophil activation was assessed by leukotriene assay.

Results: Heat-denaturation caused time- and temperature-dependent structural changes in Gal d 1 and 2, resulting in reduced IgE binding. Heat-denatured allergens induced weaker basophil degranulation than native allergens, but the effect varied depending on individual IgE sensitization profiles. Among patients reacting to heat-denatured allergens, egg-white IgE levels tended to be higher, although higher doses were needed to trigger leukotriene release.

Conclusion: Heat-denaturation of egg allergens reduces IgE binding and basophil activation, although residual reactivity persists in patients with higher sensitization. Higher allergen doses were needed to trigger basophil degranulation than native allergens, indicating reduced allergenic potency. These findings support the potential of heat-denatured egg allergens as safer starting materials for OIT.

SC23

Subclinical inflammatory endotypes within healthy individuals

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To investigate the systemic signatures of altered host-environment interactions under healthy conditions, we combined phage immunoprecipitation sequencing (PhIP-seq) profiling of serum antibody repertoires targeting 344'000 epitopes with in-depth targeted and untargeted proteomics (total 1750 proteins) in a cohort of 95 healthy adults. Our integrated analysis identified three distinct and stable inflammatory states: low, intermediate and high. When we compared healthy individuals with

low-inflammatory and high inflammatory, four important protein clusters identified, including inflammation & chemotaxis, antiviral innate immunity, dendritic cell maturation and acute phase response. The high-inflammation state was characterized by an elevation of complement-pathway components (C3, C5, C9) and acute-phase reactants, was validated by higher levels of high-sensitivity C-reactive protein and was strongly enriched for a 35-protein signature associated with all-cause mortality. PhIP-Seq analysis revealed that the low- and high-inflammatory states were characterized by distinct IgG antibody repertoires, with differential reactivity against epitopes derived from *Bacteroides*, *Clostridiales*, *Staphylococcus*, *Streptococcus* and *Lactobacillus*. Interestingly, these responses were identified in individuals with low circulatory inflammation, suggesting high inflammation group has low anti commensal IgG immunity. These findings suggest that the "healthy baseline" is not a single uniform state but rather a range of different immune-inflammatory profiles shaped by varying mucosal exposures.

SC24

Predicting Outcomes of Peanut Oral Food Challenge: A Paediatric Cohort Analysis

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Introduction and Aim: Peanut is a common food allergen. Oral food challenges (OFC) remain the gold standard for diagnosis and threshold determination, yet are resource-intensive and carry inherent risks. We analysed our peanut OFC cohort to compare allergic and tolerant patients and identify predictors of OFC outcomes.

Design and Methods: We prospectively evaluated OFCs (Jul 2022 – Feb 2026) in patients naïve to oral immunotherapy, with informed consent and conclusive outcomes. For patients with multiple eligible OFCs, only the first valid was analysed.

Results: We included 214 of 276 OFCs. Median age was 6.4 years (range 8 months – 19 years) and 43% were female. Peanut allergy was confirmed in 125 patients (median reactive dose: 300mg), while 89 were tolerant. Most allergic patients presented with oFASS-5 grade 2 (n = 50) or 3 (n = 47); 24 experienced grade 4 reactions (no grade 5). Adrenaline was required in 19 patients. In 50% of allergic patients, peanut was their sole food allergen. Allergic patients had higher median levels of peanut-specific IgE and Ara h 2. At a 0.35 kU/l cut-off, peanut-specific IgE lacked specificity, whereas Ara h 2 showed high sensitivity (88%) and specificity (85%).

Conclusion: Ara h 2 sensitization was an accurate predictor of peanut allergy in our cohort and may support targeted allocation of clinical resources. However, OFC remains essential for threshold determination and diagnostic clarification, especially in patients with equivocal sensitization profiles.

SHORT COMMUNICATION SESSION – AUTOIMMUNITY, INFLAMMATORY DISEASES, AND MORE

SC25

Deep-learning guided PET/CT Monitoring of Treatment Response in Sarcoidosis

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Introduction: The heterogeneous manifestation and unclear disease course of sarcoidosis present a continuous challenge to personalized care decisions. 18F-FDG PET/CT is the gold standard for activity assessment but is costly, scarce, and operator-dependent. This project aims at integrating PET/CT imaging with deep learning-based segmentation to derive quantitative measures of inflammatory burden, paving the way to objective and scalable disease monitoring.

Methods: We present a fully automated deep-learning pipeline for multi-organ PET/CT quantification, applied to 314 patients with 1024 longitudinal scans linked to clinical and laboratory data. Based on contrast-enhanced CT, the lungs, myocardium, spleen, and liver are segmented; co-registered PET images provide organ-level SUVmax values and metabolic activity.

Results: Pipeline-derived metrics showed strong agreement with clinician assessments of cardiac involvement ($r = 0.957$; $p < 0.001$). Organ-resolved analyses revealed significant correlations between PET metrics and inflammatory biomarkers, particularly in pulmonary/hilar involvement (e.g., sIL-2R, $r = 0.33$, FDR<0.05). TNFα inhibitor treatment in active cardiac sarcoidosis showed a rapid decline of SUVmax (Cohen's $d = 0.93$, FDR<0.001) within the first 8 months.

Conclusions: Our automated, organ-resolved PET/CT pipeline enables objective, scalable, and holistic assessment of sarcoidosis activity and organ involvement, facilitating precise treatment response monitoring and prognostication.

SC26

Role of A2 beta casein in milk-induced eosinophilic oesophagitis: novel in-vivo and in-vitro findings

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Background: Eosinophilic esophagitis is a food allergen driven chronic T2 inflammatory disorder of the esophagus with milk being the most frequently identified food culprit. A dominant point mutation in beta casein occurred in ancestors of modern type cattle with a change from A2 milk (traditional non-mutated beta casein) to A1/A2 milk (at least one point mutation). Nothing is known about the allergenicity of standard vs A2 milk and its implications in EoE pathogenesis. Methods: This was an analysis of Swiss EoE cohort patients with proven milk-induced EoE

who underwent a 3-month challenge with commercially available A2 milk. EoE-activity was assessed before vs after. Local responses to standard and A2 milk were analyzed using ex vivo allergen-stimulation models. Results: Eleven patients with proven milk-induced EoE underwent A2 milk exposure. Clinical and histological remission was maintained in 7 patients (63.6%), while relapse occurred in 4 patients (36.4%). At 12 weeks of A2 exposure, median peak eosinophil counts did not increase. Milk-induced IL-5 secretion was significantly attenuated by A2 milk in an ex vivo model using freshly collected esophageal biopsies, but not in peripheral blood mononuclear cells. Conclusion: Our study is the first to identify not only a food category but also a specific food protein as a potential allergen involved in the pathogenesis of EoE. Importantly, the finding that most patients with milk-induced EoE tolerate traditional A2 beta-casein milk further emphasizes beta-casein as a possible key driver of disease pathogenesis.

SC27

The SLC15A4-TASL complex is essential for lupus development in mice

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Nucleic acid sensing by endolysosomal Toll-like receptors (TLRs) is critically involved in systemic lupus erythematosus (SLE) and related autoimmune diseases. The SLE-associated SLC15A4-TASL complex mediates pro-inflammatory IRF5 activation downstream of TLR7/9, and genetic ablation of *Tasl* and its paralogue *Tasl2* (*Tasl*^{DKO}) impairs antiviral responses while being protective in a chemically-induced SLE models. Considering SLE heterogeneity, whether this complex is broadly required for disease pathogenesis remains unclear. Here we show that the SLC15A4-TASL signalling axis is critical for disease development in three complementary genetic SLE models reflecting different aetiologies. *Tasl*^{KO} ameliorated and *Tasl*^{DKO} fully prevented autoimmune manifestations driven by *Fas*^{lpr} loss-of-function and by patient-derived *Tlr7*^{kik} gain-of-function mutation, including splenomegaly, immune activation and autoantibody formation. Moreover, *Tasl*^{DKO} splenocyte transfer into lymphopenic *Dnase1l3*-deficient mice demonstrated that protection extends to DNA-driven autoimmunity, strongly supporting a B cell-intrinsic role. Notably, SLC15A4-TASL complex deficiency blunted the generation of pathogenic age-associated B (ABC) cells in all three autoimmune models as well as in aged animals. Collectively, these data demonstrate the central role of the SLC15A4-TASL complex in SLE, supporting its potential as therapeutic target.

SC28

The transcription factor RFX7 in the development of autoreactive B cells and autoimmunity

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Age-associated B cells (ABCs) accumulate with aging, infections, and autoimmunity, displaying high TLR7 responsiveness and an IFN signature. The mechanisms regulating their expansion remain poorly understood. The transcription factor RFX7 is an emerging regulator of metabolism and cancer; our recent work shows that its deletion in B cells increases Myc activity, enhances germinal center responses, and accelerates lymphomagenesis, establishing RFX7 as a 'brake' for B cells. Notably, Rfx7$^{-/-}$ B cells show increased blasting upon TLR7 stimulation and an enhanced IFN signature – features reminiscent of ABCs – prompting us to investigate the role of RFX7 in ABCs and autoimmunity. Using *Cd19Cre Rfx7*$^{fl/fl}$ (B cell-specific Rfx7 deletion) and *Cγ1Cre Rfx7*$^{fl/fl}$ mice (Rfx7 deletion in IgG1-switched cells), we find that splenic ABCs are increased in both models, indicating RFX7 suppresses ABC expansion upon activation. RFX7 also shapes the ABC phenotype, as shown by increased CD73 expression, a memory marker. Furthermore, autoantibodies against SLE/SSc-specific antigens trend upwards in *Cγ1Cre Rfx7*$^{fl/fl}$ mice, highlighting the autoimmune features of these ABCs. scRNA sequencing reveals several pathways through which RFX7 might modulate ABCs, pointing to new mechanisms underlying ABC biology. Together, these findings establish the relevance of RFX7 in autoimmune B cell responses, and open new avenues to investigate its mechanistic role in ABC development and autoimmune disease pathogenesis.

SC29

mRNA alternative splicing in intestinal epithelial cells directs intestinal homeostasis

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The gut requires a delicate balance between the host epithelium, immune system and microbiota, perturbations of which result in the development of inflammatory bowel disease (IBD). Alternative splicing (AS) in the intestinal epithelium is dysregulated under diseased conditions, although it is not yet understood whether this is a cause or consequence of the disease. To study this phenomenon, we deleted ESRP1, a key regulator of alternative splicing in epithelium using cre-lox system (ESRP1$^{\Delta IEC}$) in mice. Using long-read mRNA sequencing, we showed disruption of ESRP1 results in multiple dysregulated mRNA isoforms in enterocytes, and numerous dysregulated genes, with many more being altered in colonized mice compared to germ-free mice. Additionally, Lipid metabolism pathways were significantly enriched. We subsequently performed single-cell RNA sequencing and flow cytometry analysis of intestinal intraepithelial leukocytes and found a unique subset of TCRαβ CD8αα cells to be upregulated and activated in colonized ESRP1$^{\Delta IEC}$ mice. Next, we checked ESRP1$^{\Delta IEC}$ mice for differences in microbiota. In SOPF and gnotobiotic mice, a specific bacterium, *L. reuteri* was found to be underabundant in ESRP1$^{\Delta IEC}$ mice. Lastly, phenotypic analyses under stress conditions revealed that ESRP1$^{\Delta IEC}$ mouse microbiotas recovered differently after antibiotics and these mice were more susceptible to developing colitis. Overall, our results indicate disruption of epithelial AS drives the development of a pre-IBD phenotype. Investigations are ongoing into metabolite contents of the ESRP1$^{\Delta IEC}$ mouse gut.

SC30

Tapinarof restrains IL-17-producing human memory T cells through metabolic reprogramming

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Psoriasis often returns in the same areas after treatment stops, suggesting that long-lived immune cells in the skin preserve a local memory of disease. Here we show that tapinarof, a topical aryl hydrocarbon receptor agonist notable for inducing prolonged remissions after treatment cessation, directly restrains

pathogenic human memory T cell responses through metabolic reprogramming. In skin from patients with psoriasis, tapinarof preferentially reduced interleukin-17 production by skin-resident $CD4^+$ T cells. In human memory T cells, it induced a shared transcriptional program that suppressed fatty acid oxidation and cholesterol biosynthesis, with the strongest functional effects in T_H17 cells. These cells were particularly sensitive because they relied more strongly on fatty acid-supported mitochondrial metabolism and on sterol-dependent support of the T_H17 program. In human skin explants, topical tapinarof recapitulated these immune effects while also enhancing epidermal differentiation and attenuating psoriasiform inflammation. Together, our findings identify a metabolic mechanism by which aryl hydrocarbon receptor activation constrains pathogenic T cell responses in psoriasis and may contribute to durable disease control.

SC31

Clinical performance of a novel, fully automated multiplexed immunoassay for detection of anti-PR3, anti-MPO, and anti-GBM in AAV and anti-GBM disease

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Background: GBM, MPO and PR3 antibodies are important for diagnosing anti-GBM disease and ANCA-associated vasculitides (AAV): MPA, GPA and EGPA. We assessed the clinical performance of a novel, fully automated multiplex microarray immunoassay (MosaiQ AiPlex® VAS, AliveDx) for detection of IgG antibodies to MPO, PR3, and GBM, as an aid in identifying AAV and anti-GBM disease.

Methods: De-identified sera from patients with MPA (n = 98), GPA (n = 85), EGPA (n = 29), or anti-GBM disease (n = 63) were tested with the investigational device, along with disease controls samples (n = 317). Clinical sensitivity and specificity were determined for each antibody and disease category, considering equivocal results as positive or negative.

Results: For anti-MPO in MPA, sensitivity was 91.8% (95% CI 84.5–96.4) and 89.8% (82.0–95.0), with specificity of 94.6% (91.6–96.8) and 96.2% (93.5–98.0), respectively. For anti-PR3 in GPA, sensitivity was 89.4% (80.8–95.0) and 88.2% (79.4–94.2), with specificity of 96.5% (93.9–98.3) under both interpretations. In EGPA, sensitivity was 48.3% for MPO and 3.4% for PR3 with specificity of 94.6-96.5%. In anti-GBM disease, anti-GBM showed sensitivity of 98.4% (91.5–100) and specificity of 99.1% (97.3–99.8) or 99.7% (98.3–100), respectively.

Conclusion: The assay demonstrated high diagnostic accuracy for MPA, GPA and anti-GBM disease. Although anti-MPO and anti-PR3 sensitivity was limited, as expected in EGPA, specificity was high. These findings support the assay's clinical utility as a fully automated solution for streamlined serologic evaluation of AAV and anti-GBM disease.

SC32

Developmental trajectories and molecular features shaping broad and synergistic actions of human autoantibodies targeting IFNα

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Neutralizing autoantibodies (autoAbs) against type I interferons (IFNs) are a major risk factor for severe viral infections, yet they associate with improved outcomes in certain IFNα-driven autoimmune diseases. Despite their clinical relevance, the maturation pathways and molecular determinants governing their functional properties remain poorly defined. Here, we isolated and cloned monoclonal antibodies (mAbs) from the memory B-cell repertoire of a donor with high-titer anti-IFNα autoAbs. Analysis across all human IFNα subtypes revealed that affinity maturation increases both breadth and potency while steering reactivity toward specific epitopes, supporting the parallel emergence of subtype-restricted and broadly reactive antibodies. To define the basis of these properties, we determined the structure of a human mAb-IFNα2 complex, uncovering the molecular determinants of natural breadth and potent neutralization. Strikingly, antibodies targeting non-competing epitopes acted cooperatively to inhibit IFNα signaling, enhance H5N1 influenza A virus replication, and trigger Fc-mediated effector functions that may eliminate IFNα-responsive cells. Together, these findings define the molecular and structural features shaping broadly reactive anti-IFNα repertoires and uncover synergistic mechanisms that amplify their pathogenic potential. This work provides critical insight into autoantibody-mediated disease and identifies properties that could inform future therapies for autoimmune disorders.

SHORT COMMUNICATION SESSION – INFECTION, COMPUTATIONAL ANALYSES, AND MORE

SC33

Human antibodies against West Nile and related orthoflaviviruses

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West Nile virus (WNV) is a globally important mosquito-borne orthoflavivirus that can cause fatal neuroinvasive disease. No specific prophylaxis or treatment exists for WNV or related orthoflavivirus infections. In this work, we show that neutralizing autoantibodies to type I interferons present in humans do not impair antiviral antibody responses. We identified potent human monoclonal antibodies against WNV, including W010, which targets a unique epitope in envelope protein domain III (EDIII) and confers both prophylactic and therapeutic protection in a murine model, even when interferon signaling is impaired. A second protective antibody, W014, broadly cross-neutralizes multiple encephalitic orthoflaviviruses, including Japanese encephalitis, Murray Valley encephalitis, Saint Louis encephalitis, and Usutu viruses. These findings define protective epitopes in WNV EDIII and highlight candidate antibodies for broad antibody-based countermeasures against encephalitic orthoflavivirus infections.

SC34

Tissue-resident memory CD8+ T cells use mechanosensing for local immunesurveillance

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Tissue-resident memory CD8+ T cells (TRM) constitutively scan stromal cells in their tissue of residence, such as skin, gut or visceral organs, to intercept microbial spread. While chemokines and integrin ligands produced at epithelial barriers are critical mediators of this process, their elevated constitutive expression in non-barrier organs might lead to excessive influx of immune cells. We recently found that TRM lodged in exocrine glands, such as salivary glands (SG), perform tissue scanning in the absence of chemoattractant or adhesion receptor signaling, thus bypassing the requirement for canonical migration-promoting factors. Instead, SG TRM sense local physical confinement through nuclear deformation, which acts as a mechanosensor via an arachidonic acid and Ca2+-signaling pathway to increase their ability to intercept target cells.

Here, we examined the development and prevalence of chemokine-independent, mechanosensing-driven motility in virus-specific CD8+ T cells isolated from multiple internal and barrier organs during the course of an infection. Our data suggest that early effector T cells share the ability with SG TRM to migrate independently of chemokine signals. This ability is maintained in TRM lodged across most but not all internal organs. In sum, tissue confinement alone can trigger autonomous T cell surveillance across multiple tissues, providing a widespread complementary strategy to chemosensing-dependent migration.

SC35

Balanced Immune Reprogramming by Virtual Infection: Simultaneous Enhancement of Activation, Regulation, and Trafficking Markers

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Through evolution, besides the biological immune system, social species have developed a set of behavioural responses, aimed at preventing contacts and reduce the risk of infection before a pathogen can enter the host. This is known as the behavioral immune system (BIS). In our previous work, using virtual reality (VR)-delivered stimuli in humans, we demonstrated that the BIS directly controls the biological immune system, since we observed that innate lymphoid cell (ILC) frequency and activation was modulated by the prediction of contact with infectious avatars. Building on these findings, we now extended our analyses using a similar VR-based approach to conduct a longitudinal study. We comprehensively monitored all circulating cell populations to assess whether and with which kinetics the biological immune system senses brain signals induced by virtual infectious threats. Our findings demonstrate that infectious threats elicit distinct phenotypic alterations particularly within myeloid cells and $CD4^+$ T helper cells. Furthermore, to understand brain-immune communication, we performed plasma soluble factor analysis and in-depth metabolomic profiling, revealing specific alterations in lipid and aminoacid-related metabolites in response to infectious threats. Moving forward, we will correlate the modulation of the immune system by infectious avatars, with individual characteristics, to reveal how personal variability may impact the neuroimmune outcome. Our project opens novel perspectives for the development of VR-based solutions to intentionally modulate immune functions via virtual immune threats.

SC36

MICI: motility-based immune cell identifier

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Intravital microscopy enables real-time imaging of immune cell dynamics but is limited by spectral constraints and phototoxicity. Since cell motility encodes distinct behavioral signatures, we hypothesize that cell identity can be inferred from motility patterns, and introduce MICI (motility-based immune cell identifier), a deep learning model that classifies immune cell types from motion. In this work we analyzed 142 videos and 14007 tracks of neutrophils and CD4 T-cells from the Immunemap database. A bidirectional LSTM with additive attention was used to classify these populations based on their motility behaviours by extracting 33 features from tracks using a 10-step sliding window approach. Using 6-fold stratified cross-validation, the model achieved a mean macro-F1 score of 0.827 (± 0.072). Performance analysis revealed that the lowest accuracy occurred on data from a spinal cord neuroinflammation experiment, suggesting that an "universal" MICI may require multi-site training or domain adaptation to generalize across diverse physiological environments. In conclusion, we develop a

method that enables accurate discrimination between neutrophils and CD4 T cells, based on cell motility alone, supporting the idea of motility as a distinctive feature for cell identity. This suggests that dynamic behavior encodes cell-specific programs that can be leveraged for label-free characterization in vivo. Future work will focus on incorporating cell–cell interactions and applying domain adaptation techniques to

SC37

Phospholipid regulation of CD8+ T cell–dendritic cell interaction duration

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During adaptive immune responses, T cells integrate activation signals by engaging with antigen-presenting dendritic cells (DCs) anchored on the stromal network of lymph nodes and spleen. Our previous work showed that CCR7 ligands secreted by lymphoid stromal cells limit interaction duration by progressively driving CD8⁺ T cell release from DCs. Mechanistically, CCR7 signaling redistributes the F-actin–promoting guanine nucleotide exchange factor DOCK2 away from the immune synapse, triggering T cell detachment and acquisition of cytotoxic function and thereby preventing excessive stimulation. In this study, we further examine the molecular mechanisms underlying DOCK2-driven T cell detachment from DCs. Specifically, we investigate how two intracellular phospholipids, phosphatidylinositol-(3,4,5)-triphosphate and phosphatidic acid, control DOCK2 localization and activity during TCR signaling to promote T cell-DC detachment. Furthermore, we examine how actomyosin contractility contributes to this process. Defining the mechanisms governing T cell detachment from DCs will reveal how T cells integrate and terminate signaling during priming, thereby preserving CD8⁺ effector function in both acute and memory responses.

SC38

Regulatory factor X 7 limits Myc activity during B cell activation and suppresses Myc-dependent lymphomagenesis

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The regulatory factor X 7 (RFX7) is a poorly characterized regulator that is highly expressed in immune cells. While we previously identified its role in natural killer (NK)-cell metabolism, its function in B cells has remained unexplored. Here, we investigate the role of RFX7 in B cell activation and lymphomagenesis. We show that *Rfx7* deletion in B cells enhances metabolic activity and accelerates disease onset in murine Bcl6- and p53-deficient B cell lymphoma models. Rfx7-deficient B cells exhibit increased Myc activity, a phenotype that is reverted by Myc haploinsufficiency. This approach, however, conferred only partial protection against lymphoma development in *p53*$^{-/-}$*Rfx7*$^{-/-}$ double-hit model, where Myc was expressed at high levels in spite of haploinsufficiency. Interestingly, *Aicda* deletion, targeting a key driver of genomic instability in B cell lymphoma, limits disease development in this context. Importantly, we identified recurrent nonsense mutations in *RFX7* across different human B cell malignancies and demonstrate that these truncating variants exert both loss-of-function and dominant-negative effects. Moreover, reduced *RFX7* mRNA levels correlate with poorer prognosis in diffuse large B cell lymphoma. Collectively, our findings establish Rfx7 as a repressor of B cell activation, Myc activity, and Myc- and AID-dependent pro-lymphomagenic processes.

SC39

Immunodominance of the HLA class I restricted response to SARS-CoV-2 vaccine revealed by two unbiased screening approaches

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The antigenic peptides recognized by HLA class I-restricted CD8⁺ T cells are typically 9mers generated through a complex process defined as antigen processing. While peptide-HLA binding can be predicted by computational algorithms, a major challenge lies in identifying the few peptides that are efficiently produced through natural antigen processing, ultimately shaping the immunodominance hierarchy of T cell responses. To identify immunodominant peptides recognized by SARS-CoV-2 vaccinated donors, we used two complementary approaches, based on the natural antigen processing, to isolate Spike-specific CD8⁺ T cell clones: i) *in-vitro* restimulation of memory CD8⁺ T cells with the Ad5-based vaccine, and ii) direct cloning of *in-vivo* activated CD8⁺ T cells collected on day 6 following booster immunization. CD8⁺ T cell clones were characterized for peptide specificity, HLA restriction, functional avidity and *in-vivo* frequency using single cell transcriptomics. Our results allowed us to reconstruct the immunodominance hierarchies of the donors' immune response to the spike protein, identifying dominant, subdominant and cryptic peptides. Strikingly, in each donor, out of the large number of predicted strong binding peptides, only a few (2-5%) were recognized by CD8⁺ T cells in association with 2-3 of the six HLA allelic molecules. These findings provide a quantitative framework to understand CD8⁺ T cell immunodominance in response to relevant antigens, a critical step toward rational vaccine design aimed at eliciting effective CD8⁺ T cell immunity.

SC40

ArhGAP15 controls memory generation in CD8+ T cells

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Rac proteins are Rho-family GTPases that, when activated, regulate cytoskeletal remodeling, cell migration, and proliferation. Their activation cycle is controlled by guanine nucleotide exchange factors, which promote GTP loading, and GTPase-activating proteins (GAPs), which accelerate GTP hydrolysis.

ArhGAP15 is a Rac1/2-specific GAP whose membrane recruitment is mediated by binding to the phosphoinositide-3-kinase (PI3K) product phosphatidylinositol 3,4,5-trisphosphate (PIP3). ArhGAP15 is expressed across multiple immune cell types, including neutrophils and lymphocytes. Prior studies report that ArhGAP15-deficient neutrophils exhibit excessive migration owing to lack of negative regulation of F-actin formation. Here, we investigate ArhGAP15 function in $CD8^+$ T cells and find that, although migration is intact, ArhGAP15-deficient $CD8^+$ T cells show impaired differentiation into memory subsets across multiple organs. This correlated with decreased generation of memory precursor effector cells during the acute phase of an infection. In sum, our data suggests that ArhGAP15 preserves memory potential in effector cells, conceivably by controlling cytoskeletal regulation of signal integration.

SHORT COMMUNICATION SESSION – ALLERGOLOGY AND CLINICAL IMMUNOLOGY II

SC41

Sequential administration of an mRNA-based seasonal influenza vaccine in older adults

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Background: mRNA-1010 is an in investigational mRNA-based seasonal influenza vaccine for adults aged ≥50 years, encoding haemagglutinin from WHO-recommended strains (A/H1N1, A/H3N2, B/Victoria). Although evaluated in >39,000 adults, data on sequential seasonal vaccination remain limited. We assessed safety and immunogenicity of mRNA-1010 following prior seasonal vaccination with mRNA-1010 or an egg-based comparator (active comparator AC).

Methods: This post hoc analysis was conducted among participants in the phase 3 P304 study who had previously participated in a phase 3 mRNA-1010 study. Median time between vaccinations was ~23 months. In each study, participants received mRNA-1010 or AC in a randomized, blinded manner. Group 1 received mRNA-1010 in both studies; Group 2 received AC in the prior study and mRNA-1010 in P304; Group 3 received mRNA-1010 in the prior study and AC in P304; and Group 4 received AC in both studies.

Results: Among 2102 participants, unsolicited adverse events were similar across groups, with no new safety signals. Solicited local and systemic reactions were comparable among participants receiving mRNA-1010 in P304, regardless of prior vaccination. Day 29 haemagglutination inhibition geometric mean fold rises for all 3 strains were similar in Groups 1 and 2 and numerically higher than in Groups 3 and 4.

Conclusions: Sequential seasonal vaccination with mRNA-1010 demonstrated consistent safety and robust immunogenicity, supporting its use and suggesting potential advantages over repeated egg-based influenza vaccination.

Encore abstract (ESCMID 2026)

SC42

Microcrystalline tyrosine as a novel depot-forming agent in venom immunotherapy: a pre-clinical evaluation in bee-venom allergic mice

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Background: Venom immunotherapy (VIT) with aqueous venom extracts is a standard treatment for severe insect venom allergies. In other fields of allergen immunotherapy (AIT), depot adjuvants have been used for decades, with benefits for both safety and efficacy. Biodegradable microcrystalline tyrosine (MCT), is well-established in AIT, and has proven safe and effective through sustained release and adjuvancy. The objective of the study was to evaluate MCT as a depot-forming agent in VIT using a murine model of bee venom allergy.

Materials and Methods: Mice were sensitised with bee venom extract and then received subcutaneous immunotherapy (SCIT) with aqueous venom extracts or venom formulated with or MCT or aluminium hydroxide (alum) as depot-forming agents. Systemic reactions upon VIT and challenge were assessed by measuring body temperature, while antigen-specific IgE and IgG responses were analysed by ELISA. Mast cell degranulation was evaluated by serum MCPT-1 levels.

Results: VIT with MCT significantly improved survival, reduced body temperature changes, and promoted robust IgG1 and IgG2b responses. MCT-treated mice showed lower mast cell degranulation compared to untreated controls. Notably, VIT with MCT shifted the immune response toward a Th1-prone profile, associated with reduced anaphylaxis risk.

Conclusion: VIT with bee venom extract and MCT enabled safe and effective VIT by promoting protective IgG responses and reducing systemic reactions. These findings further support the evaluation of MCT as a complement to aqueous allergen extracts in VIT for human use.

SC43

Improvement of Mixed Inflammatory Environment in Nasal Secretions of Diffuse Type 2 Chronic Rhinosinusitis with Nasal Polyps under Dupilumab

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Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) is predominantly associated with a type 2 inflammatory endotype. While nasal secretion analysis shows promise for disease endotyping, current biomarkers remain limited for disease monitoring and prediction of treatment response. This study aimed to investigate the inflammatory patterns in nasal secretions of patients with type 2 CRSwNP undergoing treatment with dupilumab, an anti-IL4Rα antibody. A second objective was to evaluate markers for therapy response and monitoring. Nasal secretions were collected at four time points from 23 patients with histological type 2 CRSwNP undergoing dupilumab treatment, and compared with 10 healthy controls. Samples were analysed using proximity extension assay method by Olink®. Proteomic analysis of nasal secretions revealed 50 differential expressed proteins in type 2 CRSwNP compared to healthy. Nasal secretions of most patients revealed a mixed inflammatory endotype. Under dupilumab treatment, cytokines of all different endotypes decreased. The cytokines with the highest mean change (MCP-4,

CCL23, GDNF and CCL11) were effective predictors of dupilumab response and disease control. The inflammatory environment of the nasal mucosa in histological type 2 CRSwNP is most often characterized by a mixed type 1, 2, and 3 inflammatory endotype. Targeting type 2 inflammation with dupilumab reduces inflammation markers of all three types of inflammation. GDNF has emerged as a valuable marker for stratifying therapy and monitoring success in type 2 CRSwNP under dupilumab treatment.

SC44

Fine-needle aspiration and CyTOF immune profiling of lymph nodes after grass pollen allergen intralymphatic immunotherapy: a randomized pilot trial

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Background: Early immune responses to allergen immunotherapy (AIT) in human lymph nodes remain poorly characterized.

Objective: To investigate early local and systemic immune responses following intralymphatic (ILIT) versus subcutaneous immunotherapy (SCIT) using high-dimensional immune profiling.

Methods: In this randomized, open-label pilot trial, 28 adults with grass pollen allergy received a single allergen injection via ILIT or SCIT. Fine-needle aspiration (FNA) of inguinal lymph nodes and peripheral blood sampling were performed at baseline and 2, 6, or 24 hours post-injection. Immune cell populations and activation states were analysed by mass cytometry (CyTOF).

Results: FNA sampling was safe, well tolerated, and yielded sufficient viable cells for comprehensive immune profiling. Early immune responses were dominated by changes in innate immune cells, with monocytes showing the most pronounced increase in frequency and activation following both ILIT and SCIT. A trend toward higher monocyte responses was observed after ILIT. No severe adverse events occurred.

Conclusion: Lymph node FNA combined with high-dimensional immune profiling enables the investigation of early human immune responses following AIT. The rapid activation of monocytes highlights the importance of innate immunity in the initial phase of treatment and may represent a target for biomarker development.

SC45

Phenotype-Tailored Prophylactic Immunomodulation Enables Safe Immune Checkpoint Inhibitor Rechallenge After Severe irAEs in High-Risk Patients

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Severe and multi-organ immune-related adverse events (irAEs) are major complications of immune checkpoint inhibitor (ICI) therapy and frequently result in permanent treatment discontinuation. Whether prophylactic immunomodulation can safely enable ICI rechallenge in high-risk patients remains unclear. Distinct inflammatory pathways underlying specific irAE phenotypes suggest that phenotype-tailored biologic strategies may reduce toxicity recurrence while preserving antitumor efficacy.

We conducted a retrospective single-center cohort study at Lausanne University Hospital (CHUV) including 52 patients who experienced grade = 2 irAEs requiring ICI interruption or discontinuation and were subsequently rechallenged under prophylactic immunomodulation. Prophylactic strategies included corticosteroids and/or targeted monoclonal antibodies, including anti-IL-6 receptor, anti-TNFa, or anti-integrin a4ß7 therapies, selected according to irAE phenotype and presumed inflammatory drivers. The primary endpoint was successful ICI rechallenge status at 6 months. This study evaluates the feasibility of phenotype-tailored prophylactic immunomodulation as a strategy to support safe ICI rechallenge in patients with prior severe irAEs. Our findings may contribute to the development of personalized approaches balancing toxicity prevention with maintenance of oncologic benefit.

SC46

When the Tonic turns Toxic: a delayed Type Allergy to Tonic Water

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Background: Fixed drug eruption is a distinctive condition characterized by recurrent erythematous to violaceous plaques appearing at the same site. In most cases, fixed drug eruptions are triggered by medications. However, diagnosis can be more challenging when food is involved. We present a case of fixed drug eruption caused by quinine contained in tonic water.

Observations: A 33-year-old woman presented with multiple erythematous lesions on hands, feet, and around the mouth. This was the third episode. In each episode, the lesions appeared one to three hours after consumption of Bitter Lemon, regular tonic water, or orange-flavored Schweppes, and resolved within three weeks. A diagnosis of fixed drug eruption was made and confirmed by skin biopsy. Patch testing was performed using the patient's consumed Schweppes, quinine 1% in petrolatum, and Plaquenil (hydroxychloroquine) 30% in petrolatum. At the 72-hour reading, a positive reaction to quinine 1% was observed in loco. Based on these findings, quinine in tonic water was identified as the causative agent of the patient’s fixed drug (probably better “food”) eruption. An oral provocation test with hydroxychloroquine was performed and resulted in reactivation of the previously documented cutaneous lesions.

Conclusion: Quinine is a naturally occurring alkaloid that can trigger not only immediate-type allergic reactions but also delayed-type hypersensitivity responses. Cross-reactivity with antimalarial drugs has been reported. The positive provocation test with hydroxychloroquine confirmed cross-reactivity to quinine.

SC47

Autoantibody-Based Stratification of Extraglandular Manifestation Risk in Sjögren’s Disease

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Introduction. Extraglandular manifestations (EGMs) are major determinants of severity in Sjögren’s disease (SjD), highlighting the need for biomarkers able to stratify patients according to their risk of systemic involvement. Although anti-SSB and anti-TRIM21 antibodies have lost diagnostic relevance, they may reflect distinct immunopathogenic pathways through their association with type I interferon activity. We assessed whether their presence, in addition to anti-SSA antibodies, identifies patients at higher risk of EGMs.

Methods. We retrospectively reviewed medical records of patients referred for suspected SjD between 01.2004 and

12.2023. SjD was defined according to the 2016 ACR/EULAR criteria. Participants were stratified according to SjD status and anti-SSA, anti-SSB, and anti-TRIM21 antibody profiles to compare EGM onset.

Results. Among 260 screened participants, 146 were included: SjD- (34), SSA- SjD+ (21), SSA+SSB-TRIM21- SjD+ (13), SSA+SSB-TRIM21+ SjD+ (23), SSA+SSB+TRIM21- SjD+ (3), and SSA+SSB+TRIM21+ SjD+ (52). The SSA+SSB+TRIM21+ subgroup showed higher B-cell activity (p = 0.003). In the Bayesian survival model, anti-SSB positivity was associated with increased risk of EGMs after diagnosis (HR 2.46, 95%CI 1.48–4.18), whereas anti-TRIM21 positivity was not (HR 1.49, 95%CI 0.76–2.89).

Conclusion. Anti-SSB and anti-TRIM21 antibodies identify a more immunologically active anti-SSA+ SjD subset. However, only anti-SSB antibodies were associated with increased EGM risk, supporting their potential value for stratifying systemic disease risk in SjD.

SC48

Cat-allergen intralymphatic immunotherapy: results of the single-dose escalation phase from the ongoing CAT-ILIT study

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Introduction: In industrialised countries, sensitisation to cat hair and dander is a major cause of allergic rhinoconjunctivitis and asthma. Intralymphatic immunotherapy (ILIT) is an innovative approach in which an allergen extract is applied directly into a lymph node to achieve efficient and potentially safer immunomodulation. Previous clinical studies with pollen allergens showed shorter treatment duration with good tolerability. This two-phase open-label study investigates the safety and efficacy of ILIT with cat allergens. In the initial dose-escalation phase, the maximum tolerated single dose is defined by systemic reactions of grade 3 or higher (World Allergy Organization, WAO).

Methods: Twenty-four participants with confirmed type 1 sensitisation to cat hair/dander received a single ultrasound-guided injection of cat allergen extract into an inguinal lymph node using a modified 3+3 dose-escalation design (10 to 500 SQ-U). After, participants were monitored for two hours, and a follow-up call was conducted 48 hours later.

Results: ILIT with cat allergens showed good tolerability. During the two-hour observation period, 15 participants (63%) exhibited only mild symptoms. The most common adverse events were local tenderness (n = 5) and fatigue (n = 4). All side effects resolved within three days. No SAE occurred.

Conclusion: ILIT with cat allergens was well tolerated and supports progression to the second study phase evaluating two dosing regimens. ILIT may offer greater safety, increased patient comfort, and a shorter treatment duration compared with conventional AIT.

SHORT COMMUNICATION SESSION SYIS

SC49

Polysorbate 80 Impairs Gut Barrier and Drives Systemic Inflammation via PPARα-Mediated Fatty Acid Oxidation and Mitochondrial Dysfunction

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Polysorbate 80 (P80), a widely used food emulsifier, is linked to gut barrier disruption and inflammation, though mechanisms remain unclear. We investigated P80's effects on the intestinal barrier and systemic inflammation in Caco-2 cells, iPSC-derived intestinal organoids (HIOs), and mice. Caco-2 cells and HIOs were exposed to P80 across a dose range. Cytotoxicity was assessed by MTT, ROS by DCFDA, NF-κB and AhR activation in HCT116 and HepG2 reporters, and mitochondrial potential by JC-1. Mice received acute (2.5%, 4 days) or chronic (1%, 6 weeks) P80, followed by multi-organ proteomics, STRIDE, transcriptomics, and lipidomics. P80 reduced viability at 0.05%, with dose-dependent rises in ROS (up to 4-fold) and NF-κB (up to 150-fold), both reversed by N-acetylcysteine. JC-1 showed loss of mitochondrial potential in organoids. In mice, P80 induced oxidative and ER stress, impaired DNA repair, triggered apoptosis, elevated inflammatory mediators (S100a4, IL-5, MAP2K6, CCL2, TGF-α), and caused mitochondrial DNA breaks. SCENITH revealed a shift toward fatty acid oxidation, and PPARα or CPT-1 inhibition reversed ROS and NF-κB. Chronic exposure further altered the transcriptome and microbiome (ongoing). P80 drives oxidative stress, mitochondrial dysfunction, and NF-κB inflammation, causing barrier breakdown and systemic immune activation via PPARα-driven fatty acid oxidation. Rescue by N-acetylcysteine and CPT-1 inhibition identifies oxidative stress from fatty acid metabolism as the central driver, with chronic exposure potentially contributing to inflammatory pathologies.

SC50

An unconventional cyclin regulates cysteinyl leukotriene release from tuft cells during parasite infections

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Parasitic infections of the small intestine can be detected by rare chemosensory cells in the epithelial lining: tuft cells. Upon sensing a parasite, tuft cells release effector molecules to activate innate lymphoid group 2 cells residing in the intestinal lamina propria. How effector molecule production and release are regulated within tuft cells is unknown. Here, we identify the unconventional cyclin CyclinJ as a tuft cell-specific regulator of cysteinyl leukotriene release. Using organoid gene editing to endogenously tag CyclinJ in tuft cells, we uncover an unexpected subcellular localization and function for this largely uncharacterized member of the cyclin family.Using endogenous proximity labeling in tuft cells, we found that CyclinJ interacts with components of the leukotriene biosynthetic pathway and

the secretory machinery to regulate cysteinyl leukotriene release. In vivo, mice lacking CyclinJ exhibit impaired tuft cell-mediated ILC2 activation and consequently fail to mount an effective antiparasitic response, resulting in impaired parasite clearance.

SC51

Cross-reactive Peptides: A Mechanistic Link Between Multiple Sclerosis and Epstein-Barr Virus

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Multiple sclerosis (MS) is an autoimmune disorder characterized by central nervous system demyelination. Although certain risk factors are established, such as prior Epstein-Barr virus (EBV) infection, the etiology remains elusive. While conventional MS research has focused on CD4 T cells, CD8 T cells are the predominant T cell population in MS lesions and may play a pivotal role in disease pathogenesis, potentially driven by cross-reactivity following EBV infection. By integrating sequence alignments and AlphaFold2-aided prediction and superimposition of peptide bound major histocompatibility complexes (pMHCs) we identified over 400 EBV peptides with high sequence and structural similarity to myelin-associated peptides. Among these are several previously known and novel immunogenic peptides binding to the widespread HLA-A*02:01 and HLA-B*07:02 alleles. Strikingly, we found that, in healthy donors and MS patients, CD8 T cells specific for EBV exhibited cross-reactivity with myelin-associated peptides. Cross-reactive CD8 T cell clones mounted cytotoxic responses to myelin peptide-pulsed and, importantly, myelin protein-transduced antigen presenting cells. Differences in frequencies, dose-response and dependencies on binding residues have motivated ongoing structural and single-cell analyses to define the molecular basis and clonal architecture of cross-reactive CD8 T cell responses in MS patients and healthy donors. In summary, through the development and use of novel computational tools we identified a potential role for EBV-specific cross-reactive CD8 T cells in MS.

SC52

Investigation of the role of IL-33 for intestinal tumorigenesis

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Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide, and chronic inflammation in the gut is a key driver of its progression. Interleukin-33 (IL-33) signaling plays a controversial role in intestinal inflammation and CRC, and its exact mode of action in the tumor environment is unclear. We have established that ST2, the specific moiety of the IL-33 receptor, promotes intestinal tumorigenesis both in mice and humans. Using a chemically induced CRC mouse model, we observe that IL-33 is strongly upregulated in colonic tumor tissue compared to adjacent non-tumor regions, with epithelial cells and fibroblasts serving as its primary sources. Despite belonging to the same signaling pathway, IL-33 versus ST2 drive distinct tumor growth patterns and disease outcomes. These differences are reflected in altered immune infiltration within the tumor microenvironment, highlighting divergent roles in shaping inflammation-associated cancer progression. Remarkably, this functional difference is dependent on the intestinal microbiota, revealing a previously unappreciated interaction between this inflammatory signaling and bacterial composition in controlling tumor growth. Ongoing studies aim to define how specific microbial communities modulate IL-33- and ST2-driven immune responses. Understanding the relationship between inflammation, microbiota, and tumor growth may support the development of therapeutic approaches that incorporate microbiota modulation in CRC.

SC53

Biomarkers in Sarcoidosis: an Inflammatory Perspective

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Introduction: Sarcoidosis is a systemic granulomatous disease with heterogeneous organ involvement. Clinical manifestations and functional tests often reflect cumulative organ damage rather than ongoing inflammatory activity. Due to its high capability of detecting current inflammation,^{18}F-FDG PET may represent an ideal gold standard for therapy guidance. However, its use is limited by availability, cost and radiation exposure.

Aim: To assess whether circulating biomarkers can reflect systemic inflammatory activity and potentially reduce the need for resource-intensive imaging.

Design and Methods: Retrospective cohort of 180 sarcoidosis patients with paired ^{18}F-FDG PET-CT and blood sampling (N = 770) including different biomarkers of disease activity (TNFα, sIL-2R, neopterin, ACE activity, CRP, calciuria, lymphocytopenia). Variance and correlation analyses as well as ROC curves were used to evaluate diagnostic performance.

Results and conclusions: Biomarkers of granulomatous inflammation (TNFα, sIL-2R, neopterin) showed significant correlation with PET activity already at moderate disease levels (AUC 0.63–0.68; Spearman's r 0.32-0.48). In contrast, CRP and ACE were associated with PET activity only at the highest inflammatory burden. While associations were robust for pulmonary and nodal manifestations, no biomarker reliably predicted cardiac PET activity. These findings support an inflammation-centered approach to disease activity assessment using circulating biomarkers. Imaging techniques such as MRI and ^{18}F-FDG PET remain central for diagnosis and exclusion of cardiac sarcoidosis.

AILD RESEARCH – ORAL PRESENTATIONS ON AUTOIMMUNE LIVER DISEASE RESEARCH PROJECTS

AR01

A single-cell atlas of checkpoint inhibitor-induced liver injury links shared liver-tumour CD8+ T cell clones to cytotoxicity and macrophage crosstalk

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Introduction and Aim: Immune checkpoint inhibitors (ICIs) have transformed cancer therapy but cause immune-related adverse events. Checkpoint inhibitor-induced liver injury (ChILI) is among the most common toxicities, yet its mechanisms remain poorly understood. We aimed to investigate the spatial features of ChILI at single-cell resolution in human tissues.

Design and Methods: We assembled formalin-fixed paraffin-embedded liver biopsies from cancer patients with ChILI and normal liver controls. Using multiplexed spatial proteomics, bulk TCR sequencing, RNA in situ hybridization, and spatial transcriptomics, we analyzed the immune landscape of ChILI and performed in situ T-cell clone tracking in the liver and matched tumour samples.

Results: Spatial proteomics revealed marked expansion of cytotoxic CD8+ T cells and macrophages forming spatially organized immune niches. Bulk transcriptomics demonstrated activation of interferon response pathways. TCR sequencing identified shared, hyperexpanded clones between liver biopsies and matched tumors in all analyzed patients. Spatial transcriptomics confirmed that these clonotypes exhibited a cytotoxic CD8+ phenotype in both liver and tumor tissues, localized to immune-rich niches, and engaged in CCL5-CCR1-mediated macrophage interactions.

Conclusions: This study presents a tissue-based single-cell spatial atlas of ChILI, providing direct evidence of tumour–liver T-cell clone sharing. These findings link antitumour immunity to immune-mediated liver injury and identify the CCL5-CCR1 axis as a potential therapeutic target.

AR02

Induced regulatory T cells from patients with primary biliary cholangitis are suppressive and stable and are different from natural regulatory T cells

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Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease. Reduced number, stability, and function of regulatory T cells (Tregs) in PBC limit their therapeutic use. We aimed to generate stable, functional induced Tregs (SFiTregs) from PBC-derived CD4+ T cells *in vitro* and compare their epigenetic profile, stability, and suppressive capacity with natural Tregs (nTregs). CD4+ T cells were isolated from peripheral blood mononuclear cells (PBMCs) of PBC patients and stimulated using a modified protocol (Mikami et al., 2025). FoxP3, CTLA4, and Helios expression were assessed by flow cytometry and bisulfite sequencing. Function was evaluated *via in vitro* suppression assays. Epigenetic features, including Foxp3 gene locus for STAT5 binding, H3K27ac, and chromatin accessibility, were analyzed by Chromatin immunoprecipitation followed by sequencing (ChIP-seq) and assay for transposase-accessible Chromatin using sequencing (ATAC-seq) in nTregs, Tnaive, and SFiTregs. Single-cell RNA-sequencing of PBMCs confirmed reduced Treg stability in PBC. The SFiTreg protocol induced DNA hypomethylation in Treg signature genes, yielding a 100-fold expansion of pure, suppressive cells. SFiTregs showed greater stability than nTregs under Th1-polarizing conditions. ATAC-seq and ChIP-seq revealed comparable baseline epigenetic profiles but differences in accessible regions. This approach enables robust generation of functional, stable Tregs from PBC CD4+ T cells, overcoming limitations of autologous *ex vivo* Treg expansion and supporting their use in the PBC inflammatory liver environment.

AR03

Seladelpar Linked to Sustained Reduction in Cholestatic Markers and Consistent Safety Profile in Primary Biliary Cholangitis up to 48 Months in ASSURE

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Seladelpar (SEL) is a first-in-class delpar (selective PPAR-delta agonist) indicated for the treatment of primary biliary cholangitis (PBC), in combination with UDCA for adults with an inadequate UDCA response, or as monotherapy in UDCA-intolerant patients. We report on long-term biochemical efficacy/safety in a pooled population treated with SEL. Pts received daily oral SEL 10mg in the ongoing, open-label ASSURE rolled over from the PBO-controlled RESPONSE or legacy SEL trials, and were pooled according to SEL initiation. Efficacy endpoints included composite biochemical response (CBR; ALP <1.67×ULN, ALP decrease ≥15% from baseline [BL], and total bilirubin ≤ULN), ALP normalization, ALP% change from BL (CfB), and other parameters through 36 months (M). Safety was assessed by exposure-adjusted AEs through 48M. Of 337 pts, 258 were treated for ≥2yrs and 117 for ≥3yrs, 122 reached 36M as of the data cutoff (31-Jan-25). At all time points, a majority of pts achieved CBR: 69% (225/325) at 12M, 70% (181/258) at 24M, and 67% (82/122) at 36M. ALP normalized in 35% of pts (114/325) at 12M, 37% (96/258) at 24M, and 34% (41/122) at 36M. Sustained reductions in ALP observed with mean CfB: −43% at 12M, −43% at 24M, and −40% at 36M; sustained reductions also observed in ALT and GGT through 36M. SEL was well tolerated, with overall AEs reported in 83.2 pts per 100 pt-yrs in yr1 and 62.3 in yr4. SEL led to sustained reductions in biochemical markers of cholestasis through 36M of open-label treatment. SEL was also safe and well tolerated with no new safety signals through 48M of follow-up.

AR04

Targeting auto(mito)phagy rescues mitochondrial function and prevents aberrant immune activation in experimental models of primary biliary cholangitis

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Primary biliary cholangitis (PBC) is a chronic immune-mediated cholestatic liver disease. We previously showed that microRNA-506 (miR-506) is upregulated in PBC cholangiocytes, targeting AE2 and disrupting intracellular pH, leading to PBC-like features and immune activation. Mitophagy, a pH-dependent process that removes dysfunctional mitochondria, remains unexplored in PBC. We aimed to characterize the role of mitochondrial dynamics and auto(mito)phagy in disease pathogenesis. Single cell RNA-sequencing data from livers of PBC patients and controls, together with miR-506-overexpressing cholangiocytes (H69 miR-506) and controls were analyzed regarding mitochondrial function, auto(mito)phagy and antigen presentation. Altered genes and proteins related to mitochondrial dynamics and auto(mito)phagy were found in PBC livers and H69 miR-506 cells, as well as increased antigen presentation and inflammation. Altered mitochondrial function, impaired mitophagy and accumulation of dysfunctional mitochondria were found in these cells. Autophagy inhibition increased cell death and antigen presentation, especially in miR-506 cells, while activation reduced bile acid-induced apoptosis. UDCA and autophagy activation improved mitochondrial function and reduced PDC-E2 overexpression. PBC cholangiocytes show impaired mitochondrial integrity and mitophagy, promoting accumulation of dysfunctional mitochondria and abnormal antigen presentation. UDCA and autophagy activation restore these defects. Targeting mitochondrial dynamics and mitophagy may offer new therapeutic strategies for PBC.

AR05

Standardized Body Mapping Reveals Distinct Topographical Patterns of Hepatobiliary Pruritus

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Background & aims: Pruritus is a frequent and burdensome symptom in chronic liver diseases, but its anatomical distribution remains poorly characterized. We used standardized body mapping to assess spatial itch patterns across liver disease etiologies.

Methods: In this cross-sectional study, patients with pruritus completed standardized body maps indicating current and habitual itch locations. Patients were categorized into immune-mediated and cholestatic (ICLD), steatotic (SLD), and viral liver diseases (VLD). Itch severity was assessed using NRS and the 5D Itch Scale. Body maps were digitized and analyzed using automated quantitative image analysis.

Results: Among 656 participants, 173 (26.4%) reported pruritus; complete body maps were available for 150 patients (67.7% female). ICLD represented the largest subgroup (40.7%). Mean itch intensity was 3.8±2.7 and median 5-D Itch score was 11 (IQR 8.5–15). Pruritus predominantly affected the extremities, especially volar forearms and anterior lower legs, followed by the back, while palm and sole involvement was uncommon. Current and habitual itch patterns showed high concordance. Cirrhotic patients reported less upper-body involvement than non-cirrhotic patients, while women reported itch across more body regions than men.

Conclusions: Standardized body mapping identified a reproducible, extremity-predominant pruritus pattern across liver diseases largely independent of etiology. These findings support shared mechanisms underlying hepatobiliary pruritus and highlight body mapping as a robust tool for spatial itch phenotyping.

AR06

The immunoproteasome as a target in autoimmune hepatitis

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Natural killer T (NKT) cells are potent immunomodulatory lymphocytes implicated in the pathogenesis of autoimmune hepatitis (AIH). Upon activation by the synthetic NKT cell ligand glycolipid α-galactosylceramide (α-GalCer), NKT cells rapidly produce both IFN-γ and IL-4, cytokines with opposing roles in hepatic inflammation. The immunoproteasome (IP), a specialized proteasome variant predominant in immune cells, is known to regulate cytokine production and T cell function, yet its role in NKT cell function remains poorly understood. Here, we investigated the effects of KZR-616 in preclinical models of inflammatory and autoimmune liver disease. We observed reduced splenic NKT cell numbers in mice deficient for IP subunits. Stimulation of mouse splenocytes with α-GalCer resulted in dose-dependent reduction of IFN-γ secretion in the presence of KZR-616, while IL-4 production increased, suggesting a functional shift toward a Th2-like cytokine profile rather than overall suppression of NKT cell activation. This effect was dependent on IL-12 signaling. In vivo in mice, KZR-616 treatment in an α-GalCer-induced hepatitis model reduced hepatic NKT cell infiltration comparable to dexamethasone. In addition, serum alanine aminotransferase (ALT) levels were markedly decreased, indicating reduced liver injury. Ongoing studies in concanavalin A-induced and liver homogenate-induced AIH models will be presented. Collectively, these findings demonstrate potent anti-inflammatory effects of selective IP inhibition and support the therapeutic potential of KZR-616 in autoimmune liver diseases.

AR07

Liver Transplantation for Autoimmune Hepatitis: A Comprehensive 35 Year Single-Center Experience

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Introduction: Liver transplantation (LT) is the only curative treatment for end-stage autoimmune hepatitis (AIH). We examined the evolution of LT and reLT for AIH over 35 years at a single center.

Methods: Retrospective review of 5,862 adult LTs (1990-2024). LTs for autoimmune liver disease (AILD): AIH, primary biliary cholangitis, primary sclerosing cholangitis, or overlap syndromes were included and stratified by era: pre-MELD (1990-2001), post-MELD (2002-2011), and modern (2012-2024).

Results: Among 620 LTs for AILD in 538 patients, 531 (85.6%) were primary LT (pLT) and 89 (14.4%) were reLT, with median follow up of 15 years. Of 130 patients undergoing pLT for AIH, 15 (11.5%) required 19 reLTs. Within AILD pLTs, AIH became more prevalent over time, rising from 17.7% in the pre-MELD era to 34.7% in the modern era (p <0.001). ReLT for AIH declined significantly with 11 (22.0%) pLTs in the pre-MELD era undergoing 14 reLTs, and no pLTs for AIH in the modern era undergoing reLT (p = 0.001). In the modern era, patients with AIH had a median MELD of 38 and 66.7% required ICU care prior to pLT. Despite their high acuity, 10-year patient and graft survival for AIH after pLT improved significantly between the pre-MELD and modern era, from 58.0% to 90.5% (p = 0.002) and 50.0% to 88.1% (p <0.001), respectively.

Conclusions: This represents the largest single center experience with LT for AIH spanning 35 years. More accurate diagnosis of AIH in combination with advances in surgical technique and immunosuppression have led to significant improvements in long-term outcomes after LT.

AR08

B-cell activation signatures are independently associated with adverse clinical outcomes in primary biliary cholangitis

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Background & Aims: Primary biliary cholangitis (PBC) shows a heterogeneous clinical course. While cholestatic markers predict outcome, the role of systemic immune activation is less clear. We assessed associations between composite immune signatures and clinical outcomes in PBC.

Methods: In this retrospective cohort, inflammatory markers were grouped into composite signatures: B-cell activation (CXCL13, BAFF, APRIL), IFN-related (CXCL9, CXCL10, CXCL11), and innate inflammatory (IL-6, TNF-α, S100A9). The primary endpoint was liver transplantation or liver-related death. Cox models were adjusted for age, sex, and alkaline phosphatase (AP).

Results: Among 63 patients, 11 events occurred over a median follow-up of 4.6 years (IQR 3.5–9.8). The B-cell signature was associated with the primary endpoint in the univariable analysis (HR 1.0017, p = 0.0077) and remained independently associated after adjustment (HR 1.0022, p = 0.0058), corresponding to ~25% higher risk per 100-point increase. IFN-related and innate signatures were not associated with outcome. Sicca showed a trend towards an increased risk (HR 3.53, p = 0.076). BAFF correlated weakly with AP (rho = 0.26, p = 0.043), whereas CXCL10 and CXCL13 did not.

Conclusion: A B-cell activation signature, but not IFN-related or innate signatures, is independently associated with adverse outcomes in PBC, supporting a role for B-cell–driven mechanisms in disease progression.

GUIDED POSTER TOUR THURSDAY

A01

Dupilumab/ anti-IL-4R alpha modulates Inflammatory Macrophage Memory in T2-high Asthma

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While "trained immunity" has been extensively studied in infectious diseases and cancer, its mechanisms and functions in chronic inflammatory disorders such as asthma remain poorly characterized. Our previous work identified an inflammatory epigenetic and metabolic memory in macrophages from patients with type 2 (T2)-high asthma. However, how this program is affected by biologics targeting type 2 cytokines is unknown. Here, we aimed to dissect how dupilumab/ anti-IL-4Ralpha treatment affects "training" of monocytes and macrophages in patients and mice with T2-high asthma. In a mouse model of chronic T2-high asthma, we found that anti-IL-4Rα treatment robustly reduces type 2 airway inflammation while leaving Th17 responses unaffected. Multi-omic profiling, including bulk and single-cell RNA-seq, ATAC-seq, and lipidomics, showed that anti-IL-4Rα treatment restores healthy peripheral prostaglandin profiles or monocyte phenotype and function in allergen-challenged mice or asthmatic patients. In contrast, anti-IL-4Rα largely fails to correct the inflammatory reprogramming of airway macrophages in T2-high asthma. Finally, by combining long-term ex vivo expansion with adoptive transfer of hematopoietic stem and progenitor cells (HSPCs), we show that anti-IL-4Rα treatment reprograms asthmatic bone marrow myeloid progenitors and thereby modulates subsequent responses to allergenic molds. Thus, our study provides clinically relevant insight into the mechanistic underpinnings, functional impact, and therapeutic modulation of trained immunity as an underappreciated component of asthma.

A02

Uncovering chlorhexidine allergy in perioperative anaphylaxis

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Introduction/aim of the study: Perioperative anaphylaxis remains a major diagnostic challenge, particularly when multiple potential triggers are administered in rapid sequence. Although antibiotics and anaesthetic agents are often prioritized in the work-up, chlorhexidine remains an under-recognized cause despite its widespread perioperative use. We aimed to highlight

chlorhexidine as a relevant trigger of perioperative anaphylaxis and to illustrate the diagnostic value of basophil activation testing (BAT) in this setting.

Design and methods: Two patients were evaluated in an Immunoallergology department following perioperative anaphylaxis. A detailed review of perioperative exposures was undertaken. The diagnostic investigation included skin testing, measurement of chlorhexidine-specific IgE, and basophil activation testing (BAT).

Results: The first case involved a male patient who developed anaphylaxis shortly after urinary catheterisation with a chlorhexidine-containing lubricant, following an otherwise uneventful general anaesthetic. The second involved a 36-year-old woman with two episodes of perioperative anaphylactic shock. In both cases, anaesthetic drugs were excluded and chlorhexidine sensitisation was confirmed by positive specific IgE, skin prick tests and BAT.

Conclusions: Chlorhexidine should be systematically considered in the evaluation of perioperative anaphylaxis. BAT may be particularly useful in complex cases, increasing diagnostic confidence, helping exclude alternative culprits, and supporting safer planning of future procedures.

A03

Automated Skin Prick Test Reading: Diagnostic Accuracy and Time Efficiency Compared with Manual Assessment

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Background: Skin prick testing (SPT) is the gold standard for diagnosing IgE-mediated allergies. Traditional manual SPT is subject to operator variability and labour-intensive processes. Digital devices have been developed to standardise wheal measurement and reduce inter-operator variability.

Objective: To assess the sensitivity and specificity of a Digital SPT device (DSPT) versus manual SPT, compare time efficiency, and evaluate technology acceptability.

Methods: A single-centre, cross-sectional study enrolled 225 participants who underwent SPT using both methods with 17 allergens, with positive and negative controls. Primary endpoints were sensitivity and specificity; secondary endpoints were time to result and inter-method agreement.

Results: Of 225 participants (147 females, 78 males; mean age 39 years), the device achieved 87.6% sensitivity, 80.0% specificity, and an area under the curve (AUC) of 0.952 for histamine, with 98.2% specificity for saline. Processing time was comparable (device: 60 s, interquartile range IQR 53–68 s vs manual: 56 s, IQR 40–73 s; p = 0.042), with manual time increasing with complexity while device time remained constant. Across five allergens, sensitivity ranged 75.0–92.6% and specificity 94.9–100%, with substantial to near-perfect inter-method agreement (Cohen's kappa [κ] = 0.73–0.902).

Conclusion: The DSPT showed high specificity and strong inter-method agreement, supporting standardisation of wheal measurement. Moderate sensitivity requires manual confirmation of negative results, and multicenter validation is needed before clinical adoption.

A05

Engineered allergen-specific regulatory T cells suppress birch pollen–induced airway inflammation

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Allergic asthma affects over 300 million individuals worldwide and remains a significant clinical burden. Allergen immunotherapy is the only disease-modifying treatment but has limited applicability in severe cases. Here, we investigated the therapeutic potential of regulatory T cells (Tregs) engineered with chimeric allergen receptors (CAlleRs) targeting the major birch pollen allergen Bet v 1. Four anti–Bet v 1 human antibodies were identified and used to generate CAlleR constructs in Tregs. Antigen-specific activation and suppressive function were assessed in vitro. Therapeutic efficacy was evaluated in a murine model of birch pollen–induced allergic airway inflammation. CAlleR Tregs showed allergen-specific activation and suppressive function in vitro. In vivo, adoptive transfer of CAlleR Tregs significantly reduced airway hyperresponsiveness and inflammation. Mechanistically, CAlleR Tregs migrated to the lungs and mediastinal lymph nodes, interacted with $CD11c^+$ dendritic cells, and were activated in an Fcγ receptor–dependent manner by cross-presenting Bet v 1 stabilized by non-competitive anti-Bet v 1 antibodies. These findings unveil a novel mechanism for targeting soluble antigens and highlight the potential of CAlleR Tregs as a therapeutic strategy for severe allergic diseases.

TS01

Targeted discovery of natural NY-ESO-1-specific T-cell receptors from long-term cancer survivors for efficient and safe TCR-T cell therapy

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Introduction and Aim: TCR-T cell therapies targeting NY-ESO-1, typically using avidity-enhanced TCRs, show clinical efficacy but are associated with severe toxicities, potentially driven by excessive TCR avidity and off-target reactivity. We investigated whether naturally occurring NY-ESO-1-specific TCRs provide a safer alternative aiming for prospective clinical trials.

Methods: 30 natural TCRαβ clonotypes identified by scRNA-Seq from melanoma survivors were expressed in the Jurkat $CD8^{pos}$ TCR^{ko} T cell subline. Binding avidity was assessed using NY-ESO-1 multimers/tetramers ±CD8 and integrated into an avidity score. Functional avidity (EC_{50}) was tested with NY-ESO-1-loaded T2 cells, while off-target reactivity was evaluated in binding and functional assays with COG7 and MKI67 cross-reactive peptides. A set of avidity-enhanced and clinically-used TCRs were also analyzed in parallel.

Results: Natural TCRs spanned a wide binding avidity range, with strong positive correlation between binding avidity and functional responses. Avidity-enhanced TCRs exhibited generally much higher cross-reactive binding and activation compared to natural clonotypes. In contrast, most natural TCRs of higher binding avidity showed reduced to absent off-target reactivity while maintaining high functional activity.

Conclusions: Natural TCRs display diverse yet controlled avidity profiles with much lower cross-reactivity than the avidity-enhanced clinically-used receptors. These findings support their development as safer, physiologically relevant candidates for next-generation TCR-T therapies.

TS05

Lactate and TGFβ1 Reprogram NK Cells Toward a Tissue-Resident, Low-Cytotoxic Phenotype in Idiopathic Inflammatory Myopathies

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Idiopathic inflammatory myopathies (IIM) are rare autoimmune muscle diseases characterized by chronic inflammation, fibrosis, and progressive muscle weakness. While adaptive immune responses are well studied, the role of natural killer (NK) cells in muscle injury and regeneration remains unclear. Emerging evidence suggests that NK cells may acquire either pathogenic or reparative functions depending on the inflammatory and metabolic microenvironment. This project investigates how transforming growth factor beta (TGFβ) signaling and lactate accumulation regulate NK cell phenotype and function in IIM muscle tissue. We will combine translational clinical analyses with mechanistic in vitro studies. NK cells from patients' blood and muscle biopsies will be characterized using flow cytometry, tissue imaging, and transcriptomic approaches. Lactate and TGFβ1 levels will be evaluated as candidate biomarkers associated with disease activity and fibrosis. Functional studies will assess the effects of lactate and TGFβ1/2/3 variants on NK cell function using primary human NK cells and myoblasts. Preliminary data show that elevated lactate impairs NK cell migration and cytotoxicity while increasing tissue-residency markers such as CD69. TGFβ1 also suppresses NK cell-mediated cytotoxicity against human myoblasts. Together, these findings support the hypothesis that the IIM microenvironment promotes a tissue-retained, less cytotoxic NK cell state.

This study aims to distinguish pathogenic from reparative NK cell programs and may identify novel biomarkers and therapeutic targets for IIM.

GUIDED POSTER TOUR FRIDAY

BI07

Inborn errors of immunity promote a spectrum of gain-of-survival states of lymphocytes with autoreactive properties

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Aim of the study: Some IEI patients develop lymphomas, suggesting gain-of-survival states in which autoreactive lymphocytes evade negative selection, persist, and occasionally transform. While antigen drives clonal selection, intracellular signaling and antigen receptor configuration are also critical. Many B lymphomas express stereotyped, autoreactive antigen receptors with biased IGHV usage and conserved CDR3 motifs, yet how IGHV identity shapes signaling during selection remains unclear. Germline IEI-causing defects often affect signaling nodes recurrently mutated in lymphoma, providing adjustable models of how these changes reshape lymphocyte fitness. We profiled TCR/BCR repertoires across five monogenic IEIs to test for convergent, lymphoma-like immunogenetic signatures.

Design and methods: Bulk VDJ sequencing was performed on blood from HA20, APLAID, DADA2, IKAROS haploinsufficiency and ALPS patients.

Results: BCR repertoires were more perturbed than TCR. ALPS and IKAROS haploinsufficiency showed oligoclonal BCR architectures, while HA20 and especially APLAID exhibited reduced diversity and SHM. APLAID TCRs were hyperdiverse, clonally skewed in ALPS/IKAROS, and contracted in HA20/DADA2. IEIs affecting NF-κB/BCR signaling converged on enrichment of the autoreactive, lymphoma-associated IGHV4-34 BCRs, alongside other lymphoma-linked biases. These coincided with shared CDR3 hydrophobicity/polarity sifts, consistent with attenuated tolerance checkpoints.

Conclusions: Single mutations in BCR/TCR signaling nodes co-select autoreactive, lymphoma-like receptor architectures.

CI05

Systemic inflammatory markers define the biological response to wildfire smoke exposure

H. Babayev[1], B. Zhao[1], C. Zeyneloglu[1], O. Kline[2], P. Westermann[1], C. Messner[1], M. Akdis[1], K. Nadeau[2], C. Akdis[1], I. Ogulur[1]

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Chronic wildfire smoke disrupts respiratory epithelial barriers, but the molecular drivers and their links to allergy remain unclear. We applied a dual-omics approach to define targeted inflammatory mediators and systemic proteomic changes in controls (n = 17) and wildfire-exposed subjects with (n = 25) or without allergies (n = 38). Plasma was analyzed by NULISAseq Inflammation Panel 250 for low-abundance mediators and untargeted LC-MS/MS for global profiling. XGBoost with SHAP identified signatures of exposure and allergic status. Targeted profiling revealed a dominant inflammatory phenotype marked by increased tissue remodeling and metabolic markers. MMP3, MMP8, and MMP9 were significantly elevated, consistent with impaired barrier integrity, together with NAMPT and the pro-inflammatory cytokines IL-1β, IL-18, and IL-36A. In contrast, vascular and neural maintenance markers were reduced. GFAP, the strongest discriminator, was suppressed in exposed subjects, suggesting neuroglial effects, while FLT1 (VEGFR1) downregulation indicated impaired endothelial repair. Although linear modeling of the untargeted proteome was constrained by heterogeneity, machine learning resolved distinct allergic signatures. Asthma, eczema, and food allergy were characterized by IFNW1, CCL1, and FGF19, whereas environmental allergy was associated with IL-4 and PD-L2 (PDCD1LG2). Drug hypersensitivity was predicted by BMP7 and IL-5RA. These findings indicate that wildfire smoke drives systemic metabolic reprogramming, matrix remodeling, and vascular dysregulation beyond airway inflammation.

CI07

Tofacitinib in the Treatment of Cardiac Sarcoidosis: Towards Steroid-Sparing Disease Management

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Introduction and Aim: Cardiac sarcoidosis (CS) is associated with substantial morbidity and mortality. Treatment remains challenging in patients refractory to corticosteroids, conventional immunosuppressants and tumour necrosis factor inhibitors (TNFi). Janus kinase (JAK) inhibition has emerged as a potential therapeutic strategy in sarcoidosis, but data in CS are limited. We evaluated the efficacy and safety of tofacitinib in refractory CS.

Design and Methods: We retrospectively analysed eight patients with refractory or probable CS treated with tofacitinib at the University Hospital Zurich between 2020 and 2024. Treatment response was assessed using serial 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT), left ventricular ejection fraction (LVEF), prednisone dose and serum neopterin levels.

Results: Seven of eight patients (87.5%) achieved inactive or remitting myocardial disease activity on repeat 18F-FDG PET/CT. Mean myocardial SUVmax decreased from 7.96 to 5.06, while cardiac metabolic activity decreased from 397 to 191. LVEF remained stable or improved in all patients. Mean prednisone dose decreased from 5.94 mg/day to 2.5 mg/day. Neopterin levels and extracardiac FDG uptake decreased in most patients. No venous thromboembolic or acute ischaemic cardiac events occurred during follow-up.

Conclusions: Tofacitinib demonstrated promising anti-inflammatory and steroid-sparing effects in therapy-refractory CS and may represent a novel therapeutic option for difficult-to-treat disease.

CI09

Invasive maxillary sinus pseudotumor as a rare manifestation of IgG4-related disease: two case reports

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Introduction: IgG4-related disease (IgG4-RD) is a fibroinflammatory disorder classically described as indolent and non-destructive, with pseudotumoral lesions mimicking malignancy, vasculitis, or infection. Sinonasal involvement is not included in the 2019 European League Against Rheumatism classification criteria. We report two cases highlighting a potentially distinct sinonasal phenotype in IgG4-RD.

Case description: A 34-year-old woman underwent ethmoidectomy for presumed chronic rhinosinusitis. She later developed left maxillary pain and underwent multiple dental procedures for suspected odontogenic infection. PET-CT revealed a hypermetabolic destructive maxillary sinus mass with bone invasion and hard palate perforation. Biopsy confirmed IgG4-RD. A 42-year-old woman presented with recurrent eyelid swelling and chronic rhinosinusitis, progressing to left maxillary pain and cheek swelling. PET-CT showed salivary and lacrimal gland involvement with destructive maxillary sinus lesions. Lacrimal gland and sinonasal biopsies confirmed IgG4-RD. Serum IgG4 was normal in the first patient and elevated (2.4 g/L) in the second. Anti-neutrophil cytoplasmic antibodies were negative in both cases, and pathology review excluded granulomatosis with polyangiitis and malignancy. The first patient received glucocorticoids and rituximab, and the second rituximab alone, both with clinical improvement.

Conclusion: IgG4-RD may rarely present as a locally destructive sinonasal disease. Recognition of this phenotype is important and may support its inclusion in future classification criteria.

CI11

Integrated Barrier and Multi-Omic Analysis Identifies Molecular Signatures of Response to Tralokinumab in Atopic Dermatitis

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Atopic dermatitis (AD) is driven by epithelial barrier dysfunction and type 2 immunity, with IL-13 disrupting epidermal differentiation and barrier integrity. Tralokinumab, an anti–IL-13 antibody, is effective in moderate-to-severe AD, yet response biomarkers are lacking.

Adults with moderate-to-severe AD starting tralokinumab (n = 20) were followed for 8 weeks. SCORAD and electrical impedance spectroscopy (EIS) were measured at weeks 0, 4, 16. Response was defined as ≥50% SCORAD reduction at week 8 (SCORAD-50). Paired biopsies underwent bulk RNA-seq and imaging mass cytometry; serum was profiled by Olink. Analyses included differential expression, immune deconvolution, and Elastic Net regression. SCORAD-50 was achieved by 70% of patients (median reduction 58%); SCORAD and EIS correlated inversely ($\rho = -0.54$, $p = 3.8\times10^{-5}$). RNA-seq showed downregulation of type 2, chemokine, and HDAC-associated programs and upregulation of keratinization and barrier genes. At baseline, responders and non-responders differed in lipid metabolism, epigenetics, and inflammation, with enrichment of myeloid cells ($\rho = 0.62$, $p = 0.01$) and non-classical monocytes ($\rho = 0.61$, $p = 0.01$). Elastic Net identified serum PSIP1 as the top predictor (AUC = 0.87); longitudinal CD28 correlated with SCORAD trajectory ($\rho = -0.61$, $p = 4\times10^{-4}$). Baseline transcriptomic differences in lipid metabolism, epigenetics, and inflammation, together with myeloid enrichment, serum PSIP1, and treatment CD28 dynamics, stratify tralokinumab responders, while IL-13 blockade resolves type 2 inflammation and restores epidermal barrier programs.

TS07

Lack of porcine MHC-I rules over hPD-L1-mediated regulation of human xenogeneic cytotoxic CD8 T cell responses

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Pig-to-human xenotransplantation has progressed from concept to clinics, yet T cell-mediated rejection remains a major barrier to durable graft acceptance despite extensive immunosuppression. We investigated how genetic modifications in porcine aortic endothelial cells (PAEC) shape human $CD8^+$ T cell function. Human PBMC were co-cultured with wild-type ($PAEC_{WT}$), transgenic hPD-L1/hCD47 ($PAEC_{TG.1}$), or $PAEC_{TG.2}$ lacking MHC-I (B2M-KO/hPD-L1). Flow cytometry showed that $PAEC_{WT}$ and $PAEC_{TG.1}$ supported balanced T cell expansion (mean CD4/CD8 ratios 2.1 ± 0.9 and 2.1 ± 1.4), whereas $PAEC_{TG.2}$ impaired $CD8^+$ priming, increasing the ratio (4.5 ± 2.4).

Co-culture with $PAEC_{TG.2}$ reduced differentiation into effector memory subset (11.6 ± 4.5% vs 29.8 ± 13.9% with $PAEC_{WT}$, p = 0.004). Specific lysis was preserved against $PAEC_{TG.1}$ compared to $PAEC_{WT}$ (AUC 325.3 ± 174.4 vs 299.7 ± 215.9) but reduced against $PAEC_{TG.2}$ (AUC 76.2 ± 50.3) to levels of the 3rd party control. hPD-L1 expression selectively inhibited degranulation without reducing granzyme B content, consistent with checkpoint-mediated suppression of TCR/CD28 signalling. PD-L1 blockade partially restored cytotoxicity in bulk cultures but failed to rescue the function of purified $CD8^+$ T cells, highlighting the need for $CD4^+$ help under inhibitory conditions. Donor-dependent variability in memory differentiation and cytotoxicity further emphasized the heterogeneity of human xenogeneic responses. Overall, MHC-I dependent antigen presentation was determined CTL function, while hPD-L1 provided secondary modulation.

POSTER

A04

Prevalence of Shellfish Allergy and Sensitization in Southeast Asia

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Shellfish is one of the "big nine" food allergens, accounting for over 90% of reported food allergy cases globally. This allergen particularly impacts Southeast Asian countries such as Indonesia, the Philippines, and Thailand, which are among the highest seafood consumers worldwide. Accurate and comprehensive data on the prevalence of shellfish allergy and sensitization are essential for effective allergy management and understanding geographic variations in allergic disease burden. This systematic review aims to estimate the prevalence of shellfish allergy and sensitization in both the general and food-allergic populations across Southeast Asia and explore variations by country. A comprehensive search of multiple databases was conducted to identify relevant studies. Eligibility criteria, data extraction procedures, and quality assessment frameworks were predefined to evaluate methodological rigor, including clarity of research questions, study design, sample size, and validity. Data from included studies will be summarized using descriptive and narrative synthesis, and where appropriate, meta-analysis will be conducted to estimate pooled prevalence rates. This review will provide critical insights into the epidemiology of shellfish allergy in Southeast Asia, supporting public health planning and identifying research gaps.

AILD01

Is there a role of antinuclear antibodies in pediatric autoimmune hepatits?

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Background: Diagnostic marker of autoimmune hepatitis (AIH) type 1 are antinuclear antibodies (ANA). We characterized ANA patterns and specific autoantibodies in pediatric AIH (pAIH) patients to identify ANA-associated disease entities that may have therapeutic or prognostic relevance.

Methods: We performed centralized serological analysis of serum samples from the Swiss Autoimmune Liver Disease Cohort Study (AILD). ANA titers and patterns were assessed, and specific autoantibodies were characterized in patients with pAIH onset (age <18 years).

Results: We analyzed 21 samples with previously reported positive ANA titers; in centralized testing 10 samples had titers ≥ 1:80 (positive) and 11 <1:80 (negative). Baseline characteristics including demographics, biochemistry at diagnosis, comorbidities, and treatment, did not differ between patients with positive and negative ANA titers. Likewise, no differences were observed in AILD-associated autoantibodies at diagnosis or at sampling time. A common ANA pattern was AC-4 followed by AC-1, often occurring in combination. The AC-1 pattern was mainly associated with anti-nucleosome and/or -histone autoantibodies, whereas AC-4 positive sera none of the two most common autoantibodies, TROVE-2 (Ro-60) and LA (SS-B), were detected.

Conclusion: Results suggests that ANA-titer, -pattern, and the few confirmed autoantibodies (anti-histone, anti-nucleosome) have no correlation with biochemistry markers and no relevance in therapy decision. Isolated evaluation of ANA titers and patterns in this context may not be clinically conclusive.

AILD02

Identifying the Culprit in Drug-Induced Autoimmune-Like Hepatitis: Tibolone vs. Diclofenac—Insights from Cytokine-Lymphocyte Transformation Testing

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Background: Drug-induced autoimmune-like hepatitis (DI-ALH) mimics idiopathic autoimmune hepatitis but is triggered by specific pharmacological agents. We report a case of severe icteric DI-ALH with tibolone and diclofenac as possible triggers.

Case Presentation: A 62-year-old woman presented with jaundice, marked elevation of transaminases, bilirubin, alkaline phosphatase, and hypergammaglobulinemia, with positivity for ANA, ENA, anti-actin, and anti-dsDNA antibodies. Liver biopsy demonstrated lymphomononuclear portal inflammation without interface hepatitis or increased plasma cells, as well as acute lobular hepatitis with predominant zone 3 involvement, features of acute cholestasis, hepatocellular necrosis, and ballooning degeneration. The patient had received tibolone for 10 years and diclofenac in the months preceding symptom onset.

Methods: To discriminate between suspected agents, a cytokine-based lymphocyte transformation test (Cyto-LTT) was performed, assessing drug-specific T-cell activation by measuring interferon-γ and interleukin-5 release.

Results: Treatment with oral prednisone led to gradual biochemical improvement. Despite withdrawal of both drugs, corticosteroid therapy remains required. Progressive decline in autoantibody titers and IgG levels has been observed. Cyto-LTT results are pending.

Conclusion: This case underscores the diagnostic challenge of DI-ALH with multiple potential offending agents. Cyto-LTT may help identify the responsible drug and avoid hazardous re-exposure.

AILD03

Biochemical–structural discordance in hepatic sarcoidosis: a single-center cohort study

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Background: Monitoring of hepatic sarcoidosis mainly relies on biochemical parameters, although clinical progression despite biochemical improvement has been observed. The role of liver elastography as a longitudinal marker of structural disease evolution remains unclear. We assessed the relationship between biochemical response, liver stiffness, and disease evolution.

Methods: We conducted a retrospective single-center cohort study of patients with hepatic sarcoidosis. Biochemical response was categorized as complete, partial, absent, or worsening. Structural disease evolution was assessed by longitudinal liver elastography measurements. Clinical progression was defined using a composite clinical endpoint.

Results: Twenty-two patients were included with a median follow-up of 9 years (IQR 3.5–14.8). Nineteen patients (86%) achieved a complete or partial biochemical response. Biochemical improvement was generally associated with decreasing liver stiffness, whereas biochemical non-response was associated with increasing liver stiffness. All patients with worsening liver stiffness experienced clinical disease progression, while all patients with improving liver stiffness remained clinically stable. Notably, two patients (9%) showed biochemical improvement despite progressive structural liver disease.

Conclusion: Biochemical response correlates with structural improvement in most patients with hepatic sarcoidosis but does not fully capture disease evolution. Longitudinal liver elastography may add value for disease monitoring and treatment decisions.

AILD04

Multi-center Validation of a Machine learning powered Fibrosis-6 (FIB-6) index for Ruling out advanced fibrosis in Autoimmune hepatitis.

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Introduction and Aim: Fibrosis-6 (FIB-6) is a non-invasive diagnostic index derived from routine laboratory parameters and developed using machine learning with a random forests algorithm to predict hepatic fibrosis stage. It has been validated in chronic liver disease related to hepatitis C, hepatitis B, and metabolic dysfunction-associated fatty liver disease. This study aimed to validate FIB-6 in patients with autoimmune hepatitis (AIH).

Materials and Methods: The performance of FIB-6 was evaluated in 217 patients with confirmed AIH from Egypt (n = 87), Saudi Arabia (n = 52), and Greece (n = 78). Liver biopsy samples were scored by experienced pathologists using the METAVIR system. Results were compared with FIB-4, APRI, and AAR.

Results: FIB-6 showed high sensitivity and negative predictive value (NPV) for excluding advanced fibrosis and cirrhosis, but limited specificity. For cirrhosis, sensitivity, specificity, PPV, and NPV were 91.7%, 22.9%, 31.3%, and 87.8%, respectively. For advanced fibrosis (F3-4), values were 94.6%, 17.0%, 54.4%, and 75.0%, respectively. For significant fibrosis (F2-4), values were 93.5%, 9.4%, 70.6%, and 33.3%, respectively. Compared with FIB-4, APRI, and AAR, FIB-6 achieved the highest sensitivity and NPV for ruling out severe fibrosis and cirrhosis (98.2% and 80.0% vs. 74.8% and 61.1%, 74.8% and 61.6%, and 57.7% and 60.2%, respectively).

Conclusion: FIB-6 is a simple, non-invasive tool with high sensitivity and NPV, making it useful for ruling out advanced fibrosis and cirrhosis in AIH patients. Further validation in larger cohorts is recommended.

AILD05

Discovery of Novel MRGPRX4 Agonists and Antagonists with Implications for Hepatobiliary Pruritus

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Background: MRGPRX4 is a bile acid- and heme metabolite-sensing receptor expressed in peptidergic sensory neurons of dorsal root and trigeminal ganglia. It has emerged as a mediator of hepatobiliary pruritus, a debilitating symptom with limited therapeutic options, yet its pharmacology remains poorly characterized and selective antagonists are lacking.

Methods: Natural product and pharmacological compound libraries were screened for MRGPRX4 ligands using β-arrestin recruitment assays (PathHunter, DiscoverX) at 10 µM. Concentration–response studies determined EC_{50} or IC_{50} values.

Results: Novel agonists included dioscin (EC_{50}: 3.83 µM), echinocystic acid (4.17 µM), sophoraflavanone G (5.93 µM) and18-β-glycyrrhetinic acid (11.2 µM). FXR agonists cilofexor (52.1 µM), tropifexor (19.4 µM) and obeticholic acid (23.1 µM) also activated MRGPRX4. Antagonists included psoralidin (0.608 µM), disulfiram (1.50 µM), flavonol (2.82 µM) and berbamine (IC_{50}: 5.16 µM). Clinically used PPAR agonists also inhibited MRGPRX4, including bezafibrate (79.6 µM), elafibranor (23.2 µM), fenofibrate (2.77 µM) and seladelpar (2.25 µM).

Conclusions: Structurally diverse MRGPRX4 agonists and antagonists were identified. FXR agonist-mediated activation may contribute to hepatobiliary itch, whereas inhibition by PPAR agonists may underlie antipruritic effects and therapeutic repurposing opportunities. These findings support further investigation into MRGPRX4 signalling and targeted antipruritic therapy development in hepatobiliary pruritus.

AILD06

Anti-SLA positivity in the absence of definite autoimmune hepatitis: two cases expanding the spectrum of diagnostic interpretation

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Background: Anti–soluble liver antigen (anti-SLA) antibody is considered highly specific for autoimmune hepatitis (AIH), but its significance outside classical AIH remains uncertain. We report two patients with anti-SLA positivity without clinicopathological evidence of AIH.

Case presentation: A 56-year-old woman with mixed connective tissue disease treated with hydroxychloroquine showed persistent high-titer anti-SLA positivity (70–85 U/mL) and ANA positivity (1:5120), while liver enzymes and IgG remained normal. Transient elastography, abdominal ultrasound, and liver biopsy were unremarkable except for minimal steatosis. According to simplified IAIHG criteria, she did not meet criteria for probable or definite AIH. Liver tests and stiffness remained normal after 2 years. A 75-year-old man with diffuse large B-cell lymphoma complicated by hemophagocytic lymphohistiocytosis developed acute cholestatic liver injury associated with transient anti-SLA and ANA positivity. Liver histology showed cirrhotic remodeling, inflammatory changes, and cholestasis, without characteristic features of AIH or lymphoma infiltrates, although hepatic involvement was suspected given the high PET/CT uptake. Viral hepatitis was excluded. After hematological treatment and resolution of systemic inflammation, anti-SLA became undetectable and cholestasis resolved.

Discussion and Conclusion: Anti-SLA positivity may rarely occur outside classical AIH, either as persistent isolated seropositivity in systemic autoimmunity or as transient positivity during profound immune dysregulation.

AILD07

Early Diagnosis and Favorable Risk Profiles in Swiss Patients with Primary Biliary Cholangitis: A Comparative Analysis Using the GLOBE and UK-PBC Scores

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Background: Primary Biliary Cholangitis (PBC) has a variable natural history. The GLOBE and UK-PBC scores predict liver-related outcomes but regional diagnostic practices may influence disease stage at presentation. We compared clinical characteristics and predicted outcomes of Swiss PBC patients with the original GLOBE (n = 2,488) and UK-PBC (n = 1,916) derivation cohorts, hypothesizing that Swiss patients present at an earlier stage.

Methods: Retrospective analysis of Swiss PBC patients treated with UDCA. Baseline demographics, biochemical markers, and GLOBE/UK-PBC scores after 12 months of UDCA were compared against published derivation cohort data.

Results: In the GLOBE cohort (n = 159), median age was 55.2 (47–64) years; 135 (85%) were female. Swiss patients had lower baseline ALP (1.3 [0.74–2.75] vs. 1.9 [1.2–3.5] × ULN) and higher platelet ratio (1.65 vs. 1.0). After 12 months of UDCA, ALP remained lower (1.2 [0.71–1.90] vs. 1.34 [0.93–2.26] × ULN). The median GLOBE score was 0.44 vs. 0.78–0.86 in the derivation cohort (p 0.05). In the UK-PBC cohort (n = 115), median age was 50.3 (43–59) years; 108 (94%) were female. The UK-PBC 10-year risk of end-stage liver disease was 4.8% vs. 9–15% in the original cohorts.

Conclusion: Swiss PBC patients present at an earlier disease stage with more favorable prognostic profiles than the original international cohorts, suggesting that robust diagnostic pathways may facilitate earlier intervention and improved transplant-free survival.

AILD08

Challenge of accurate diagnosis in rare liver disease: Suspected autoimmune hepatitis in a pediatric survivor of acute lymphoblastic leukemia

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Introduction and Aim: Chronic comorbidities, including hepatopathies, are increasingly recognized in pediatric cancer survivors, but their pathophysiology during long-term follow-up remains incompletely understood. This case highlights the challenges of investigating abnormal liver tests in this population.

Design and Methods: Case report of a 5-year-old boy with persistent mixed liver injury following chemotherapy for common acute lymphoblastic leukemia (c-ALL).

Results: A five-year-old boy with c-ALL was treated according to an ALL BFM 2015–analog protocol. Maintenance therapy included 6-mercaptopurine, methotrexate, and antimicrobial prophylaxis. Following chemotherapy, persistent elevation of transaminases and gamma-glutamyl transferase (GGT) was observed. Extensive diagnostic workup was negative. Drug-induced hepatotoxicity was suspected; however, liver enzyme abnormalities persisted despite discontinuation of hepatotoxic agents. Liver histology revealed mixed steatosis, hepatocellular ballooning, portal inflammatory infiltrates with interface activity, and porto-portal fibrosis. Seronegative autoimmune hepatitis (AIH) was suspected, and treatment with prednisolone followed by azathioprine resulted in progressive normalization of liver enzymes, supporting the diagnosis.

Conclusion: This case underscores the importance of monitoring for hepatic comorbidities in cancer survivors and highlights the challenges of distinguishing chemotherapy-related toxicity from autoimmune hepatitis in pediatric ALL survivors. A multidisciplinary approach is essential in managing this rare condition.

BI01

Analytical performance of a novel, fully automated multiplexed microarray immunoassay for detection of anti-PR3, anti-MPO, and anti-GBM autoantibodies

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Background: Autoantibodies to GBM, MPO and PR3 are key diagnostic markers for anti-GBM disease and ANCA-associated vasculitides (AAV): MPA, GPA and EGPA. Conventional testing

often relies on single-analyte assays, which may delay diagnosis and increase operational burden. We evaluated the analytical performance of a novel, fully automated multiplex microarray immunoassay (MosaiQ AiPlex® VAS, AliveDx, Switzerland) intended for concurrent detection of IgG antibodies to PR3, MPO, and GBM as an aid in the identification of AAV and anti-GBM disease.

Methods: The investigational device was evaluated using de-identified sera, reactive or non-reactive for PR3, MPO, or GBM IgG antibodies. Analytical performance was assessed in comparison with a routine method (ALBIA: addressable laser bead immunoassay) by calculating the positive percent agreement (PPA) and negative percent agreement (NPA).

Results: Excluding equivocal results, PPA was 98.5% (64 of 65 samples, 95% CI: 91.7—100) for anti-GBM, 92.9% (224 of 241 samples, 95% CI: 88.9—95.8) for anti-MPO, and 91% (132 of 145 samples, 95% CI: 85.2—95.1) for anti-PR3. NPA was 97.6% (566 of 580 samples, 95% CI: 96—98.7) for anti-GBM, 97.5% (472 of 484 samples, 95% CI: 95.7—98.7) for anti-MPO, and 94.8% (560 of 591 samples, 95% CI: 92.6—96.4) for anti-PR3.

Conclusion: The investigational multiplexed microarray immunoassay showed high analytical concordance with ALBIA, offering an efficient alternative for the concurrent serologic evaluation of PR3, MPO, and GBM antibodies, supporting its utility in the diagnostic workup of AAV and anti-GBM disease.

BI02

Mechanisms underlying altered gut microbiome: Compositional and metabolic effects of food flavor enhancers

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Background: The gut microbiome is essential for intestinal barrier integrity and immune homeostasis, yet the direct effects of food additives on microbial growth and function remain unclear. We assessed the impact of common additives on human fecal microbiome dynamics under anaerobic conditions.

Methods: Fecal microbiota from healthy donors were cultured with graded concentrations of monosodium glutamate (MSG), maltol, and ethyl maltol. Growth was monitored by OD600 over 48 h. Selected conditions were analyzed by shotgun metagenomics and SP3-based metaproteomics.

Results: MSG did not affect overall growth, whereas maltol and ethyl maltol inhibited growth in a dose-dependent manner within 12h. At the family level, MSG induced selective, sex-specific shifts (↓Oscillospiraceae, ↑Odoribacteraceae in males) without global disruption. Metaproteomics revealed functional reprogramming under MSG, characterized by enhanced glutamate metabolism (↑glutamate dehydrogenase, glutaminase, glutamyl-tRNA synthetase; ↓glutamine synthetase). In contrast, maltol and ethyl maltol caused stronger ecological effects, with high-dose maltol reducing key fermentative families, including Lachnospiraceae and Oscillospiraceae.

Conclusions: Food additives induce selective, compound-specific microbiome responses. MSG drives metabolic adaptation without affecting growth, while maltol-derived compounds exert stronger inhibitory and taxonomic effects, particularly on core fermentative taxa. These findings highlight subtle but functionally relevant microbiome restructuring.

BI04

Inhibition of Sec61 by KZR-834 impairs MHC-I antigen presentation and antiviral immune responses

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The heterotrimeric translocon Sec61 plays a central role in endoplasmic reticulum (ER) function by mediating the translocation of newly synthesized proteins into the ER lumen and facilitating the retrotranslocation 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. Kezar Life Sciences has developed two Sec61 inhibitors, KZR-261 and KZR-834, both of which exhibit broad antitumor activity in vitro and in vivo. In this study, KZR-834 was evaluated for its impact on MHC-I presentation, focusing on its effects on bulk MHC-I surface expression at non-toxic concentrations as well as on the presentation of selected MHC-I peptides. Flow cytometric analysis revealed a concentration-dependent reduction in MHC-I surface expression in MC57 cells. Notably, the effects of KZR-834 extended to other, unrelated surface proteins, indicating a broader disruption of protein surface expression. Consistent with these findings, antigen presentation assays demonstrated diminished presentation of specific MHC-I peptides. To assess the in vivo consequences of Sec61 inhibition on immune function, antiviral immune responses were examined following Lymphocytic Choriomeningitis Virus (LCMV) infection. Treatment with KZR-834 impaired immune cell responses and led to a reduction in LCMV-specific CTLs.

CI01

Clinical presentations, treatments, and outcomes in an international cohort of 35 patients with ZNFX1 deficiency

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ZNFX1 is a zinc-finger helicase that binds viral RNA and triggers a type I interferon response. Pathogenic biallelic *ZNFX1* variants cause ZNFX1 deficiency, an inborn error of immunity (IEI) predisposing to severe viral infections and multisystem inflammation.

We performed a combined retro- and prospective international multicentered study of 35 patients, including 20 previously unreported cases. We identified 14 novel variants. Seventeen different virus species were detected during inflammatory episodes. Most patients experienced severe inflammatory episodes within the first year of life; 15 met the revisited 2004 HLH criteria. Lung involvement was present in 27 patients (77%), neurological involvement in 13 (37%), and renal involvement in 15 (43%). Pulmonary hemorrhage occurred in eight patients. Of 17 deceased patients, 11 died before one year of age. Among survivors, six developed inflammatory manifestations after the age of two. Twenty-seven (80%) patients received immunosuppressive therapy, including glucocorticosteroids (n = 25), IL-1R antagonist (n = 6), and JAK1/2 inhibition (n = 5). Six patients underwent HSCT, of whom four survived (one 12 years post-transplant, three at 1-year follow-up post-HSCT). Other two patients required lung transplantation. ZNFX1 deficiency is characterized by a broad phenotypic spectrum ranging from severe, early-onset HLH to milder, later-onset disease. Targeted therapies and HSCT showed benefit in selected patients. Further studies are needed to define optimal management and long-term outcomes.

CI02

Active osteoarthritis with asthma responding to Tezepelumab: evidence for a shared TSLP-driven pathway?

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Introduction: Immune-mediated diseases are traditionally classified as distinct clinical entities, yet they may share common upstream inflammatory pathways, leading to sometimes unexpected systemic interactions. Thymic stromal lymphopoietin (TSLP) is a key alarmin in type 2 inflammation and increasingly recognized as a systemic immune regulator.

Aim: Based on a clinical case of concomitant asthma and osteoarthritis responding to TSLP blockade, we explore potential mechanistic interactions.

Methods and Design: Case report of a 39-year-old woman with severe uncontrolled asthma and active treatment-refractory inflammatory osteoarthritis. Clinical course, MRI findings and a pain diary were analyzed before and after initiation of the anti-TSLP antibody tezepelumab. Literature review of preclinical and translational evidence explored potential connections.

Results and Conclusion: In our case study, tezepelumab led to rapid asthma control and, with delayed onset, to an unexpected marked improvement of the chronic lumbar pain. Symptom relief was dependent on injection interval and dose. Follow-up MRI showed reduced inflammatory changes. This observation suggests a potential role of TSLP-driven inflammation beyond classical type 2 diseases and supports the concept of shared upstream immune pathways across distinct clinical entities. Epidemiological and genetic association studies support a link between Th2 diseases and osteoarthritis, and experiments in mouse-models suggest a TSLP-driven phenotype in articular pathology. We discuss the available evidence exploring this potential interaction.

CI03

Duodenal Inflammatory Infiltrates and Signs of Gut Barrier Dysfunction in Atopic Dermatitis Patients

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Atopic dermatitis (AD) frequently co-occurs with food allergy (FA), affecting 24% of adult AD patients. While gut barrier dysfunction is linked to FA pathogenesis, direct tissue-level evidence of intestinal involvement in AD remains limited. We investigated duodenal immune remodeling and barrier dysfunction in AD, and whether features differ between AD, FA, and comorbid AD+FA. Duodenal biopsies from 23 adults (healthy controls n = 6; AD n = 5; FA n = 9; AD+FA n = 3) were analyzed by imaging mass cytometry for cellular composition, spatial organization, and intraepithelial lymphocyte density, and by NanoString transcriptomic profiling. All disease groups shared barrier damage, mucosal inflammation, and disturbed antigen presentation: increased epithelial cell spacing, expanded cytotoxic T cells and eosinophils, upregulated epithelial stress markers (XBP1, SOCS3), reduced MHC-II, and disrupted M1 macrophage–DC/NK co-localization. Disease specific patterns emerged: AD showed the highest cytotoxic T cell and M1 macrophage densities with transcriptomic signs of barrier repair (MUC2, MUC4, TFF3, claudins) alongside dampened innate sensing (reduced TLRs, MHC-II). FA exhibited active inflammatory priming (NLRP6 inflammasome, chemokines). AD+FA displayed pronounced type 2-skewed polarization (IL13, CCL2).AD patients exhibit duodenal immune remodeling and epithelial barrier dysfunction, supporting the gut-skin axis concept. Rather than a uniform type 2 driven pathology, each condition shows a distinct mucosal signature.

CI06

Dynamic remodeling of the plasma proteome during cashew oral immunotherapy

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Omalizumab-facilitated multi-allergen oral immunotherapy (OIT) desensitizes patients with multiple food allergies, yet mechanisms of cashew desensitization remain unclear. We investigated targeted and proteomic changes linked to cashew tolerance by comparing pre- and post-OIT samples from 22 desensitized participants in a phase 2 trial. The protocol combined omalizumab (weeks 1-16) with dose-escalation OIT (weeks 8-30). Matched plasma samples at baseline and week 52 were analyzed using targeted 250-plex NULISA and untargeted LC-MS/MS. Data analysis included variance partitioning, paired statistics, and XGBoost with SHAP. Exploratory analysis identified sex as the main driver of variance, requiring stratified analysis. In females, targeted profiling revealed attenuated Th2 in-

flammation, with decreased IL-4, CXCL8, and TGF-β1 and increased IL-36A. Machine learning analysis of untargeted proteomics data identified ENO1 and S100A9 as top predictors of post-treatment. In males, response centered on metabolic regulation and tissue remodeling, with increased FGF19, FGF21, and MMP3. Machine learning analysis of untargeted proteomics data identified AADAT and VASN as top predictors. Males also showed distinct B-cell changes, with reduced CXCL13 and increased TNFSF11 (RANKL). Omalizumab-facilitated OIT induces sexually dimorphic immunomodulation during cashew desensitization. Females display classical inflammation suppression, whereas males undergo metabolic and structural remodeling. Dual-proteomics identified sex-specific biomarkers supporting sex-stratified monitoring strategies.

CI08

When Inflammation Knows When to Stop: Finkelstein–Seidlmayer Vasculitis as a Model of Immune Resolution

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Introduction. Finkelstein–Seidlmayer vasculitis (acute hemorrhagic edema) presents with a distinctive phenotype of purpura and edema in a well-appearing child. Its features and pathogenesis remain poorly characterized.

Methods. To further elucidate this condition, our Italo-Swiss Acute Hemorrhagic Edema Study Group compiled a database of all 599 published cases since 1913 and performed a detailed analysis.

Results. Our studies (available on request) characterized the condition as follows: it typically affects children aged 4 weeks to 24 months and presents with abrupt-onset annular or nummular purpura and inflammatory edema. It is frequently preceded by a benign infection or vaccination, remains skin-limited in 90% of cases, and resolves spontaneously within three weeks without recurrences. Autoimmune markers (ANA, ANCA, rheumatoid factor, complement C3 and C4) are generally negative. Histology shows leukocytoclastic vasculitis, with absence of IgA deposition in most cases.

Discussion Finkelstein–Seidlmayer vasculitis represents a model of self-limited small-vessel vasculitis, likely driven by transient immune complex–associated inflammation with predominant innate immune activation, without evidence of persistent adaptive autoimmunity. The absence of recurrence and serological abnormalities suggests a tightly regulated inflammatory response with intrinsic termination mechanisms. This condition provides a unique human model to investigate pathways of immune resolution, with potential implications for understanding and modulating chronic inflammatory and vasculitic diseases.

CI10

Upadacitinib for central nervous system involvement in multisystem sarcoidosis: a novel therapeutic approach

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Introduction and aim: Central nervous system (CNS) involvement in systemic sarcoidosis is uncommon but associated with significant morbidity and therapeutic challenges. Treatment mainly relies on corticosteroids and immunosuppressive agents or biologics, while targeted therapies remain limited. Dysregulation of the JAK–STAT pathway has been implicated in sarcoidosis, supporting a rationale for JAK inhibition in refractory disease. The aim of this report was to evaluate JAK inhibition in multisystem sarcoidosis with CNS involvement.

Methods: We report a 51-year-old woman with multisystem sarcoidosis involving the lungs, lymph nodes, and CNS. Neurological features included central vertigo, gaze-evoked nystagmus, and gait ataxia. Work-up included brain and spinal MRI, whole-body PET/CT, pulmonary function tests, and clinical evaluation. After an initial course of high-dose corticosteroids, upadacitinib was initiated. Clinical, radiological, and laboratory data were collected.

Results: During treatment with upadacitinib 30 mg/day, MRI showed stable supra- and infratentorial white matter lesions without enhancement or signs of inflammation. After 13.4 months, partial regression of a thoracic spinal cord lesion was observed, with no new CNS lesions. PET/CT showed complete metabolic regression of pulmonary and lymph nodal disease. Neurological symptoms remained stable, and pulmonary function was preserved.

Conclusions: JAK inhibition may be a promising option in multisystem sarcoidosis with CNS involvement. Further studies are needed to confirm its efficacy and safety.

TS02

Peripheral tolerance limits antitumor immunity without reshaping the T-cell repertoire

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Introduction and aims: Central and peripheral immune tolerance limit autoimmunity mediated by self-reactive T cells, but tolerance to tumor-associated self-antigens can also constrain the efficacy of immunotherapies like cancer vaccines. Here, we investigated the antigen-specific T-cell receptor (TCR) repertoire in mice who do and do not exhibit immune tolerance to the melanoma-associated antigen tyrosinase-related protein 2 (TRP2), both before and after immunization.

Design and methods: Using TRP2 knockout mice and heterozygous littermate controls, we investigated the same antigen as both a tumor-specific and a tumor-associated antigen.

Results: While the TCR repertoires in untreated mice were comparably diverse, immunization induced markedly greater expansion of TRP2-specific T cells, including the dominant clone, when TRP2 functioned as a tumor-specific antigen. TRP2-deficient mice also completely rejected established B16F10 melanomas after therapeutic vaccination and displayed a significantly larger population of stem-like tumor-infiltrating T cells.

Conclusions: These findings demonstrate that peripheral T-cell tolerance is sufficient to prevent melanoma rejection after vaccination, despite minimal effects on overall TCR repertoire composition. Modulating the interplay between peripheral tolerance and antitumor immune responses may therefore increase the efficacy of cancer vaccines targeting self-antigens.

TS03

OX40/OX40L as a Driver of Chronicity in Atopic Dermatitis

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Introduction/Aim of the Study: Atopic dermatitis (AD) chronicity is sustained not only by effector cytokines, but also by co-stimulatory pathways that maintain T-cell activation and memory. The OX40/OX40L axis has emerged as a relevant

contributor to these processes in AD [1-3]. We reviewed its role in AD pathogenesis and the rationale for therapeutic blockade.

Design and Methods: A narrative review of recent preclinical and clinical literature on the OX40/OX40L axis in AD was performed, focusing on immunopathogenesis and therapeutic relevance.

Results: OX40/OX40L signaling is upregulated in AD lesional skin and may contribute to disease chronicity through interconnected mechanisms [1-3]. TSLP released by damaged keratinocytes induces OX40L expression on dendritic cells, promoting OX40-dependent T-cell priming and Th2 polarization [4,5]. This interaction activates NF-κB and PI3K-AKT signaling, supporting the persistence of multiple inflammatory T-cell subsets, including Th2, Th1, Th17, and Th22 [3,6]. OX40 signaling also impairs Treg function by reducing IL-10 production [1,7] and promotes the survival of activated T cells through upregulation of anti-apoptotic molecules such as Bcl-2 and Bcl-xL [3,8]. These findings help explain persistent inflammation and recurrent flares in AD. Early clinical data support this pathway as a therapeutic target.

Conclusions: The OX40/OX40L axis links innate immune activation, Th2 polarization, impaired immune regulation, and memory persistence in AD. This supports the biologic relevance of the pathway in chronic and relapsing AD.

TS04

Immunomodulation of human PBMCs by peptide amphiphiles

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Peptide amphiphiles (PAs) are supramolecular biomaterials that self-assemble into nanofibrous networks resembling natural matrix components and can modulate the immune microenvironment during tissue repair. We investigated the immunomodulatory properties of a glutamic acid-based PA (PA-E3) and 2 variants, TGF-β1-binding PA-T3 and BMP-2-binding PA-B3. Hydrogels were exposed to peripheral blood mononuclear cells (PBMCs). After 48 hours, PBMC viability and spontaneous proliferation were evaluated together with anti-CD3 and anti-CD28 mAb-stimulated proliferation of $CD4^+$ T cells, $CD8^+$ T cells, and $CD19^+$ B cells. Mechanistic insights were obtained by RNA-seq. Both functionalized PAs were biocompatible, with viability and spontaneous proliferation statistically indistinguishable from PA-E3. PA-E3, PA-T3, and PA-B3 induced comparable suppression in stimulated PBMCs, indicating that this reflects a shared property of the scaffold and that PA-T3 and PA-B3 do not confer additional immunosuppressive activity. Transcriptomic profiling showed that PA-B3 induced minimal transcriptional alterations, with 47 differentially expressed genes, whereas PA-T3 elicited a broader response involving 366 genes. Pathway enrichment indicated that PA-T3 modulates chemotaxis, leukocyte migration, angiogenesis, inflammatory response regulation, fibrinolysis, extrinsic apoptotic signaling, cell-cell adhesion, leukocyte proliferation, and ossification. These findings highlight the selective immune-regulatory potential of PA-T3 and support epitope-specific PAs as immune-instructive scaffolds for bone repair.

TS06

Expression of Human CD47 in a Novel Transgenic Pig Protects Porcine Endothelial Cells Partially from Human NK Cytotoxicity

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Natural killer (NK) cells are pivotal in xenograft rejection, targeting porcine endothelial cells. CD47 acts as a "don't eat me" signal by binding to signal regulatory protein alpha (SIRPα), thereby suppressing immune activation. While this axis has been well characterized in macrophages, its influence on NK cell-mediated xenograft rejection is less understood. We investigated whether expression of human CD47 (hCD47) on porcine aortic endothelial cells (PAECs) from transgenic pigs inhibits human NK activity. Using static cultures and microfluidic systems to simulate physiological conditions, we found that hCD47 expression on PAECs significantly impaired direct NK cytotoxicity. Under flow, NK cell migration[GP1] across hCD47-expressing PAECs was significantly reduced compared with WT PAECs. However, when heat-inactivated human plasma (containing anti-pig non-αGal antibodies) was added, hCD47 expression did not protect αGal-knockout PAECs from NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC). Single-cell RNA sequencing overall homogeneous NK subtype distribution between WT and hCD47-expressing PAEC conditions. However, a small set of differentially expressed genes showed increased inhibitory receptor expression and reduced effector, activation, and proliferation signatures in NK cells exposed to hCD47. These findings identify hCD47 as an effective checkpoint against direct NK cytotoxicity, but insufficient to prevent ADCC, underscoring the need for combinatorial strategies to achieve durable protection from NK-driven xenograft rejection.

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