1st EU-RESOLVE Conference & Training School

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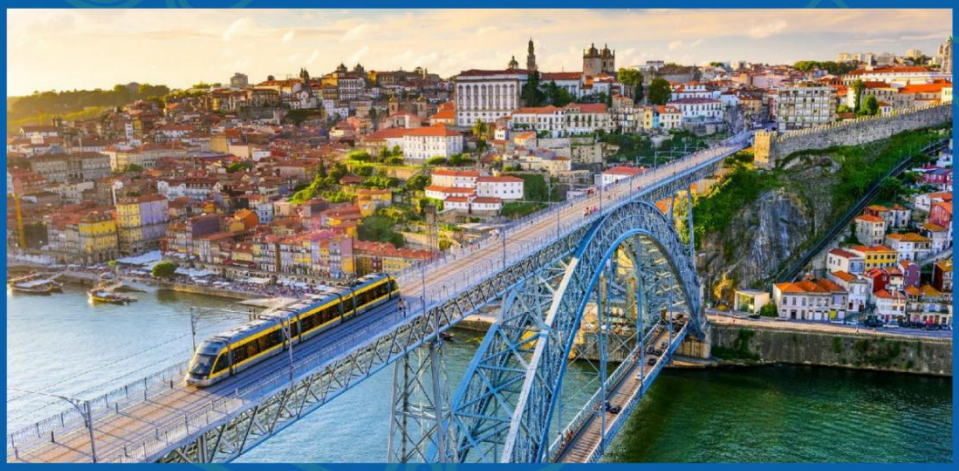

BOOK OF ABSTRACTS

EU-RESOLVE

From inflammation to resolution

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EU-RESOLVE RESOLUTION BIOLOGY NETWORK

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Keynote Talk

Resolvins and Novel Pro-Resolving Mediators lessons from the Acute Inflammatory Response

Charles Nicholas Serhan

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This Keynote lecture will first review the importance of a well-integrated inflammatory response in maintaining health and overall resilience in humans. By studying self-limited infectious and sterile inflammation in animal models, the author and collaborators uncovered novel lipid derived mediators that I've termed the resolvins, protectins, maresins. Collectively known today as the specialized pro-resolving mediators (SPM) superfamily because each molecule isolated proved to activate endogenous resolution of inflammation pathways in a wide range of animal inflammatory disease models. Each of these structural distinct families of local mediators are confirmed via total organic synthesis. SPM control the duration and magnitude of inflammation in animal disease models and stimulate novel resolution programs at the cellular level that clear inflammation. The mapping of these resolution circuits and pathways provide entirely new avenues for appreciating the cellular and molecular basis of many widely occurring diseases characterized by excessive inflammation. This keynote presentation will give a high-level overview on recent advances from our studies on 3 newly identified resolvins and SPM biosynthesis with focus on the critical role of transient allylic epoxide intermediates and novel recently elucidated resolvin structures and functions. These new mediators, their synthetic mimetics and pathways to be presented in this EU-Resolve conference add to the foundations of resolution physiology and serve as the basis for novel directions and potential therapies to evoke Resolution Medicine.

Clinical Translation of Resolution Biology

1

Advancing Pro-Resolving Therapies in Psoriasis: From Biological Insight to a New Therapeutic Paradigm

Runhild Gammelsaeter

Medical Director, Arctic Bioscience, Oslo, Norway

The recognition that resolution of inflammation is an active, regulated biological process is reshaping how we think about therapy in immune-mediated diseases. Specialized pro-resolving mediators (SPMs) sit at the centre of this paradigm shift, offering the possibility not simply to suppress inflammation, but to restore physiological balance. Emerging data from marine phospholipid systems, including herring roe–derived lipids, illustrate how modulation of endogenous resolution pathways can be harnessed in a translational context. In relevant human cell systems modelling psoriasis, these phospholipids have been shown to enhance biosynthesis of multiple SPM families, supporting a pro-resolving cellular environment. The central challenge for using such pre-clinical data in a drug development program is not so much the biology itself, but its translation into clinically viable therapies. From a biotech perspective, advancing pro-resolving therapies requires navigating a series of interconnected hurdles: defining robust and reproducible biomarker strategies in a field lacking standardisation; aligning novel mechanisms of action with evolving regulatory frameworks; and designing clinical studies that capture meaningful disease modification. These challenges are further compounded by the inherent complexity of lipid-based therapeutics, including manufacturing consistency, scalability, and demonstration of clear clinical differentiation in a competitive treatment landscape. For early-career researchers, this evolving field presents both an opportunity and a responsibility to bridge discovery science with clinical reality. Progress will depend on interdisciplinary thinking, where mechanistic insight is integrated early with assay development, clinical design, regulatory strategy, and commercial feasibility.
Take-home message: The future of pro-resolving therapies will be shaped not only by the strength of the biology, but by our ability to translate complex mechanisms into scalable, regulated, and clinically meaningful treatments.

2

Dual clinical development strategy for resomelagon (AP1189), a biased melanocortin receptor agonist, in inflammatory diseases and as host-directed therapy in viral infections

Thomas Jonassen

University of Copenhagen, Copenhagen, Denmark

Resolution Biology in the Clinic

1

Rethinking cardiovascular prevention from antiinflammation to proresolution

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Inflammation plays a central role in cardiovascular disease, and its balance with timely resolution determines whether an immune response remains protective or becomes pathological for the cardiovascular system. When appropriately controlled, cardiovascular inflammation may be protective, whereas when unresolved, downstream signalling becomes pathophysiological drivers. Inflammation is now recognized as a unifying feature across major cardiovascular diseases, including atherosclerosis, myocardial infarction, heart failure, and valvular heart disease. Anti-inflammatory cardiovascular treatment options are emerging but may carry risks of immunosuppression and increased susceptibility to infection. Proresolving mediators, such as bioactive lipid-derived signals, actively promote termination of cardiovascular inflammation while preserving immunocompetence. Beyond their immunomodulatory roles, emerging evidence highlights direct effects of proresolving mediators on cardiovascular function. These findings challenge the conventional paradigm of broadly suppressing inflammation in cardiovascular prevention. Anti-inflammatory therapeutic pathways may not only induce immunosuppression but also prevent inflammation-induced protective cardiovascular adaptation. Proresolution offers a novel and clinically translatable therapeutic frontier in cardiology as an alternative to the emerging 12nti-inflammatory cardiovascular treatments.

2

The clinicians' perspective on the role of dysregulated resolution programmes in chronic diseases

Andreas Ramming

Friedrich Alexander University Erlangen-Nuremberg and Universitatsklinikum Erlangen, Erlangen, Germany

Chronic inflammatory diseases have long been interpreted as perpetual immune activation with inflammation continuing until pro-inflammatory signals are suppressed. This view neglected the active, orchestrated nature of resolution; we now recognize that returning to homeostasis requires engagement of dedicated resolving programmes that operate in balance with inflammatory pathways. Anti-inflammatory signalling is only a small, situational part of a broader equilibrium that includes tissue responses and a spectrum of resolving processes, revealing new therapeutic targets and a shift in diagnostic and prognostic thinking. Clinically, we distinguish primary from secondary loss of efficacy, acknowledging distinct mechanisms that drive initial non-response and waning response over time, which informs timely treatment changes. Importantly, tissue itself is an active participant: the microenvironment shapes inflammation, repair, and resolution beyond immune cells alone. Advances in spatial architecture reveal patchy, organ-level patterns where inflammatory and resolving niches coexist and compete, producing a dynamic battlefield that influences disease localization and progression. Onset of inflammation is further shaped by tissue memory, affecting trajectory and reversibility. These insights demand a move beyond single-pathway interventions toward strategies that account for disease duration, niche architecture, and the balance of inflammatory and resolving programmes to optimize clinical outcomes.

Oral Presentations

Session 1 - Receptors, Signalling & Drug Discovery

OP1

The Bist of Burden: Harnessing biased STING agonists to enhance the resolution of inflammation and limit tissue fibrosis

Amiram Ariel, Nofar Ben Jashar, Shahar Levy, Anat Ablin, Sagie Schiff-Zuck Uzma Saqib
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Stimulator of IFN Genes (STING) is a cytosolic DNA sensor that plays a central role in host protection against pathogens upon binding DNA-derived ligands. STING primarily controls the transcription of type I interferons (IFNs) and pro-inflammatory cytokines. Notably, STING can be tuned pharmacologically to mitigate human immune pathologies. DMXAA is a pharmacological activator of murine STING that induces IFN-β and its affected genes. Here, we report that macrophages from DMXAA-treated mice engulfed significantly higher numbers of apoptotic cells ex vivo, and exhibited enhanced reprogramming reflected by an increased IL-10 and reduced inflammatory cytokine secretion upon LPS exposure. Macrophage reprogramming was significantly hampered in STING and IFN-β -deficient macrophages. Furthermore, we used virtual docking and batch screening to identify biased STING agonists (BiSTs) that enhanced IL-10 and IFN-β production by splenocytes while inhibiting TNFα. One of these compounds, termed BiST 2.1, also induced the murine STING pathway in vivo and in human macrophages. Finally, we found BiST 2.1 to enhance wound repair by mouse embryonic fibroblasts and promote the resolution of liver fibrosis induced by CCl4. Thus, our findings indicate that STING can be harnessed to drive IFN-β-mediated IL-10 secretion by resolution phase macrophages and consequently shape macrophage and fibroblast function to enhance the resolution of inflammation and treat fibrotic disorders.

OP2

Regulation of pro-resolving lipid mediators by the H_2S–FPR2 axis in vascular inflammation

Ludovica Lela[1], Flavia Carriero[1], Giuseppe Terrazzano[1], Luigi Milella[1], Jesmond Dalli[2], Vincenzo Brancaleone[1]
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Background: Specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, protectins and maresins, activate G-protein-coupled receptors such as formyl peptide receptor-2 (FPR2/ALX), promoting inflammation resolution and vascular homeostasis. The FPR2/annexin A1 (AnxA1) pathway represents a major pro-resolving signaling axis and a pharmacological target. Hydrogen sulfide (H_2S), generated by cystathionine-γ-lyase (CSE), exerts vasculoprotective and anti-inflammatory effects, but its interaction with pro-resolving signaling remains unclear. This study investigated how H2S modulates FPR2/AnxA1 pathway in vascular and immune cells and its impact on endothelial function and lipid mediator biosynthesis during inflammation.
Methods: BAECs were exposed to TNF-α (10 ng/mL, 6 h) and treated with Ac2-26 (0.1–1 μM, FPR2 agonist) or AP123 (1–10 nM, H_2S donor). Expression of CSE, endothelial nitric oxide synthase (eNOS), AnxA1, FPR2, and intracellular H_2S levels was assessed. In vivo, C57BL/6 mice received TNF-α (500 ng/mouse, 6 h) alone or combined with Ac2-26 (30 μg/mouse) or AP123 (10 μg/mouse) and vascular reactivity and SPMs generation were measured. In parallel, LPS-stimulated M1 macrophages were treated with the CSE inhibitor D,L-propargylglycine (PAG, 10 mM) and AP123 (1 nM–1 μM) to analyze SPM production.
Results: TNF-α downregulated AnxA1, eNOS, FPR2, and CSE expression in endothelial cells decreasing nitric oxide and H_2S availability. Activation of FPR2 with Ac2-26 or AP123 supplementation restored these pathways. In vivo, TNF-α induced endothelial dysfunction, which was prevented by Ac2-26 and AP123. In plasma, SPMs, including RvD2n-3DPA, were upregulated by AP123. Similarly, in macrophages, AP123 increased RvD2n-3DPA, while CSE inhibition reduced SPM generation.
Conclusions: Pharmacological modulation of the H_2S pathway regulates FPR2/AnxA1 pro-resolving signaling and preserves endothelial function during inflammation. The H_2S–FPR2 axis may represent a potential therapeutic target in vascular inflammatory disorders.

OP3

Interaction between the Annexin A1 mimetic peptide RTP-026 and prostanoid signalling in the regulation of human coronary vascular tone

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Introduction: AnnexinA1 (ANXA1) is a glucocorticoid-regulated pro-resolving protein acting through formyl peptide receptor (FPR)2 and protecting against cardiovascular injury. RTP-026, a stable mimetic, is currently in phase-IIa clinical evaluation in ST-Elevation Myocardial Infarction patients. Coronary artery disease (CAD) is a cause of heart dysfunction and characterized by chronic inflammation with increased vasoconstrictors [Prostaglandin (PG)E2 and serotonin (5-HT)] levels. While several studies have focused on the pro-resolving actions of ANXA1 and mimetics, their vascular effects remain to be fully explored.

Aim: Investigate effects of ANXA1 and RTP-026 in human coronary artery (HCA) muscular tone and explore underlying mechanisms.

Methods: HCA from explanted hearts (n=23) were studied in organ baths. Direct effects were assessed on PGE2 (0.1 μM)-precontracted rings by cumulative concentrations of ANXA1 or RTP-026 (0.1 nM-1 μM). Short-(1h) and long-term (18 h) incubations with ANXA1 or RTP-026 (1 μM) were followed by concentration-response curves (CRC) to PGE2, 5-HT, ONO-248 (EP3 receptor agonist) or PGI2 analogues (iloprost, treprostinil). Pharmacological tools [WRW4 (FPR2 antagonist), L-NOARG (NOS inhibitor)] were added 30 min before CRC. Protein expression (EP3, IP, TP, PGIS) and prostanoid release (6-ketoPGF1α, PGE2) were quantified by Western blot and ELISA, respectively.

Results: RTP-026 and/or ANXA1 (≤1h) significantly reduced PGE2, ONO-248 and 5-HT induced contractions. RTP-026 effects were abolished by WRW4 and L-NOARG.

Similarly, after 18h incubation, RTP-026 and ANXA1 reduced contractions to 5-HT and PGE2. RTP-026 significantly increased PGIS expression, which positively correlated with 6-ketoPGF1α release ($r=0.88$, $p=0.03$). IP protein expression was also upregulated, leading to enhanced relaxations to Iloprost and Treprostinil. While EP3 and TP protein expression showed non-significant upward trends, PGE2-level was reduced.

Conclusion: RTP-026 (more potently than ANXA1) reduces HCA muscular tone through a dual mechanism: an early FPR2/NO/EP3 functional antagonism followed by a modulation of protein-expression resulting in an increased PGI2/PGE2-pathway ratio, suggesting therapeutic potential in CAD.

OP4

Macrophage-Derived PROS1 and GAS6 have Distinct Functions in Resolving Inflammation, dictating lung metastatic permissiveness

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Resolving inflammation is a strictly regulated process essential for tissue homeostasis, primarily governed in macrophages by MERTK - a member of the TAM (TYRO3, AXL, MERTK) receptor family. Although its ligands, PROS1 and GAS6 are structurally homologous, their specific roles in restricting inflammation at steady state and in disease remain unclear. Using myeloid-specific Pros1-cKO and Gas6-KO mouse models, we examined their functions in modulating lung inflammation and consequential metastatic susceptibility.
Deleting either Pros1 or Gas6 revealed a striking divergence in baseline lung inflammation. Loss of myeloid PROS1 triggers a significant infiltration of interstitial macrophages (IMs) into the lungs, accompanied by a "frustrated resolution" signature characterized by elevated TNFa and IL10. This pro-inflammatory landscape in Pros1-cKO lungs was associated with increased lung metastasis following Lewis Lung Carcinoma (LLC) challenge. In contrast, GAS6 deficiency reduced primary tumor growth and metastasis, with a slight decrease in IM lung infiltration and minimal change in inflammatory cytokines.
Mechanistically, PROS1-deficient bone marrow-derived macrophages (BMDMs) expressed elevated TNFa and IL6, unlike GAS6-deficient cells. Additionally, while neither ligand was required for macrophage polarization into either pro or anti-inflammatory phenotypes, Pros1 was upregulated in pro-resolving (M2-like) macrophages whereas pro-inflammatory (M1-like) BMDMs upregulated Gas6 expression.
In line with their divergent inflammatory secretome, conditioned media (CM) from PROS1-deficient BMDMs induced the p-AKT and p-ERK pro-tumorigenic pathways in LLC cells, supporting in-vivo lung metastasis. By contrast, p-AKT and p-ERK levels were slightly reduced by CM from GAS6-deficient BMDMs, which manifested with lower metastasis in-vivo.
Taken together, these results demonstrate that PROS1 actively functions to mitigate inflammation at steady state. Moreover, PROS1 and GAS6 play non-redundant, state-specific roles: PROS1 acts as a key regulator required for inflammation resolution, whereas GAS6 may directly support tumor progression. Restoring PROS1-driven "resolution checkpoint" represents a promising therapeutic strategy for stabilizing the metastatic niche.

This project is funded by the Israel Science Foundation (ISF).

OP5

Deciphering the Mode of Action of Plant-Based Multicomponent Drugs in Inflammation Resolution Using Network Pharmacology

Shailendra Gupta[1], Suman Muralidharan[1], Vaishnavi S.Velega[1], Paulina Christen[1], Matti van Welzen[1], Konstantin Cesnulevicius[2], David Lescheid[2], Myron Schultz[2], Olaf Wolkenhauer[1]
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Introduction: Understanding how complex plant-based multicomponent drugs modulate inflammation-resolution pathways remains a major challenge, particularly because such formulations contain hundreds of bioactive compounds acting across interconnected molecular networks. Inflammation resolution is an active process regulated by specialized pro-resolving lipid mediators (SPMs), their biosynthetic enzymes, and downstream signaling pathways. Network pharmacology and disease-map approaches offer an opportunity to investigate how multicomponent drugs shift inflammatory systems toward resolution.
Methods: We used the Atlas of Inflammation Resolution (AIR) and related disease-map analysis workflows as a network pharmacology platform to investigate the mode of action of natural multicomponent formulations, including Tr14 and plant-based preparations relevant to metabolic dysfunction-associated steatotic liver disease (MASLD). Drug–protein interactomes were assembled by mining natural product and drug-target databases, complemented by untargeted mass spectrometry and pharmacophore-based virtual screening. The resulting bioactive compounds and their predicted targets were mapped onto large-scale molecular interaction maps. Previously established network-inference algorithms were then used to simulate signal propagation across the maps and infer downstream effects on resolution-associated phenotypes.
Results: The analyses indicate that multicomponent natural formulations modulate inflammation-resolution networks through distributed interactions rather than single-target effects. Across AIR and MASLD disease maps, many bioactive compounds converged on lipid metabolic enzymes and regulatory modules associated with the switch from pro-inflammatory mediators to SPM-related signaling. In the Tr14 case study, network perturbation suggested that specific compounds, including sitosterol and umuhengerin, have the capacity to shift the inflammatory landscape toward resolution by targeting multiple regulators simultaneously. In the plant-based MASLD study, more than 350 unique compounds were identified, with potential biological targets assigned to around 300 compounds. Mapping these interactions onto the MASLD map suggested phenotypic effects consistent with inflammation resolution, including increased M2 macrophage behavior and apoptotic process, alongside modulation of metabolic and immune pathways.
Conclusion: Our results demonstrate that disease maps combined with network pharmacology provide a powerful framework to decipher the mode of action of plant-based multicomponent drugs. This approach highlights how bioactive compounds can cooperate with endogenous SPM-associated pathways to promote inflammation resolution and supports the development of mechanism-guided biomarker discovery and therapeutic stratification.

OP6

Targeting FPR2 Signaling: A New Frontier in Treating Inflammatory Arthritis-Associated Cardiomyopathy

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Introduction:Rheumatoid arthritis (RA) patients have twice the risk of cardiovascular disease, including heart failure, particularly heart failure with preserved ejection fraction marked by diastolic dysfunction. The causes of diastolic dysfunction in RA remain unclear, and current treatments offer limited cardioprotection.
Aims: This study is to advance our understanding of mechanisms and support the development of novel therapies targeting FPR2 receptor, ultimately improving survival and quality of life for patients with this serious complication.
Methods: To address the clinical gap in RA-related diastolic dysfunction, we characterised the K/BxN F1 mouse model, which develops diastolic dysfunction ~4 weeks post-arthritis onset. Focusing on the annexin A1 (AnxA1)/FPR2 pro-resolving pathway, we found echocardiographic changes correlated with immune infiltration and fibroblast proliferation. Daily hrAnxA1 (1 μg, s.c.) halted or reversed dysfunction, linked to reduced fibroblast activation and M2-like macrophage polarisation. K/BxN F1 mice also showed increased lung wet-to-dry weight ratios, indicating heart-failure-associated pulmonary edema. To address heart and lung dysfunction in inflammatory arthritis, we then developed a novel model: arthritic mice on a high-homocysteine diet, exhibiting both cardiac and lung dysfunction. Two small molecules were tested, BMS986235 (FPR2-selective) and Compound 43 (dual FPR1/2 agonist), given daily from week 4 (3 mg/kg and 10 mg/kg orally, respectively).
Results: Treatment of mice with BMS986235 prevented diastolic dysfunction and restored lung compliance. These tissue-specific effects were secondary to reduced neutrophil infiltration, modulation of fibroblast (heart) as well as attenuation of monocytes/macrophages (lung) numbers and activation. In contrast, Compound 43 failed to prevent lung compliance loss and promoted inflammatory monocyte and pro-fibrotic macrophage accumulation in the lung, downstream FPR1-mediated CCL2-dependent monocyte chemotaxis and activation.
Discussion: This study suggests that application of selective FPR2 agonists adds value to non-selective FPR agonist for the development of effective therapies to mitigate two life-changing comorbidities of inflammatory arthritis.

OP7

Ureidopropanamide-based Formyl Peptide Receptor 2 (FPR2) agonists: from hit identification to biased signalling

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Formyl Peptide Receptor 2 (FPR2) is a G protein-coupled receptor (GPCR) and belongs to the Formyl Peptide Receptor (FPR) family. FPR2 is a key player in the resolution of inflammation, as it mediates the physiological effects of Lipoxin A4 and Resolvin D1. Over the last decade, we have developed several ureidopropanamide-based FPR2 agonists, exemplified by MR-39 and CMC-23, which exhibit a drug-like profile. These FPR2 agonists showed anti-inflammatory and pro-resolving properties in in vitro models of neuroinflammation. Moreover, they were able to improve neuroinflammation in animal models of Central Nervous System disorders, including Alzheimer's Disease, autism spectrum disorder, and depression.In this contribution, we will illustrate how we discovered this group of agonists, and we manipulated their ureidopropanamide scaffold to obtain drug-like FPR2 agonists. Moreover, we have begun studying the ability of our FPR2 agonists to induce biased receptor activation because FPR2 is a highly promiscuous receptor that produces diverse downstream effects in a ligand-dependent manner. To this end, we selected a set of structurally related ureidopropanamide-based FPR2 agonists and assessed their functional activity in Ca2+ mobilization, cAMP inhibition, and β-arrestin recruitmenthe selected agonists showed distinct bias profiles depending on the presence of specific structural features. Preliminary molecular docking and molecular dynamics simulations further support the feasibility of rationally designing biased FPR2 agonists.

Session 2 - Cardiovascular, Metabolic & Gastrointestinal Diseases

OP8

Resolvin e1 and chemerin receptor 1 in human acute heart failure and cardiogenic shock with and without mechanical circulatory support

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Introduction: Resolvin E1 (RvE1) exerts cardioprotective effects via the chemerin receptor 1 (Chemerin1), yet its role in human acute heart failure (AHF) and cardiogenic shock (CS) remains unclear. We evaluated RvE1 and its receptor Chemerin1 in patients with AHF and CS, including those on veno-arterial extracorporeal membrane oxygenation (VA-ECMO), and explored their correlation with inflammatory, endothelial, pro-oxidant, and clinical markers/parameters.

Methods: This ethics-approved study prospectively included AHF (n=23) and CS (n=25) patients. Blood was collected at days 1–2, 3–4, and 5–8 in patients, and at a single time point in controls (n=22). Inflammatory, pro-resolving, endothelial, and pro-oxidant markers were measured by multiplex immunoassays (IL-1β; IL-6; TNF-α; VCAM-1; E-Selectin) or ELISA (IL-10; RvE1; nitrotyrosine; MPO). Chemerin1 expression in peripheral blood mononuclear cells was assessed by RT-qPCR. Cardiac markers (hsTnI, BNP), and CRP were measured by automated methods. Clinical data, prognostic scores, and outcomes were recorded.

Results: RvE1 increased with AHF severity ($p=0.004$ for linear trend), being higher in CS ($p=0.005$ vs controls) and showing no temporal or survival-related changes. Among CS patients, those on VA-ECMO had significantly higher RvE1 at days 5–8, alongside increased MPO and neutrophil count. Chemerin1 expression was lower in AHF ($p<0.001$) and CS ($p<0.05$) vs controls, without temporal, VA-ECMO or survival-related differences.

In AHF, RvE1 inversely correlated with blood pressure, and positively correlated with IL-10, IL-6, TNF-α, CRP, neutrophil-to-lymphocyte ratio, VCAM-1, MPO, and ICU/hospital length of stay. In CS, RvE1 positively correlated with CRP, E-Selectin, MPO, and nitrotyrosine.

Chemerin1 expression inversely correlated with cardiac markers and prognostic scores, and positively correlated with pulmonary function, exclusively in AHF.

Conclusions: RvE1 increases with haemodynamic impairment, inflammatory burden, and VA-ECMO, suggesting a compensatory response. The association of Chemerin1 with better outcomes only in AHF patients points to a failure of the RvE1–Chemerin1 axis in CS.

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OP9

Lipid-Associated Macrophages in Murine Metabolic Dysfunction-Associated Steatohepatitis and Associated Fibrosis

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Introduction: Metabolic dysfunction-associated steatotic liver disease is a continuum of liver pathologies ranging from steatosis, inflammatory metabolic dysfunction-associated steatohepatitis (MASH), and fibrosis/cirrhosis. During disease progression, the liver's macrophage environment shifts from resident Kupffer cells to infiltrated monocyte-derived macrophages, including the lipid-associated macrophage (LAM). MASH and associated fibrosis exhibit known sex differences, yet preclinical research has investigated sex differences with respect to immune cell dynamics during MASH progression.
Objective: To define sex-specific trajectories of MASH liver phenotypes, with a focus on macrophages, in female and male mice fed the Gubra-Amylin NASH (GAN) diet.
Study design: Age-matched female and male mice were fed the fructose-, cholesterol-, and palmitate-rich GAN diet or matched control diet for 10, 15, 20, or 25 weeks. Liver histological, biochemical, and immunological characteristics were compared within and between sexes over time.
Results: Liver steatosis and lipid burden were more pronounced in females, while fibrosis development was confined to male mice. Overall, females had more liver immune cells and macrophages than males. Compared to their controls, GAN-fed females exhibited an earlier recruitment and expansion of monocyte-derived macrophages, including LAMs, than males. All observed liver phenotypes occurred independent of systemic or adipose tissue inflammation.
Conclusion & future outlooks: Despite higher steatosis and macrophage counts, female livers were more protected against fibrosis than male livers. This may, in part, be due to their earlier recruitment of LAMs; previous research has revealed a protective role of LAMs against MASH-associated fibrosis and implicates them as essential regulators of fibrosis resolution. Thus, our future work aims to investigate the kinetics, phenotype, and role of LAMs during fibrosis resolution in male mice.

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OP10

A macrophage lipid mediator circuit programs distal gut immunity and sex-biased colitis

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Ulcerative colitis (UC) is a chronic disorder that primarily affects distal colon and exhibits male-biased severity. The mechanisms underlying this compartment- and sex-specific susceptibility remain unknown. Here, we identify a previously unrecognized pathway in which gut-resident macrophages (GrMacs) regulate distal intestinal inflammation through the biosynthesis of the specialized pro-resolving lipid mediator (SPM) MaR1n3-DPA (n-3 docosapentaenoic acid–derived Maresin-1).

We report a significant reduction of 12- and 15-lipoxygenase (ALOX)-expressing GrMacs in the distal colon of active UC patients, accompanied by decreased levels of MaR1n3-DPA, suggesting disrupted resolution circuits. ScRNA sequencing analyses of distal colon datasets from UC patients further revealed sex dimorphism in ALOX-expressing GrMacs in humans.

In mice, males and females exhibited similar proportions of Alox15-expressing GrMacs in the proximal colon. However, males displayed a basal deficiency of Alox15-expressing GrMacs in the distal colon, with correspondingly lower levels of the Alox15-derived SPM MaR1n3-DPA.

Targeted deletion of Alox15 in GrMacs (MacAlox15KO mice) confirmed that MaR1n3-DPA levels in distal colon is macrophage dependent. ScRNA sequencing of distal colon from MacAlox15KO mice revealed deregulated basal homeostasis, characterized by an autocrine dysregulated GrMac phenotype and paracrine upregulation of epithelial barrier inflammatory TNF-α/IL-6 pathways, which were reversed by MaR1n3-DPA reconstitution.

Functionally, experimental colitis revealed that Alox15-proficient female mice displayed reduced susceptibility to distal colitis, whereas Alox15 deletion in GrMacs increased disease severity in males and females. Strikingly, therapeutic restoration of MaR1n3-DPA levels in MacAlox15KO mice reinstated mucosal homeostasis and conferred robust protection against distal colitis in both sexes.

Supporting translational relevance, MaR1n3-DPA downregulated TNF-α/IL-6–driven pro-inflammatory signatures in ex vivo cultures of UC patients distal biopsies as well as reprogrammed monocyte-derived macrophages.

Collectively, these findings uncover a sex- and compartment-specific macrophage–lipid mediator axis that governs susceptibility to intestinal inflammation and identify MaR1n3-DPA as a promising candidate for resolution-targeted therapy in ulcerative colitis.

OP11

Activated T-cell signatures in blood are independently associated with endothelial cell dysfunction: The Maastricht Study

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Background: Low-grade inflammation and endothelial dysfunction (ED) are important for cardiovascular disease development. We investigated the relation of different immune cell signatures and ED in a large cohort study.
Method: In the Maastricht Study, a population-based cohort with oversampling of individuals with type 2 diabetes, we measured circulating immune cells in fresh blood of 798 participants using flow cytometry (CD38, CD45RO, CD28, CD25, CD3, CD4, CD8, CD127, CD19, IgD, CD66B, HLA-DR, CD14, CD16, CD11B, CD11C, CX3CR1, and CD56) to identify a blood immunological signature that is associated with ED (Z-score of sVCAM1, vWF, E-selectin, and sICAM1). To establish the independent relationship between immune cell signatures and ED, we developed an approach to correct principal component analysis-based multivariate flow cytometry analysis for confounding factors (age, sex, waist circumference, HbA1c, LDL/HDL ratio, statin use, smoking status, systolic blood pressure, presence of CVD and education level).
Results: Crude analysis showed that B-cell, granulocyte, and NK cell signatures were not associated with ED, while T-cell (Beta=0.2758), classical monocyte (Beta= 0.2050) and intermediate monocyte (Beta=0.1756) signatures were significantly associated with ED. Correction for age and sex resulted in a significant association between T-cell (Beta=0.1844), classical monocyte (Beta=0.1756) and intermediate monocyte (Beta=0.0906) signatures with ED. After correction for all confounders, there was only a significant relationship between T-cells and ED (Beta=0.1031). The immune cell signature showed that T cells, represented by a subset of T helper cells expressing high levels of CD45RO and CD28, and by a subset of cytotoxic T cells expressing high levels of CD25 and low levels of CD28 and CD45RO were elevated in people with ED. The loss of the association of monocytes with ED was impacted mostly by correcting for waist circumference.
Conclusion: After correction for confounding factors, activated T cell signatures are linked with ED.

OP12

Soluble epoxide hydrolase-derived leukotoxins drive immunosuppression in patients with advanced liver disease

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Patients with acutely decompensated cirrhosis (ADC) present exuberant inflammation and persistent immunosuppression rendering them at increased risk of recurrent bacterial infections and developing acute-on-chronic liver failure (ACLF). Here, we investigated the profile of immunomodulatory lipid mediators in ADC patients and explored their effects on leukocyte effector functions in vitro and in vivo in an experimental model of ADC in mice. LC-MS/MS-based targeted lipidomics analysis of 308 plasma samples longitudinally collected from 93 ADC patients with and without ACLF identified the linoleic acid-derived leukotoxin 9,10-dihydroxy-12-octadecenoic acid (9,10-DiHOME) as the only lipid mediator elevated in ACLF. 9,10-DiHOME levels followed the disease severity course and peaked when patients acquired infections and developed ACLF. Leukocytes from ADC patients showed increased expression of soluble epoxide hydrolase (sEH), the enzyme responsible for 9,10-DiHOME biosynthesis. In peripheral monocytes, 9,10-DiHOME induced the expression of the immunosuppressive marker MerTK, distorted required mechanisms for the adequate host defense response against pathogens including the ability to produce cytokines in response to LPS and impaired mitochondrial dynamics and autophagic responses. In in vivo studies, inhibition of sEH in mice with CCl4-induced cirrhosis impeded immunosuppressive responses in peritoneal macrophages and significantly attenuated MerTK expression in liver macrophages. In parallel, sEH inhibition induced the reactivation of macrophage immunocompetence and restored the M1-M2 phenotype balance. Taken together, these findings indicate that increased circulating levels of the leukotoxin 9,10-DiHOME weakens immune-cell defensive responses, thus enhancing the susceptibility of ADC patients to bacterial infection and precipitating ACLF. These data also position sEH as an actionable drug target in this condition. Ongoing experiments are addressing the impact of this leukotoxin on the pro-resolving circuits.

OP13

Nanocarrier-Mediated Delivery of Pro-Resolving Mediators Reprograms Innate Immunity in ApoE−/− Mice with Atherosclerosis

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Background: Atherosclerosis (AS) is a chronic inflammatory disease in which defective resolution of inflammation contributes to persistent immune activation and plaque progression. Specialized pro-resolving mediators (SPMs) actively regulate inflammatory responses, but their therapeutic application is limited by rapid degradation and inefficient targeting to vascular lesions.
Aim: This study aimed to investigate whether targeted nanocarrier delivery of SPMs can promote inflammation resolution and induce durable reprogramming of innate immune responses in AS.
Results: SPM-loaded lipid nanocarriers dual-targeted to VCAM-1 and collagen IV were administered to ApoE-deficient mice with established AS. Targeted nanocarriers preferentially accumulated in the aorta, reduced circulating neutrophils, and promoted an anti-inflammatory monocyte phenotype. Importantly, bone marrow-derived macrophages (BMDMs) isolated from treated mice retained an enhanced reparative phenotype ex vivo, characterized by increased CD206 and IL-10 expression and reduced production of pro-inflammatory cytokines despite the absence of continued treatment.
Main Objective: To evaluate whether targeted delivery of SPMs can induce sustained innate immune reprogramming while reducing vascular inflammation.
Conclusion: Targeted SPM nanocarriers not only attenuate atherosclerotic inflammation but also induce durable innate immune reprogramming consistent with a pro-resolving trained phenotype, highlighting a promising therapeutic strategy for cardiovascular disease.

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Session 3 - Neuroinflammation Infection, Systemic Resolution

OP14

Oxylipin dysregulation and impaired inflammation resolution are associated with pathology progression in Parkinson's Disease

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Peripheral and central inflammation appear to be a major contributor to Parkinson's Disease (PD) pathology and a potential driver of progressive neurodegeneration. Oxylipins, oxygenated metabolites derived from polyunsaturated fatty acids, act as key regulators of immune responses, influencing both the initiation and resolution of inflammation. In this study, we performed targeted oxylipin profiling using a MEPS-UHPLC-ESIMS/MS platform in plasma, colon, and brainstem tissues from the PrP human A53T α-synuclein (αS) transgenic (Tg) mice, a prodromal PD mouse model that exhibits early peripheral inflammation and gut dysfunction followed by appearance of classical motor symptoms, neuroinflammation, and neurodegeneration after 9 months of age. Compared to controls, analysis of oxylipins in pre-motor and motor stages revealed a clear modification of the oxylipin profile in the colon, indicating substantial alterations in lipid-mediated inflammatory and metabolic signaling, mainly characterized by a reduction in specialized proresolving lipid mediators (SPMs) that worsened with symptoms progression. Specifically, at premotor stages, Tg mice exhibited a marked reduction in colonic tissue of several omega-3 and omega-6 PUFA–derived mediators, including docosanoids and prostaglandins. This deficit became more pronounced in motorimpaired mice, with αS pathology in full display and was characterized by a polarized inflammatory state with broad suppression of COX-, LOX-, and CYP-derived products alongside a disproportionate upregulation of only resolvin D2. Plasma analyses at late pre-motor stages further confirmed a systemic reduction in SPMs prior to overt disease onset. More importantly, a similar oxylipin signature (e.g., overexpressed 20-epi-20-F4tNeuroP levels) was identified in plasma from PD patients, indicating a systemic imbalance in inflammatory resolution pathways and highlighting the potential of oxylipins as minimally invasive PD biomarker. In conclusion, progressive impairment of SPM pathways may exacerbate systemic inflammation and contribute to neuronal vulnerability in PD.

OP15

Resolvin D3 reprograms inflammatory platelets toward a pro-resolving phenotype in cystic fibrosis

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Although platelets (PLTs) are well established as drivers of inflammation and can also support its resolution through transcellular biosynthesis of specialized pro-resolving mediators (SPMs), distinct PLT functional states remain poorly defined. In cystic fibrosis (CF), PLTs display a persistent hyperactivated phenotype that is defective in resolution and contributes to pathogenic airway inflammation. This unresolved inflammatory state provides an opportunity to define PLT phenotypes linked to inflammation versus resolution.

Here, using integrated proteomics, phosphoproteomics, and high-parameter flow cytometry, we identified a distinct pro-inflammatory signature in purified PLTs from people with CF. We then screened for mediators capable of counterregulating this phenotype and identified resolvin D3 (RvD3) as a potent SPM that selectively reprograms platelet activation. In isolated CF platelets, RvD3 reshaped key protein and kinase signaling hubs, shifting PLTs toward a pro-resolving phenotype.

Importantly, this reprogramming translated in vivo into PLT-dependent protection in preclinical CF models, where RvD3 enhanced bacterial clearance while limiting neutrophil-driven inflammation. These effects were associated with a more controlled and productive host response, consistent with activation of resolution pathways rather than broad immunosuppression.

Together, these findings identify and characterize a pharmacologically inducible pro-resolving PLT phenotype in CF. More broadly, they expand current understanding of PLT biology by positioning PLTs as dynamic immune cells whose functional state can be therapeutically redirected to promote resolution of inflammation. Our results support RvD3 as a candidate immunoresolvent and highlight PLT reprogramming as a potential resolution-based therapeutic strategy in CF.

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OP16

The synthetic lipoxin A4 mimetic AT-01-KG modulates shared transcriptional programmes across organs to promote the resolution of inflammation and tissue protection in experimental sepsis

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Polymicrobial sepsis is driven by a dysregulated host response in which excessive inflammation and impaired resolution contribute to multi-organ injury. While current therapeutic approaches primarily target inflammatory pathways, strategies that actively promote the resolution of inflammation remain limited. Here, we investigated the potential of a synthetic lipoxin mimetic AT-01-KG to modulate host responses to experimental sepsis. Treatment with AT-01-KG attenuated systemic and tissue inflammation, and conferred significant protection against sepsis-induced cardiac and renal injury. Bulk RNA sequencing of heart and kidney tissues revealed extensive transcriptional reprogramming, with over 2500 differentially expressed genes in the heart (1536 upregulated, 1074 downregulated) and over 3800 in the kidney (2238 upregulated, 1622 downregulated). Pathway enrichment analysis of organ-specific gene sets demonstrated suppression of key inflammatory and immune signalling pathways in both organs. Intersection analysis identified a subset of differentially expressed genes shared across both tissues (708 up-regulated, 505 down-regulated), representing a conserved cross-organ transcriptional response. Transcription factor motif enrichment and transcription factor activity inference analyses of this shared gene set revealed coordinated suppression of NF-κB- and interferon regulatory factor (IRF)-associated regulatory networks, indicating downregulation of upstream inflammatory transcriptional control mechanisms and suggesting modulation of a core conserved transcriptional regulatory network underlies cross-organ responses to AT-01-KG. In silico cell deconvolution indicated that AT-01-KG promoted a shift in immune cell subsets, with increased abundance of monocyte/macrophage-related signatures and decreased granulocyte signatures. This was supported by elevated Adgre1 expression and reduced Mpo levels in response to AT-01-KG in both tissues, potentially indicating a shift from neutrophil-driven injury to macrophage-mediated repair. Collectively, these findings demonstrate that AT-01-KG induces conserved cross-organ transcriptional reprogramming, converging on a core regulatory network governing inflammatory signalling and innate immune cell composition, associated with preservation of cardiac and renal function in experimental sepsis.

OP17

Decoding Inflammation Resolution Failure in Multiple Sclerosis

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Persistent and uncontrolled inflammation characterizes autoimmune and neurodegenerative diseases such as multiple sclerosis (MS), the most common chronic inflammatory demyelinating disease of the central nervous system (CNS). In MS, major diagnostic and therapeutic needs remain unmet due to high intra- and inter-individual heterogeneity in pathogenic mechanisms, prognostic factors, clinical course, and treatment responses. Recent evidence from our studies on human blood indicates impaired inflammation resolution in MS. Thus, we aimed to identify targets of failed resolution in the brain of MS patients by evaluating pathway alterations in cerebrospinal fluid (CSF) and post-mortem tissues, as well as assessing their protective effects in vivo. Targeted CSF lipidomics revealed distinct profiles mirroring disease progression: patients with relapsing–remitting MS (RRMS) or progressive MS showed elevated omega-6 arachidonic acid–derived pro-inflammatory mediators (PGE_2, PGD_2, LTB_4) together with reduced SPMs, particularly DHA-derived resolvins (RvD1–6) and maresins (MaR1/2). In contrast, specific SPMs such as RvD5 and PD1 were selectively elevated in MS patients during remission. Post-mortem MS brain tissues exhibited upregulated prostaglandin-producing COX-2 and downregulated SPM-producing enzymes (15/12-lipoxygenases). In vivo treatment with several SPMs (LXB_4, RvD3, MaR1) attenuated disease course in experimental autoimmune encephalomyelitis, preserved myelin and oligodendrocytes, reduced immune cell infiltration, reprogrammed microglia toward anti-inflammatory M2-like states, and restored metabolic profiles of $CD4^+$ T cells and macrophages/microglia. Together, these findings decode resolution failure in MS and identify pro-resolving lipids as promising therapeutic candidates to promote neuroinflammation resolution, brain–immune repair, and remyelination.

OP18

Long-lasting complications in post-sepsis state and search for pro-resolution trajectories in sepsis

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Sepsis is a life-threatening syndrome affecting approximately 166 million people worldwide each year and is associated with long-term complications, referred to as post-sepsis syndrome, in which many patients fail to achieve full recovery. Here, we aimed to identify determinants of recovery, stratify patients at risk of post-sepsis syndrome, and characterize a pro-resolution immune phenotype.
Using state-of-the-art approaches, including NGS-based proteomics (OLINK REVEAL), deep immunophenotyping, and single-cell metabolic analysis (SCENITH), we defined sepsis-induced alterations in innate immune cells from pediatric patients (n=31). To reveal determinants of successful recovery, we analyzed peripheral blood from orthopedic surgery (ORT) patients (n=33), who typically exhibit favorable recovery trajectories. Both cohorts studied longitudinally within several time points. Sepsis survivors show altered cytokine signalling up to 6 months after sepsis onset, compared with age-matched controls This includes changes in IL-10 and IL-33, indicating ongoing low-grade inflammation. In monocytes, we observed metabolic disturbances marked by increased expression of CD36, CD38, and CD39. Monocytes from ORT patients underwent immunophenotyping and bulk transcriptomic analysis, revealing IL-18 as a key driver of the resolution-associated immune signature. These findings were validated in vitro by comparing IL-18 and TNF-α effects on monocytes, and in 3D human intestinal organoids using single-cell RNA sequencing. We further demonstrated that IL-18 promotes monocyte-to-macrophage transition and migration, while its effects were attenuated in the presence of TNF-α. Finally, the TNF-α/IL-18 ratio showed strong predictive value for clinical severity in septic patients.
Integration of these data with long-term outcomes reflecting health-related quality of life, combined with machine-learning approaches, may enable prediction of severe complications and support timely, pro-resolution-focused interventions.

OP19

Annexin A1 dynamics during COVID-19 hospitalization: relationship with clinical outcomes and resolvin E1

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Introduction: Annexin A1 (ANXA1) is a glucocorticoid-regulated protein with proresolving properties. Although glucocorticoids remain the cornerstone treatment for severe and critical COVID-19, there is limited evidence about ANXA1's involvement in hospitalized COVID-19 patients. This study investigated the temporal profiles of ANXA1 and its receptor FPR2 in hospitalized COVID-19 patients with different disease severities and clinical outcomes. Additionally, we explored their potential associations with inflammatory markers, endothelial dysfunction, and other resolution mediators.
Methods: Ethical approval was obtained from the Health Ethics Committee. Blood was collected from COVID-19 patients classified as “severe” (n=27), “critical” (n=17) and “critical on veno-venous extracorporeal membrane oxygenation” (n=17) at hospital admission, days 3-4, 5-8, and weekly thereafter, and in controls (n=23) at a single time point. Serum ANXA1, resolvin D1 and resolvin E1 (RvE1) were quantified by ELISA, while FPR2 and Chemerin1 receptor expression was measured by RT-qPCR. Cytokines (TNF-α, IL-6, IL-1β, IL-10) and endothelial markers (VCAM-1, E-selectin, endocan) were assessed by multiplex immunoassays/ELISA.
Results: Most patients received the standard 10-day dexamethasone protocol, with sample collection beginning after treatment initiation. Admission ANXA1 and FPR2 were significantly

elevated in all patient groups compared to controls. Throughout hospitalization, ANXA1 increased predominantly in “severe” patients and survivors, becoming higher at weeks 3 and 4 in survivors versus non-survivors. Variable cumulative dexamethasone doses did not produce differential effects on ANXA1 or FPR2. During the dexamethasone effect period, ANXA1 was positively associated with RvE1. Exploratory analyses across all patient cohort revealed inverse correlations of ANXA1 with Chemerin1 (RvE1 receptor) and markers of endotheliitis, while both ANXA1 and FPR2 positively correlated with inflammatory parameters.
Conclusion: ANXA1 may be involved in COVID-19 recovery processes, representing a promising therapeutic strategy to complement dexamethasone efficacy. Furthermore, the parallel rise in ANXA1 and RvE1 suggests an interplay between these proresolving mediators to mitigate the hyperinflammatory state.
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OP20

Oxylipins in stroke pathology

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Introduction: Oxylipins play a pivotal role in stroke pathology, acting as bioactive lipid mediators that drive neuroinflammation and influence neuronal survival in stroke. TXB2 amplifies platelet activation and endothelial dysfunction in ischemic stroke that enhances tissue damage.
Methods: Rodent ischemia-reperfusion models oxylipin profiling (targeted UPLC-MSMS), Rap1b-GTP binding (immunoprecipitation/Western blot)). Assays include platelet aggregation, phospho-ERK/cPLA2, systemic CDNF administration and time-course analyses, and histological assessment of infarct volume/BBB integrity.
Results: Stroke elevates oxylipins correlating with GTP-Rap1b upregulation, ERK/cPLA2 activation, TXB2 overproduction, and neuronal loss; CDNF binds Rap1b, suppresses these pathways, normalizes plasma oxylipins, reduces microglial inflammation, and reduces infarcts.
Conclusion: Targeting Rap1b with CDNF disrupts oxylipin-driven thrombo-inflammation, presenting a therapeutic strategy for stroke neuroprotection. These insights further advocate oxylipin profiling and interventions as novel strategies for stroke neuroprotection.

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Session 4 - Resolution in Respiratory & Fibrotic Disease

OP21

The involvement of pDC and ER stress in systemic sclerosis-associated fibrosis

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Plasmacytoid dendritic cells (pDC) are innate immune cells specialized in rapidly producing large amounts of type I interferon (IFN-I) that have been associated with systemic sclerosis (SSc). They infiltrate affected tissues, drive overproduction of IFN-I, and their depletion alleviates fibrosis in murine models. Due to their high secretory capacity, pDC have a large endoplasmic reticulum (ER) and basal levels of ER stress, resulting from the accumulation of misfolded proteins. pDC activation is impacted by ER stress, and there is dysregulation of ER stress-related genes in pDC of SSc patients. Therefore, we are exploring the contribution of pDC and ER stress for fibrosis development.

We established an in vitro platform to study interactions between human pDC, and IMR-90 lung fibroblasts. Mono and co-cultures were exposed to the ER stress inducers tunicamycin, subtilase cytotoxin (SubAB) and HA-15. Cells were also treated with the TLR7 agonist CL307. Extracellular matrix (ECM) protein production and cellular activation were evaluated by immunoblotting and RT-qPCR.

It was found that the pDC cell line CAL-1 physically interacts with IMR90 cells. Exposure of pDC-IMR90 co-cultures to SubAB or HA15 resulted in increased expression of fibronectin and α-smooth muscle actin (α-SMA). This effect required the presence of the ER stress sensor protein kinase R-like ER kinase (PERK), but not stimulator of IFN genes (STING) on CAL-1 cells. Treatment with a TLR7 agonist in conjunction with ER stress induction had a synergistic effect on production of IFN-I, but it did not interfere with fibroblast activation in the co-cultures. Moreover, cell-to-cell contact between IMR-90 and CAL-1 was required, since soluble factors produced by SubAB-exposed cells were insufficient to induce fibroblast activation.

Altogether, our results suggest that both pDC and ER stress induction contribute to fibroblast activation and that IFN-I is not the driver of ER stress induced-ECM production in the co-cultures.

OP22

Development of an innovative vascularized triple-culture airway-on-a-chip to model inflammation in cystic fibrosis

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Cystic fibrosis (CF) pulmonary disease is characterized by unresolved neutrophilic inflammation, leading to progressive tissue damage and respiratory failure. We previously developed the first CF airway-on-a-chip model composed of CF bronchial epithelium and endothelial cells (ECs), which enabled monitoring of polymorphonuclear neutrophil (PMN) migration in a controlled human-relevant microenvironment. Building on this platform, here we developed an advanced triple-culture airway-on-a-chip incorporating CF epithelial cells, ECs, and fibroblasts (FBs), to better recapitulate the complexity of the CF airway unit.
Co-culture conditions were first established on transwells and then translated to the chip by testing different cell seeding strategies and timing of EC introduction. PMN perfusion assays were performed to monitor adhesion to EC and migration to the epithelial site. Release of cytokines and chemokines, as well as of proteolytic enzymes by respectively ECs and FBs, were also evaluated.
The triple-culture airway-on-a-chip reproduced key CF inflammatory features, including enhanced PMN recruitment and a pro-inflammatory endothelial phenotype. CF-ECs showed increased adhesion molecule expression and cytokine release, contributing to increased PMN adhesion. On the other side, CF-FBs displayed altered protease release, suggesting impaired extracellular matrix remodelling. Co-culture of ECs and FBs allowed endothelium-stroma interactions, resulting in the formation of vascular-like structures on transwell and mimicking a pseudo-vessel in the bottom channel of the chip. Partial restoration of CFTR activity with CFTR modulators reduced PMN adhesion to CF-ECs, but it did not significantly affect the overall PMN recruitment within the chip, reinforcing the need for efficient pro-resolving strategies to combat CF airway inflammation.
This vascularized CF airway-on-a-chip represents an improved and physiologically relevant in vitro preclinical model of the CF airway, capturing critical epithelial-endothelial-stromal interactions. This platform may provide a valuable tool to investigate on regulatory mechanisms of airway inflammation as well as on resolution pharmacology in respiratory diseases characterized by aberrant, non-resolving inflammatory responses.

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OP23

Immunomodulatory Environment of Bone Marrow Niche in Myeloid Leukemia

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Introduction: The bone marrow microenvironment in acute myeloid leukemia (AML) exerts profound control over antitumor immunity and remains a key obstacle to successful natural killer (NK) cell–based therapies. This niche is defined not only by an immunoregulatory cytokine landscape but also by a dense three-dimensional (3D) stromal organization that can restrict immune cell access to leukemic targets. Standard suspension and two-dimensional culture models fail to reflect these combined biochemical and spatial constraints, limiting their predictive value for NK cell function in vivo.
Goals: In this project, some of the key soluble factors of the AML niche should be identified and employed in the 3D model of the AML niche in order to assess their role in NK cells dysfunction.
Methods: Spheroid cultivation in aggrewell plates, luciferase cytotoxicity assay, ELISA, LegendPlex, flow cytometry, confocal microscopy.
Results: 3D spheroid model of the AML bone marrow niche was established using mesenchymal stromal cells (MSCs) and leukemic cell lines as well as primary leukemic cells to more accurately recapitulate niche conditions. Plasma cytokine profiles from AML patients and healthy donors, including TGF-β, SDF-1, MIF, and IL-8, were quantified and used to condition NK cells prior to functional testing. Confocal imaging revealed leukemic cell integration into MSC spheroids and subsequent NK cell infiltration. NK cell cytotoxicity was evaluated using luciferase-based assays and directly compared between 3D spheroid cultures and conventional suspension systems.
Conclusions: Our results demonstrate that AML-associated cytokine exposure combined with a 3D stromal context markedly impairs NK cell cytotoxic activity relative to suspension cultures. These findings emphasize that both soluble and structural components of the leukemic niche cooperatively suppress NK cell function. By integrating patient-derived cytokine cues with a spatially organized model, this platform offers an improved framework for interrogating NK cell dysfunction and refining NK cell–based immunotherapeutic strategies for AML.

OP24

A pro-resolving approach to control cystic fibrosis airway inflammation

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Introduction and Objectives: Unresolved lung inflammation remains a clinical issue for people with Cystic Fibrosis (pwCF). Pro-resolving pharmacology may cover the unmet need for efficient treatment for CF inflammation. We documented that Resolvin D1 down tones CF inflammation and has anti-microbial activity. Here, we investigated on Melanocortins, peptide hormones that activate five subclasses of receptors (MCR1-5) and exert pro-resolving bioactions. To this end, we built a human CF airway-on-chip and evaluated the impact of BMS-470539 (BMS), a selective MCR1 agonist, on key mechanisms of CF airway inflammation.
Methods: BMS was delivered to human bronchial CF epithelial cells (HBE) and lung vascular CF endothelial cells (HEC), grown separately or assembled in a CF airway-on-a-chip perfused with CF-PMN, in the presence or not of infection. Endothelial function was assessed using xCELLigence® RTCA; trans epithelial electric resistance (TEER) was monitored with a voltmeter EVOM™ Manual); mucus was quantitated by Alcian Blue staining and MUC5A fluorescence; PMN adhesion/migration was evaluated by confocal microscopy. Differentially expressed genes were identified by DESeq2 analysis in Partek (Illumina).
Results: BMS corrected CF-HEC dysfunction ($p < 0.01$) and reduced CF-PMN adhesion to CF-HEC, both under static conditions ($p < 0.005$) and under flow in PAO1-infected CF airway-on-a-chip ($p < 0.03$). It increased TEER ($p < 0.0005$), and reduced mucin production ($p < 0.005$) in HBE on transwell, and in non-infected airway-on-a-chip, ($p < 0.004$), where it also reduced PMN migration ($p < 0.003$). Transcriptomic profiles of CF-HEC and CF-HBE were consistent with pro-resolving actions of BMS.
Conclusions: These results uncover pro-resolving actions of Melanocortins in preclinical models of CF, thus expanding the repertoire of pro-resolving agents against CF inflammation. The construction of the first prototype of a full CF airway on-a-chip represents a significant advancement for the development of a human preclinical device for drug discovery and personalized medicine.

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OP25

Role of SPM in Pulmonary hypertension and control of the human pulmonary vascular tone

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Introduction: Pulmonary hypertension (PH) is a severe disease characterized by increased pulmonary arterial pressure, leading to right ventricular failure and death. Current treatments mainly target the reduction of vascular tone but remain insufficient. We hypothesized that, in Group-3 PH secondary to lung diseases (COPD, fibrosis), inflammation contributes to abnormal vasoconstriction in human pulmonary arteries (HPAs). Given their anti-inflammatory properties, we focused on omega-3 fatty acids (EPA, DHA, DPA) and their metabolites, specialized pro-resolving mediators (SPMs: resolvins, protectins, maresins), as potential modulators of pulmonary vascular tone.
Methods: HPAs from PH Group-3 and non-PH patients were collected at Bichat-Hospital. Lipidomic analysis (LC/MS-MS) quantified endogenous SPM levels in HPA, with and without EPA/DHA stimulation. Immunofluorescence assessed the expression and localization of key biosynthetic enzymes (15A/15B/12 -LOX) and SPM-receptors (GPR32, LGR6 & FPR2), giving insight into their distribution in the vascular wall. The second part focused on the effects of omega-3 fatty acids on vascular tone. Using an ex vivo organ bath system, we evaluated the direct effects of EPA, DHA, and DPA alone or their modulations of HPA vascular tone induced by prostaglandin (PG)E2, Iloprost (PGI2-analogue) or Endothelin-1. Molecular mechanisms were explored via Western-blot, ELISA, and fluorometric assays to identify signaling-pathways involved.
Results: Our data show differential expression of omega-3 fatty acids, biosynthetic enzymes and SPM receptors in PH vs non-PH HPA. Functional studies demonstrated that EPA induces a nitric oxide dependent vasorelaxation in non-PH HPA, but this effect is attenuated in PH. Interestingly, the omega-3 DHA and Maresin-1 enhanced Iloprost-induced vasorelaxation while DHA, DPA, Maresin-1 and RvD1 reduced PGE2-mediated vasoconstriction in both groups. These last effects could be explained by a reduced expression of the EP3 (PGE2)-receptor.
Conclusion: Our study highlights the key role of omega-3 and SPMs in inducing and modulating pulmonary vascular tone, offering new therapeutic potential for Group-3 PH.

OP26

Molecular characterization of neutrophils defects in cystic fibrosis: dysregulation of lipid metabolism and inflammatory resolution pathways

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Background: Cystic fibrosis is characterized by persistent pulmonary inflammation that severely impairs respiratory function. Neutrophils dominate this inflammatory milieu and exhibit marked phenotypic and functional alterations, including dysregulated microbicidal activity, impaired apoptosis, and dysregulated immunophenotype. CFTR modulators have significantly improved disease management. Kaftrio, a triple combination therapy (Elexacaftor/Tezacaftor/Ivacaftor, ETI), provides major clinical benefits and reduces pulmonary inflammation. However, its specific impact on neutrophil biology remains poorly understood.
Aims: This study aims to characterize neutrophil phenotypic and functional dysregulations in cystic fibrosis and determine whether ETI treatment restores neutrophil homeostasis.
Methods: Blood samples were collected from cystic fibrosis patients before (V1) and after ETI treatment (V2), and from healthy donors (HD). The immune phenotype of neutrophils was analyzed using 24-marker spectral flow cytometry in whole blood. Neutrophils were isolated and processed for metabolomics and proteomics followed by mass spectrometry and integrated bioinformatic analyses (MetaboAnalyst, STRING, PANTHER, Ingenuity). Biological pathways were reconstructed by integrating enzymes with metabolites identified through metabolomics. Neutrophil apoptosis, a key step in inflammatory resolution, was assessed after 16h of culture by flow-cytometry.
Results: 4500 proteins and 120 metabolites were identified. Significant differences were observed between HD and V1 and were accentuated in V2. Comparisons between V1 and V2 revealed additional differentially expressed proteins and metabolites. Most dysregulated pathways involved lipid metabolism, triglyceride storage, immune suppression and pro-resolving mechanisms including resolvins. Key pro-resolving proteins (ALOX5, arginase-1, phospholipases, galectin-3, annexins) were altered, and PD-L1 expression was increased. These findings indicate profound metabolic reprogramming of neutrophils with enhanced fatty acid synthesis and storage, potentially impairing inflammatory resolution. Neutrophils from patients showed reduced apoptosis which was restored by ETI treatment.
Conclusions: These multi-omics analyses reveal key mechanisms of neutrophil dysfunction in cystic fibrosis and show that ETI partially restores altered pathways. In this context, lipid metabolism and apoptosis emerge as promising targets to improve inflammatory resolution.

OP27

Absence of TGF-β secretion in Cyclops lesion–derived cells: Evidence for non-canonical fibrotic pathways in Cyclops syndrome

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Cyclops syndrome is a localized form of knee arthrofibrosis affecting ~10% of patients undergoing anterior cruciate ligament (ACL) reconstruction - the most performed surgical procedures worldwide, where the torn ligament is replaced by a graft taken from the patient's own hamstring or patellar tendon. It is characterized by the formation of fibrotic nodule (Cyclops lesion) anterior to the graft, leading to leg extension deficit, pain/swelling, and a characteristic "click" sound near full leg extension This condition alters body's biomechanics, increasing the risk of further knee damage. Despite its clinical burden, its etiology remains poorly understood, and no pharmacological treatments are currently available. Revision surgery remains the only treatment option.

This study aimed, for the first time, to comprehensively characterize the cellular and histological composition of Cyclops lesions and identify key molecular mediators driving their development. Tissue biopsies were collected from patients undergoing revision surgeries (N=5).

Synovial fluid analysis showed elevated levels of IL-1β and TNF-α, confirming a strong inflammatory component. Histological analysis and electron microscopy of the tissue revealed dense collagen deposition and highly disorganized architecture of Cyclops lesions, distinct from healthy ligament or graft tissue. Fibroblasts were the predominant cell type, interspersed with immune cells and vascular structures. Flow cytometry identified two main cell populations: $CD206^+$ macrophages (M2-like phenotype) and activated fibroblasts (FAP+).

Single-cell microfluidic phenotyping provided insight into the secretory profile of Cyclops-derived cells, revealing general IL-6 production but an absence of TGF-β. This unexpected finding challenges the classical paradigm of fibrosis and suggests that Cyclops syndrome may arise from a non-canonical, inflammation-driven pathway associated with impaired inflammation resolution rather than excessive TGF-β–mediated healing.

To our knowledge, this is the first study providing an integrated cellular and histological characterization of Cyclops lesions. These results provide the basis for identifying predictive biomarkers and druggable targets for Cyclops syndrome.

Session 5 - SPMs: Biochemistry, Synthesis & Mediator Landscape

OP28

SPIN: Specialized Pro-resolving lipid mediator INteractome, a knowledge graph to explore mechanism of SPM function

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Introduction & Objectives: Specialized Pro-Resolving Mediators (SPMs) are bioactive lipid molecules that orchestrate the resolution phase of inflammation and restore tissue homeostasis without compromising host defense. Over the past two decades, more than 50 structurally diverse SPMs – including resolvins, protectins, maresins, cysteinyl-SPMs, and lipoxins – have been identified in models of acute and chronic inflammatory diseases such as arthritis, cardiovascular disease, neurodegeneration and metabolic disorders. Despite their therapeutic relevance, a comprehensive and machine-readable representation of SPM biosynthetic pathways, receptor interactions, biological targets, and downstream signaling networks remains limited. To address this gap, we developed an integrative computational framework leveraging Large Language Models (LLMs) to enable structured representation and mechanistic exploration of SPM biology by extending biosynthetic and signaling maps from the Atlas of Inflammation Resolution (AIR).
Methods: A predefined list of 57 SPMs and their chemical synonyms from PubChem was used to retrieve relevant publications from PubMed. Interaction triplets (SPM-interaction-protein/gene) were extracted using a prompt-based Mistral AI workflow and annotated with the BIONLP13CG Named Entity Recognition model. Nodes with undefined entity types were removed, and curated interactions were manually validated using PubMed identifiers to assign regulatory directions (e.g. activation or inhibition). Validated interactions were mapped to Systems Biology Graphical Notation (SBGN) to enable integration with AIR and support in silico perturbation analysis. Retrieved publications were further incorporated into a Retrieval-Augmented Generation (RAG) framework using FAISS(Facebook AI Similarity Search) for literature-grounded knowledge retrieval.
Results & Conclusion: The framework enables systems-level visualization of SPM-centered molecular interaction networks and supports identification of shared and mediator-specific biological targets across SPM subsets. In a knee osteoarthritis case study, β2-Adrenergic Receptor (ADRB2), Vitamin-D Receptor (VDR), Bone Morphogenetic Protein Receptor Type-2 (BMPR2), and Activin A Receptor Type-1 (ACVR1) were identified as potential SPM-associated targets. Overall, SPIN provides a structured, machine-readable web resource supporting systems-level analysis of inflammation resolution.

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OP29

Mapping the pro-resolving lipid mediator landscape across biological matrices and diseases: from acute inflammation to age-related chronic pathologies

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Inflammation resolution is an active biological process mediated by specialized pro-resolving mediators (SPMs), including lipoxins, resolvins, protectins and maresins, which are biosynthesized from polyunsaturated fatty acids and promote termination of inflammation, clearance of inflammatory cells and tissue repair. Altough impaired SPM pathways have been linked to multiple inflammatory and age-related diseases, their systemic distribution across biological matrices and clinical conditions remains poorly characterized. Here, we present a cross-matrix and cross-pathology overview of the pro-resolving lipid mediator signatures measured in both conventional and unconventional biological fluids.
Using a high-sensitivity analytical platform based on MEPS-UHPLC-MS/MS, we quantified approximately one-hundred lipid mediators and their biosynthetic precursors in plasma, saliva, and dried blood spots The study encompassed acute inflammatory responses, including exercise-induced inflammation and viral infection (COVID-19), as well as chronic age-related conditions characterized by persistent low-grade inflammation, including cardiovascular diseases, neurodegenerative disorders, and stroke. Acute conditions showed transient activation of SPM pathways consistent with physiological resolution responses, whereas chronic pathologies exhibited distinct and disease-specific alterations in circulating lipid mediator profiles. Comparative analysis across matrices highlighted a combination of shared and matrix-specific SPM signatures. Importantly, we demonstrate that non-conventional matrices, such as saliva and dried blood spots, capture complementary information of the pro-resolving mediator landscape, highlighting their potential for minimally invasive assessment of inflammatory status. These findings advance the characterization of inflammation-resolution pathways across diverse biological matrices and support the development of accessible biomarker platforms for assessing inflammation resolution and stratifying patients across acute and chronic inflammatory conditions.

OP30

Stereoselective Total Synthesis of Resolvin E4, 20-Hydroxy-Resolvin E4, and a Novel 20-Trifluoromethyl Analogue

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Introduction & Objectives: Resolvin E4 (RvE4) is a recently identified member of the E-series resolvins, but limited access has restricted its biological investigation. Herein, we report the first total synthesis of RvE4, its omega-oxidation further metabolite 20-hydroxy-RvE4 (20-OH-RvE4), and a novel analogue, 20-trifluoromethyl-RvE4 (20-CF3-RvE4).
Methods: A convergent and stereocontrolled synthetic strategy was developed, featuring Sonogashira cross-couplings, organocatalytic α-oxyamination, Midland reduction, and Z-selective Wittig olefinations. These transformations enabled precise installation of the polyunsaturated framework and stereocenters. Structural validation was performed using NMR, HRMS, LC-MS/MS, UV-vis spectroscopy, and multiple reaction monitoring (MRM) matching studies.
Results: The target compounds were synthesized with high stereochemical fidelity. RvE4 significantly enhanced efferocytosis of senescent red blood cells (sRBCs) by M2-like macrophages in a dose-dependent manner, whereas 20-OH-RvE4 did not exhibit this activity. Notably, this work provides the first evidence of the conversion of RvE4 to 20-OH-RvE4 in human neutrophils, supporting a metabolic inactivation pathway.
Conclusion: This study establishes the first synthetic access to RvE4 and related derivatives and demonstrates their utility in biological investigations. The loss of activity upon omega-hydroxylation, together with its formation in human neutrophils, highlights the importance of metabolic investigations. The 20-CF3-RvE4 analogue represents a promising strategy to resist metabolic inactivation and probe structure-function relationships. Biological evaluation of the 20-trifluoromethyl analogue will be investigated in due time.

Flash talks

FT1

Tetradenia riparia (Hochst.) Codd, activates pro-resolving pathways via a multi-component chemical landscape

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Introduction: *Tetradenia riparia* is an indigenous South African medicinal plant widely used across seven countries of the southern African region to relieve musculoskeletal pain, headaches, and joint aches. However, its ability to impact inflammation by engaging resolution pathways remains underexplored. This study investigates the immunomodulatory effects of *T. riparia* crude extract and fractions on human macrophage reactivity.
Methods: Lipopolysaccharide (LPS)-stimulated human macrophages (obtained from 7-day culture of peripheral blood mononuclear cells) were treated with *T. riparia* (dichloromethane (DCM) extract. Tumour necrosis factor alpha (TNF-α), interleukin (IL)-1 beta (IL-1β), IL-6, and IL-8 were quantified by qPCR. Gene expression of signal transducer and activator of transcription 3 (STAT3), Janus kinase 2 (JAK2), and phosphoinositide 3-kinase (PI3K), alongside resolution-associated determinants (arachidonate 12-lipoxygenase (ALOX12), ALOX15, G protein-coupled receptor 18 (GPR18), and GPR32), was evaluated by qPCR. Targeted lipid mediator profiling quantified prostaglandins, leukotrienes and pro-resolving lipid mediators, including 17-hydroxydocosahexaenoic acid (17-HDPA). Untargeted LC–MS/MS metabolomics coupled with molecular networking characterised the plant extract's chemical space.
Results: The leaf extracts and their fractions showed significant downregulation of pro-inflammatory cytokines, and suppressed STAT3, JAK2, and PI3K signalling. The lipid mediator profiling revealed increased 17-HDPA, modulation of prostaglandins and other inflammatory mediators. These changes were accompanied by upregulation of ALOX12, ALOX15, GPR18, and GPR32, independent of M2 markers (CD163, MRC1). Furthermore, molecular networking data analysis of the DCM extract revealed that over 80% of chemical constituents found in T. riparia have no spectral matches in global natural product's databases.
Conclusions: *T. riparia* modulates inflammatory responses of macrophages through a coordinated regulation of cytokine signalling, pro-inflammatory and pro-resolving lipid pathways, consistent with an engagement of endogenous resolution programs. These findings provide a mechanistic framework linking ethnobotanical knowledge systems with resolution biology and highlight the value of integrating lipid mediator profiling with systems-level metabolomics to interrogate complex plant-derived therapeutics.

FT2

Two-arachidonoylglycerol restoration attenuates pulmonary complications in acute pancreatitis through CB1 and CB2 pathways

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Acute pancreatitis (AP) is an inflammatory disease that can progress to acute respiratory distress syndrome, which is the most critical systemic complication and leading cause of early mortality. The endocannabinoid system (ECS), including the ligand 2-arachidonoylglycerol (2-AG) and the cannabinoid receptors CB1 and CB2, has emerged as a key modulator of systemic inflammation. A severity-dependent reduction in circulating 2-AG levels was observed in patients and a murine model of AP induced by intraperitoneal cerulein injections. To restore systemic 2-AG, mice were treated with JZL184 (10 mg/kg), a selective monoacylglycerol lipase inhibitor. The role of cannabinoid receptors was assessed using CB1 knockout mice ($Cnr1^{-/-}$) and pharmacological CB2 blockade with AM630 (3 mg/kg).

AP induced acute lung injury (ALI), characterized by histological disruption and increased pulmonary expression of pro-inflammatory cytokines. Elevation of systemic 2-AG levels significantly attenuated lung damage and prevented upregulation of Tnf, Il1b, and Il6 in the lung. Deletion of CB1 or blockade of CB2 reduced pulmonary Tnf and Il6 levels; however, inhibition of either receptor alone did not improve lung histopathology, indicating that structural protection requires coordinated CB1 and CB2 receptor signaling. Notably, when 2-AG levels were restored, protection against lung injury was maintained through activation of either receptor.

Disruption of coordinated receptor signaling also altered pancreatic myeloid infiltration, linking local inflammatory dysregulation to systemic responses that contribute to distal organ injury, as in the lung. In conclusion, normalization of systemic 2-AG protects against AP-associated ALI via CB1- and CB2-dependent mechanisms. Targeting ECS homeostasis represents a promising strategy to reduce pulmonary complications in severe acute pancreatitis.

FT3

Lessons from PROS1-TAM signalling: Resolution of inflammation is an active component of homeostasis in the central nervous system

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Introduction & Objectives: The TAM (Tyro3, Axl, Mertk) receptors constitute a central anti-inflammatory axis active in resolving inflammation through efferocytosis and gene regulation. The TAM ligands are GAS6 and Protein S (PROS1), however, the role of PROS1 in resolution biology in general, and particularly in the nervous system is incompletely understood. Here we explore the roles of Pros1 in microglia - the brain immune cells in development, homeostasis and inflammatory-related conditions.
Methods: We generated mice conditionally deleted for Pros1 expression in microglia (Pros1-cKO) using LysM-Cre or Cx3Cr1-Cre-ER. Microglial development and function was assessed by immunohistochemistry, gene expression and histology. The role of PROS1 in microglial response to inflamed diseased states was also assessed.
Results: Pros1-cKO mice had fewer microglia throughout the brain at 2 months of age due to abnormal microglia development. Additionally, TAM receptor-dependent key microglia functions such as phagocytosis and regulation of inflammation are impaired at steady state. Additionally, loss of PROS1 within microglia alone resulted in inflamed brain tissue at steady state. Moreover, we find that PROS1 is key to efficient resolution of inflammation following systemic challenge. Finally, inflammation and microglia-derived PROS1 play a role in regulating neurogenesis in adult mice, impacting normal brain function.
Conclusions: Through studying the PROS1-TAM axis in the CNS we reveal the ongoing need for active anti-inflammatory pathways at steady state. Using Pros1-cKO mouse models, we identify microglia-derived PROS1 is necessary for microglia development and for microglial resolution-related immune functions both at steady state and following systemic inflammation. This study reveals the role of the PROS1-TAM axis in maintaining a healthy, functional brain during development, and in resolving inflammation at steady state and following a systemic challenge.

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FT4

Hormetic effects of polyphenols on inflammatory signaling in obese Zucker rats

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Introduction: Reactive oxygen species (ROS) act as signaling molecules and mediators of inflammation. Excessive inflammatory activation can disrupt endothelial integrity and promote tissue injury. Polyphenols are widely recognized for their antioxidant and anti-inflammatory properties; however, increasing evidence indicates that their biological effects are context-dependent and may follow a hormetic dose–response pattern. The aim of this study was to evaluate the effects of different polyphenol-rich sources on inflammatory signaling in obese Zucker rats, a model of chronic low-grade inflammation.
Methods and Results: Inflammatory markers, including IL-6, phosphorylation of the NF-κB p65 subunit, and iNOS protein expression, together with structural changes, were assessed in the heart and aorta. Compared with lean controls, obese animals exhibited significantly elevated inflammatory markers, including IL-6 (+24%), phosphorylation of the NF-κB p65 subunit (+31%), and increased iNOS protein expression in the aorta (+27%), with a similar trend observed in the heart. Administration of dried fruits of Cornus mas (varieties Koralovij Marka and Wild Type) or Lonicera caerulea at a dose of 5 g/kg/day (~10 mg/kg polyphenols, GAE) for six weeks significantly reduced IL-6 levels, NF-κB p65 phosphorylation, and iNOS expression. In contrast, treatment with an extract of Aronia melanocarpa at a dose of 57.9 mg/kg/day (~25 mg/kg polyphenols, GAE) induced fibrotic changes in the myocardium and thickening of the aortic wall, accompanied by further increases in NF-κB activation and iNOS expression in both the heart and aorta.
Conclusion: Polyphenol-rich interventions exerted markedly different biological effects depending on their form and dose. Whole-fruit supplementation attenuated inflammatory signaling, whereas a concentrated polyphenol extract enhanced inflammatory activation and structural cardiovascular alterations. These findings support the concept of hormetic, context-dependent effects of polyphenols and highlight the importance of considering both dose and food matrix when evaluating their impact on inflammatory regulation in cardiometabolic disorders.

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FT5

The peculiar action of Sirtuin 1 modulation on IL-1b and TNF-a production in neutrophils during chronic inflammation

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Introduction & Objectives: Mammalian Sirtuin 1 (SIRT1) is a member of a family of nicotinamide adenine dinucleotide (NAD+)-dependent deacetylases catalyzing the removal of acetyl groups from a variety of proteins localized in the nucleus (histones, transcription factors) and cytoplasm. Synthetic molecules which modulate Sirtuin activity are a promising approach for drug development. Herein, we aim to study the effects of pharmacological modulation of SIRT1 on neutrophils during chronic inflammation.
Methods: A model of collagen antibody-induced arthritis (CAIA) was used in the study. Balb/c mice were treated intradermally for 5 consecutive days either with a SIRT1 activator, or inhibitor. Bone marrow (BM), serum and joints were collected at the early (14 days) or destructive phases (28 days) of arthritis. Flowcytometry was performed to characterize the neutrophil phenotype and intracellular production of cytokines. Paw swelling and histology of knee joints were used in the score systems to evaluate the degree of injury/damage.
Results: The modulation of SIRT1 activity by the activator or inhibitor alleviated the clinical symptoms and histological score of joint injury in CAIA. The beneficial effect of the SIRT1 inhibitor was transient, associated with an enlarged BM pool, changes in neutrophil homing, elevated levels of TNF-a and NF-kB binding activity, as well as decreased IL-1b production by the BM and blood neutrophils during disease progression. In early and late stages of disease, as well as in the non-arthritic controls, the SIRT1 activator enhanced IL-1b expression while tuning the mature BM neutrophil pool. At the destructive stage of arthritis, the SIRT1 activator normalized TNF-a production, while IL-1 levels in blood neutrophils remained elevated.
Conclusion: Pharmacological activation of SIRT1 could be a promising therapeutic target in arthritis, but in neutrophils it may differentially modulate TNF-a and IL-1 signalling.

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FT6

A multi-level pain signaling map for inflammatory phenotypes: from knee osteoarthritis to a generalizable systems medicine resource

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Introduction: Pain in knee osteoarthritis (KOA) emerges from interacting molecular, cellular, tissue, neural, and clinical processes, yet existing resources rarely connect these layers in a unified mechanistic framework. The current project addresses this gap by extending a multi-level KOA pain map toward a broader inflammatory pain signaling resource. The long-term goal is to capture pain mechanisms associated with inflammatory phenotypes in general, using KOA as the initial disease context. The resulting resource is intended for community access through the MINERVA platform and conceptual integration with the Atlas of Inflammation Resolution (AIR).
Methods: The base map was constructed in CellDesigner using manually curated literature, transcriptomics, and clinically relevant pain assessment tools, and was anatomically organized from joint pathology through peripheral and spinal pathways to brain processing. We are expanding the map with dedicated submaps for opioid/nociceptor signaling, ascending and descending pain transmission/modulation, Wnt, Notch, and NLRP3 inflammasome signaling, and inflammatory mediators linked to pain. The CellDesigner model connects molecular species, phenotypes, and clinical readouts.
Results: The current map captures key inflammatory and neurobiological hubs (IL6, IL1B, TNF, NGF, BDNF, CCL2, ATP, ROS) together with pain-relevant phenotypes such as nociceptor activation/sensitization, impaired descending modulation, hyperalgesia, allodynia, neuropathic, and chronic pain. It also links mechanistic signaling to clinical assessment layers (VAS, WOMAC, KOOS, PainDETECT, DN4, LANSS, ICOAP, MPQ, and QST). These features support a systems-level representation of pain extending from joint inflammation and remodeling to peripheral and central sensitization, and altered pain perception.
Conclusion: This work establishes the foundation for a scalable pain signaling map that begins with KOA, but is designed to evolve into a general inflammatory pain resource. By combining mechanistic submaps, clinical phenotypes, and interactive deployment in MINERVA with AIR-linked systems biology, the project provides a community-oriented platform for hypothesis generation, data contextualization, and future translational studies in inflammatory pain.

FT7

Metabolic dysregulation disrupts ApoE-dependent resolution of neuroinflammation in Alzheimer's disease

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The apoE4 isoform of apolipoprotein E (ApoE) is the strongest genetic risk factor for late-onset Alzheimer's disease (AD), yet the mechanisms by which ApoE isoforms regulate neuroinflammatory responses and their resolution remain poorly understood. In the present study, we investigated the role of ApoE in modulating brain inflammation and how metabolic comorbidities may influence ApoE-dependent inflammatory resolution pathways. To address this question, we utilized two targeted replacement mouse lines expressing human ApoE3 or ApoE4 (ApoE3-TR and ApoE4-TR). Mice were subjected to a 12-week high-fat diet beginning at 12 weeks of age to model metabolic dysfunction, including dyslipidemia, obesity and insulin resistance, conditions known to exacerbate systemic and central inflammation. Behavioral analyses revealed that ApoE4-TR mice on a high-fat diet exhibited impaired performance in the spontaneous alternation Y-maze test, indicating deficits in working memory. Moreover, sex-specific effects were observed in temporal memory, with ApoE4-TR female mice displaying significant impairments compared to controls. These findings suggest that metabolic stress may aggravate ApoE4-dependent disturbances in brain homeostasis, potentially through impaired regulation and resolution of neuroinflammatory responses. Mechanistic studies in microglial cell cultures further revealed that purified recombinant ApoE regulate inflammatory gene expression. Multiomics data obtained from mouse brain and cultured cell extracts identified novel ApoE-interacting proteins and chromatin regions that could contribute to the role of ApoE in shaping microglial inflammatory programs, which are critical for the initiation and resolution of neuroinflammation. Collectively, our results support a model in which ApoE acts as a key regulator of inflammatory signaling in the brain, integrating metabolic cues with microglial responses. Disruption of these regulatory mechanisms in individuals carrying the ApoE4 isoform may impair the proper resolution of neuroinflammation, thereby contributing to increased vulnerability to Alzheimer's disease.

FT8

ApoE genotype dependent remodelling of astrocyte eicosanoid profiles

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Apolipoprotein E (ApoE) genotype is a major genetic determinant of Alzheimer's disease risk with the ApoE4 allele associated with increased neuroinflammation and altered lipid metabolism. Astrocytes, the primary source of ApoE in the brain, play a central role in regulating lipid homeostasis and inflammatory signaling. This study aims to characterise genotype-dependent differences in eicosanoid profiles between ApoE3/3 and ApoE4/4 human astrocytes using mass spectrometry–based lipidomics.

Astrocytes derived from isogenic ApoE3/3 and ApoE4/4 iPSC cell lines were cultured under standardised conditions, and cellular lipids were extracted and quantified using targeted liquid chromatography–tandem mass spectrometry. A focused panel of eicosanoids, including prostaglandins, leukotrienes, thromboxanes, and hydroxyeicosatetraenoic acids (HETEs), was analysed to assess changes in inflammatory-resolution lipid mediators.

ApoE4/4 astrocytes exhibited a pro-inflammatory lipid signature compared to ApoE3/3 cells. Specifically, increased levels of cyclooxygenase (COX)-derived prostaglandins (PGE2, PGD2) and lipoxygenase (LOX)-derived metabolites (5-HETE, leukotriene B4) in ApoE4/4 astrocytes reflected higher basal inflammatory tone. Conversely, ApoE3/3 astrocytes showed relatively higher levels of anti-inflammatory or pro-resolving lipid mediators, such as epoxy-eicosatrienoic acids (EETs) and lower overall eicosanoid production. These differences may arise from altered phospholipid remodelling, increased arachidonic acid availability, or differential expression/activity of COX, LOX, and cytochrome P450 enzymes in ApoE4-expressing cells.

Overall, this study will provide mechanistic insight into how ApoE genotype influences astrocyte lipid metabolism and inflammatory signaling. Identifying distinct eicosanoid signatures associated with ApoE4 may reveal novel therapeutic targets aimed at modulating neuroinflammation and lipid dysregulation in Alzheimer's disease.

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FT9

A systems approach linking clinical and imaging scores to molecular networks for predicting therapy response in knee osteoarthritis

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Knee osteoarthritis (KOA) is a multifactorial, progressive disease characterized by structural degeneration and chronic inflammation across joint tissues. Current therapeutic strategies remain largely symptomatic, despite advances in imaging-based assessment using semi-quantitative scoring systems such as the Whole-Organ Magnetic Resonance Imaging Score (WORMS). This study presents a systems-level framework that links imaging-derived WORMS parameters to tissue-specific molecular and signaling networks, enabling in silico simulation of disease mechanisms and therapeutic responses.
For each of the eight WORMS features (e.g., cartilage defects, bone marrow lesions, synovitis), the underlying biological processes were first characterized through a targeted literature review to extract relevant anatomical and functional keywords. These keywords were then individually queried in the AmiGO database to retrieve associated Gene Ontology (GO) terms, specifically filtered under the Biological Process (BP) category. GO terms were selected based on careful evaluation of their definitions to ensure biological relevance to the feature of interest. The curated list was also expert-reviewed. Subsequently, all annotated human genes corresponding to the selected GO terms were exported along with their UniProt identifiers and supporting PubMed (PMID) references. The associated literature corpus and feature-specific gene set were then utilized to construct feature-specific submaps using CellDesigner, capturing relevant molecular interactions and pathways. These submaps were subsequently integrated into the Atlas of Inflammation Resolution (AIR) to enable structured representation and downstream analysis of tissue-specific mechanisms.
The framework identified key cross-tissue mechanisms, including extracellular matrix remodeling, osteoclast activation, angiogenesis, macrophage polarization, oxidative stress, and pro-resolving mediator signaling. Simulations reproduced gradient-like activity patterns reflecting WORMS severity scales and highlighted critical regulatory genes such as RUNX2, MMP13, VEGFA, ALOX15, COL2A1, VEGFC, and TGFB1.
This integrative approach bridges imaging phenotypes with molecular dynamics, offering a foundation for simulating therapeutic interventions and advancing personalized, mechanism-based treatment strategies in KOA.

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FT10

Exploring sleep-immune interactions with healthy controls with insights for Schizophrenia

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The brain and the periphery exhibit bidirectional monitoring of immune activity through immunoception. Mounting evidence indicates a role for sleep in immune activity regulation in health and disease. Recent studies suggest that non-REM-specific synchronized cortical slow wave activity is a driving force for glymphatic activity. However, whether sleep stage-specific activity and peripheral immune processes are linked remains unaddressed. We hypothesized that simultaneous observation of the brain and the periphery during sleep would improve our understanding of molecular conduits of CNS/peripheral communication. Furthermore, we predicted that this regulation would be disrupted in schizophrenia as schizophrenia is known to affect both sleep architecture and immune function. To address this, we conducted a comparative study between nineteen healthy individuals and five drug naïve first episode psychosis schizophrenia patients, tracking the CNS and peripheral activity at four distinct stages: before sleep, after non-REM, after REM, and after sleep. Magnetic Resonance (MR) spectroscopy was performed before and after sleep, CNS activity was evaluated using polysomnography. Weighted protein expression analysis from plasma proteomics revealed the complement and coagulation cascades were the most significantly enriched pathways. The correlation maps demonstrated that hierarchical clusters are reorganized between complement activation and blood coagulation profiles as individuals progress into sleep. Despite the small sample size, the SCZ group lacked this dynamic regulation and displayed a kinetic profile for complement activation across all sleep stages. Interestingly, ALPS was found to mediate lectin pathway activator Colec10 levels in plasma. Likewise, peripheral MASP1 protein level responded to the continuous quality of slow-wave sleep but not to how many oscillations occur or how high their absolute power is. Taken together, our results suggest the interplay between sleep and peripheral lectin pathway activity is crucial for homeostasis. Disruption of this interplay may, therefore, serve as a marker and/or diagnostic tool for psychiatric conditions like schizophrenia.

FT11

EPA+DHA and their monohydroxy-oxylipin metabolites increase mitochondrial respiration capacity in M0 but not M1 macrophages

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Introduction & Objectives: Obesity is characterised by chronic low-grade inflammation, which contributes to cardiometabolic diseases. Adipose tissue macrophages play a central role in this process through the secretion of lipid mediators including oxylipins that influence adipocyte function and inflammation. Previous work by Fisk demonstrated reduced levels of DHA-derived oxylipins alongside accumulation of pro-inflammatory macrophages in subcutaneous adipose tissue in human obesity, which were not modified by omega-3 fatty acid (EPA+DHA) supplementation.
Direct oxylipin supplementation may offer an alternative strategy to restore these and modify macrophage function. This study aims to examine the effects of the oxylipins 14-HDHA, 17-HDHA, and 18-HEPE (OXLP), alone or combined with EPA+DHA, on homeostatic (M0-like) and pro-inflammatory (M1-like) macrophages.
Methods: M0- and M1-like macrophages were cultured with EPA+DHA, OXLP, or both for 48-hours. Cell fatty acid composition was analysed by gas chromatography; supernatant oxylipins by UPLC-MS/MS; and mitochondrial respiration by Seahorse respirometry.
Results: EPA+DHA and OXLP increased basal and maximal respiration, ATP production and proton leak ($P<0.026$) in M0-like macrophages only. Inflammatory polarisation of macrophages to M1-like phenotype resulted in a trend for reduced maximal respiration ($P=0.055$) and proton leak ($P=0.068$) by ~50% each. EPA+DHA increased total cell EPA+DHA content ($P<0.002$), and supernatant levels of several oxylipins (HEPEs, HDoHEs, EpDPAs, 5,6,15-triHETE, PGD3, and PGE3) for both macrophage phenotypes ($P<0.05$). Media controls highlighted non-enzymatic oxidation of EPA+DHA which was further elevated in cell experiments. Combined EPA+DHA+OXLP did not produce additive effects.
Conclusion: Treatment of macrophages with EPA+DHA or OXLP in culture modifies homeostatic macrophage respiration. Treatment with EPA+DHA results in non-enzymatic oxidation of EPA, DPA, and DHA to -derived oxylipins. These findings suggest EPA+DHA and OXLP have potential to alter mitochondrial respiration of selected macrophage populations which may have downstream effects for macrophage-adipocyte communication and obesity associated inflammation. Adipocyte-macrophage co-culture experiments are underway to explore this further.

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FT12

Biomimetic lipid nanocarriers of specialized pro-resolving mediators for targeted resolution of atherosclerotic plaque inflammation

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Chronic inflammation is a major contributor to atherosclerotic lesion progression, but current therapies often fail to resolve it effectively. We explored a novel therapeutic approach using a cocktail of specialized pro-resolving mediators (SPMs) encapsulated in biomimetic lipid nanoemulsions cloaked with macrophage membranes (Bio-LN/SPMs) to enhance stability, targeting, and anti-inflammatory activity.
Using both in vitro and in vivo models, we demonstrated that Bio-LN/SPMs significantly reduced inflammatory markers in endothelial cells, smooth muscle cells, and macrophages, outperforming free SPMs. In ApoE-deficient mice with diet-induced atherosclerosis, intravenous administration of Bio-LN/SPMs improved plasma lipid profiles and renal function, modulated circulating monocyte populations toward an anti-inflammatory phenotype, and promoted reparative M2 macrophage polarization within plaques. These effects were accompanied by decreased pro-inflammatory cytokines and reduced lipid accumulation in the aorta.
Our findings highlight the superior efficacy of Bio-LN/SPMs compared to unincorporated SPMs and standard lipid nanoemulsions, demonstrating their potential as a targeted, inflammation-resolving strategy for atherosclerosis and other chronic inflammatory diseases.

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FT13

Maresin 1 remodels hepatic transcriptome, attenuating inflammation and mitochondrial dysfunction in aged female mice with obesity and MASLD

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Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major global health challenge, particularly affecting aging populations and individuals with obesity. The high prevalence and serious consequences of MASLD, including progression to steatohepatitis (MASH), cirrhosis and hepatocarcinoma, underscore the need for therapeutic strategies. Specialized pro-resolving mediators, as Maresin 1 (MaR1), have emerged as promising candidates due to their anti-inflammatory and pro-resolving properties.

This study aimed to elucidate the therapeutic potential and underlying mechanisms of MaR1 in ameliorating hepatic inflammation and mitochondrial dysfunction in a model of aged female mice with obesity and MASLD.

Two-month-old C57BL/6J female mice were fed a high fat diet (HFD, 45%) for 15 months to induce obesity and MASLD. Then, HFD-fed mice were daily treated (i.p.) with MaR1 (15 µg/kg) or vehicle for 20 days. Body weight, body composition, GTT and serum biochemical assays were assayed. Liver samples were obtained and histological analyses were performed. Transcriptomic profile of liver was analysed by RNAseq. Oxygen consumption rate (OCR) was evaluated in isolated liver mitochondria by Seahorse.

MaR1 moderately reduced hepatic triglyceride content and TBARS levels. Transcriptomic analysis revealed that MaR1 orchestrated a remodelling of the hepatic gene expression profile. GO-enrichment analysis revealed that liver of MaR1-treated mice exhibited significant differences in processes related to acute inflammatory response, cytokine-mediated signalling, response to endoplasmic reticulum (ER) stress, protein folding, and regulation of lipid metabolism. Indeed, MaR1 downregulated the expression of genes involved in inflammation and ER stress while upregulating genes involved in liver metabolic homeostasis and mitochondrial biogenesis. Notably, isolated hepatic mitochondria from MaR1-treated mice showed higher OCR. Overall, these results show that MaR1 alleviates hepatic metabolic dysfunction by dampening inflammatory and ER stress pathways while promoting mitochondrial function, supporting MaR1 therapeutic potential in aging and obesity related MASLD.

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FT14

Increased lipid dyshomeostasis in metabolic syndrome due to deletion of Resolvin D2 receptor GPR18

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Introduction and objectives: Metabolic syndrome (MS), with world-wide increasing prevalence, is characterized by cardiovascular risk factors including abdominal obesity, impaired glucose metabolism, and dyslipidemia, often associated with fatty liver disease. The G-protein-coupled receptor (GPR)18 is the receptor for the specialized pro-resolving lipid mediator resolvin D2 (RvD2), and it was recently reported that middle aged mice lacking GPR18 in myeloid cells show increased steatosis and hepatic fibrosis (Fitzgerald et al. Am J Pathol 193:1953, 2023). We aim to evaluate the GPR18 contribution in the plasma and liver lipid metabolism during MS.
Methods: Male adult wild-type (WT) and GPR18 knock-out (KO) mice were placed on a high fat (45% kcal)/high fructose (30%) (HF/HF) diet for 16 weeks. Measurements included: body mass, plasma glucose, plasma and liver lipidomics analysis, and plasma lipoprotein profiles (UHPLC). Liver steatosis (hematoxylin/eosin) and fibrosis (Sirius red) were assessed in by histology. Real-time qPCR was used for gene expression analysis.
Results: We observed increased body mass, blood glucose, and plasma total cholesterol in both WT and KO mice, as well as steatosis, confirming MS development. Plasma and liver free cholesterol and cholesteryl esters were increased in both WT and KO mice on HF/HF diet. However, there were significantly HF/HF-induced higher plasma cholesterol levels in male KO as compared to WT mice, associated with the appearance of plasma LDL. In addition, qPCR analysis showed, only in KO mice on HF/HF diet, decreased expression of hepatic lipoprotein receptors, including the LDL-R, and the lipolysis stimulated lipoprotein receptor, LSR, as well as increased PPARγ expression. Furthermore, lipidomics analysis showed higher levels of hepatic lipids involved in lipid storage in KO as compared to WT mice, consistent with PPARγ's role in lipid storage regulation.
Conclusion: Taken together, these results suggest that the absence of GPR18 exacerbates lipid dyshomeostasis in MS.

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FT15

Inflammatory markers as predictors of postoperative atrial fubrillation in patients undergoing aortic valve replacement

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Background: Postoperative atrial fibrillation (POAF) is a common complication following aortic valve replacement (AVR), associated with increased morbidity and prolonged hospitalization. Inflammation is believed to play a key role in its pathogenesis. Easily accessible inflammatory markers such as neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) may have predictive value for POAF.
Objective: To evaluate the role of preoperative and early postoperative inflammatory markers (NLR, PLR, MLR, SII) as predictors of POAF in patients undergoing isolated AVR.
Methods: This retrospective cohort study included 100 patients who underwent isolated AVR between 2018 and 2025. Patients were divided into two groups: those who developed POAF (cases) and those who did not (controls). Inflammatory markers (NLR, PLR, MLR, SII) were assessed preoperatively and on postoperative days 1, 2, and 3. GraphPad Prism with Two-Way ANOVA test was used to compare marker levels between groups across time points.
Results: A significant increase in NLR was observed on postoperative day 1 (POD1) in patients who developed POAF ($p = 0.0004$). Similarly, PLR values were significantly higher in the POAF group on POD1 ($p = 0.0174$). The SII showed a highly significant elevation on POD1 in cases compared to controls ($p = 0.0001$), indicating a strong inflammatory response. In contrast, MLR did not show statistically significant differences between groups at any time point.
Conclusion: Our findings support the role of systemic inflammation in the development of POAF following AVR. Among the studied markers, NLR, PLR, and SII measured on POD1 may serve as useful predictors for POAF, while MLR appears to have limited predictive value. Incorporating these markers into routine perioperative assessment may improve early risk stratification. Further large-scale prospective studies are needed to validate these findings and establish standardized cutoff values.

FT16

Neutrophil functional polarization in post-myocardial infarction healing: from inflammation to resolution

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Introduction: Cardiac fibroblasts (CFs) demonstrate remarkable plasticity, adopting distinct phenotypes to meet the demands of infarcted myocardium. Although inflammation is a critical driver of post-myocardial infarction (MI) healing, the role of neutrophils in modulating CF phenotypes remains insufficiently explored. We investigated the impact of mediators secreted by neutrophil subtypes - the pro-inflammatory (N1) and anti-inflammatory (N2) - on shaping CFs in vitro, and on the pro-inflammatory and resolution phases post-MI in vivo.

Methods: CFs grown on hydrogel were co-cultured with N1/N2 neutrophils, and various inflammatory, remodeling, and pro-fibrotic molecules were evaluated in CFs and conditioned media. Moreover, the N1/N2 secretome was injected into the infarcted area of a MI-mouse model, and pro-inflammatory, fibrotic, and remodeling mediators were investigated at days 1 and 7 post-MI in plasma and heart tissue.

Results: In vitro findings showed that N1-neutrophils promote a pro-inflammatory and matrix-degrading phenotype to fibroblasts, characterized by overexpression of IL-1β, IL-6, MCP-1, and metalloproteases MMP-3/MMP-9, while suppressing pro-fibrotic molecules. In vivo data showed that at day 1 post-MI, SN1 treatment significantly reduced the IL-1β and IL-6, while increasing α-SMA, and SN2 treatment also significantly downregulated IL-1β, IL-6, and MCP-1, while promoting MMP-1. By day 7, SN1/SN2 treatment maintained the anti-inflammatory state while mitigating fibrotic remodeling by reducing CCN2, α-SMA, and key ECM components, indicating suppression of myofibroblast activation.

Conclusion: Together, these findings suggest that while N1-derived mediators promote a pro-inflammatory fibroblast phenotype in vitro, administration of N1/N2 secretome supports a more balanced reparative response in vivo, potentially mitigating adverse remodeling post-MI.

FT17

In vitro models for epigenomic profiling of respiratory virus infections

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Background: Influenza is a global problem in both humans and livestock, and the virus is continuously evaluating. The current mitigation strategies against influenza are not yet successful in eliminating the virus. Therefore, there are high economic losses every year due to the inefficiency of available strategies. Epigenetic mechanisms may significantly influence the effectiveness of the anti-viral therapies. Understanding of epigenetic mechanisms in hostpathogen systems becomes crucial before designing any disease prediction and prevention strategies.
Objective: This study is designed to characterize the modulation and the possible implication of the epigenetic status of influenza infection in human and avian influenza model. The knowledge may contribute to map the key molecules for defining candidates for biomarker and drug development.
Methods İn vitro infection models were tested whether the epigenetic status of infected cells are modulated during influenza infection or not. The human A549 alveolar epithelial cell line and the avian pulmonary CLEC213 cell line were infected with H1N1 and H7N1 subtypes of influenza. Avian cell model was used to extend our understanding to non-mammal systems. During the course of influenza infections, various histone modifications (acetylation and methylation) were analysed by high-resolution microscopy using fluorescent immunodetection of epigenetic marks. We also determined the global content of DNA methylation using enzymatic approach called the Luminometric Methylation Assay (LUMA). We have extended our analysis to map the infected cell transcriptome to have an overview of the up/down regulated gene profiles involving epigenetic mechanism. The transcriptomic analysis provided us more evidence on the genes involved in epigenetic regulation.
Results & Conclusions: We successfully revealed the influenza infection is accompanied by specific histone modifications in both infection models by immunofluorescent microscopy. The LUMA analysis showed clear DNA hypomethylation of the genome of H1N1 infected A549 cells (non-infected; 49.575%, H1N1 infected; 24.88% and H7N1 infected; 43.685%). Transcriptomic studies evidenced a modulation of the expression of genes associated to DNA methylation. In particular, A549 cells, the host group showed that expression of MDB2 is exacerbated during infection. MDB2 binds to and directs the Nurd complex to methylated DNA while DNMT1 copies existing methylation patterns following DNA replication. DNMT3A and DNMT3B establish new DNA methylation patterns.

FT18

Effects of Resolvin D1 and epi-Resolvin D1 in a mouse model of chlorhexidine induced peritoneal fibrosis

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Resolvin D1 (RvD1) and its aspirin triggered epimer, epiRvD1, are well characterized regulators of inflammatory and fibrotic responses, yet their effects in peritoneal fibrosis remain insufficiently explored. We investigated the influence of intraperitoneal administration of RvD1 and epiRvD1 on inflammation and fibrosis using a mouse model of chlorhexidine (CHX)-induced peritoneal fibrosis. Male C57BL/6J mice received CHX every other day to induce fibrosis, while 100 ng of RvD1 or epiRvD1 were administered daily. Animals were sacrificed at days 7 and 21 to capture early inflammatory and later fibrotic phases.
Systemically, both RvD1 and epiRvD1 significantly reduced the proportion of circulating polymorphonuclear cells at day 7, indicating a potential pro-resolving effect on neutrophil dynamics. However, despite confirmed expression of the RvD1 receptor ALX/FPR2 in inflammatory cells, endothelial cells and muscle-associated cells of the abdominal wall, neither mediator altered local inflammatory cell infiltration, gene expression of IL-6 or SAA isoforms, nor levels of inflammatory cytokines in serum. Likewise, histological assessment and qPCR analysis revealed no detectable effects on fibroblast abundance, extracellular matrix deposition, or expression of key fibrotic genes (COL1A1, ACTA2, TGFB).
Transcriptomic profiling identified limited but consistent changes in gene expression following epiRvD1 treatment. Notably, both RvD1 and epiRvD1 downregulated RARRES2, encoding the inflammatory regulator chemerin, in CHX treated and control mice. This suggests an unexpected cross regulatory interaction among ligands of pro resolving and chemerin-related pathways.
Overall, while RvD1 and epiRvD1 did not mitigate local fibrosis or inflammation in this aggressive model, their systemic effects on neutrophils and negative regulation of RARRES2 highlight important mechanistic insights. These findings contribute to understanding resolution biology and may guide development of therapeutic strategies targeting active resolution rather than classical anti-inflammatory suppression.

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FT19

Effect of resolvins on CFTR expression in lung epithelial cell lines

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Resolvins have been shown to be decreased in patients with cystic fibrosis. However, it is unknown the specific effect of resolvins on the chloride channel and the current assessment. The aim of the study was to use two validated cell lines to analyze the effects of resolvins D1, and D2on CFTR expression in our Hitbit-modified model and to compare them with the effect of Forskolin. There is a mild but significant increase in the expression of the channel and transport upon resolvin D1 stimulation; however, the effect is not observed with resolvin D2. The effect correlates with the decreased amount of resolvin D1 reported in the lung lavage of CF patients. However, the effect of resolcin D2 is unclear. Further analysis is needed to understand the process that induces CFTR channel expression and function.

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FT20

Structural, functional and regulatory aspects of leukotriene biosynthesis

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Leukotrienes are potent bioactive lipid mediators that regulate immune responses and contribute to the pathogenesis of inflammatory diseases, including cardiovascular disorders, asthma, and allergy. Leukotriene biosynthesis is initiated by 5-lipoxygenase (5-LOX) and involves coordinated interactions with partner proteins, cofactors, and membrane environments, forming a dynamic leukotriene biosynthetic complex. While the enzymatic steps of leukotriene production are well established, the structural organization and regulatory mechanisms governing this pathway remain largely unresolved.
This work focuses on the structural, functional, and regulatory aspects of the leukotriene biosynthetic machinery, with particular emphasis on 5-LOX. By integrating structural biology, biochemical approaches, and computational analysis, the project investigates how protein conformation, cofactor interactions, and dynamic structural changes control enzyme activity and pathway output.
Given the central role of 5-LOX in pro-inflammatory leukotriene production and involvement in the generation of pro-resolving lipid mediators, understanding these regulatory mechanisms is essential for defining how lipid mediator balance is achieved under physiological and pathological conditions.
Overall, this work provides a molecular framework for leukotriene pathway regulation and opens new avenues for the development of therapeutic strategies targeting inflammatory responses.

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FT21

Structure-functions of protectins

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Introduction & Objectives: Protectins constitute one of the four superfamilies of specialized pro-resolving mediators (SPMs) and are biosynthesized locally at sites of injury, infection, or pain.
Methods: Using stereocontrolled total synthesis, our group has prepared protectin D1 and its monohydroxylated C22 metabolite (22-OH-PD1), as well as PCTR1, PD1n-3 DPA, and PD2n-3 DPA. Structural validation of each SPM was performed using NMR, HRMS, LC-MS/MS, UV–vis spectroscopy, and multiple reaction monitoring (MRM) matching studies.
Results: The target compounds were synthesized with high stereochemical fidelity, enabling several collaborative structure–function studies. Results from these studies will be presented, along with discussions of new collaborations within the EU RESOLVE network.
Conclusion: Access to synthetic materials for each SPM is essential for conducting extensive biological investigations, as well as for accurate configurational assignment.

FT22

Extracellular vesicles act as critical intermediaries that extend lipid signalling beyond individual cells

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Extracellular vehicles (EVs) have emerged as key mediators of lipid-based intercellular communication, linking membrane phospholipid composition to functional immune responses. Derived from parent cells such as mesenchymal stromal/stem cells (MSCs) or platelets, EVs carry a lipid bilayer enriched with glycerophospholipids and polyunsaturated fatty acids (PUFAs), which serve as precursors for bioactive lipid mediators (LMs).

A central finding across our studies is that EVs not only reflect the lipid composition of their origin cells but also actively participate in regulating inflammation and its resolution. EV membranes are enriched with PUFA-containing phospholipids and harbour key enzymes involved in LM biosynthesis, including phospholipases, cyclooxygenases, and lipoxygenases. This enables EVs to function as mobile platforms capable of producing or delivering both pro-inflammatory mediators (e.g., prostaglandins) and specialized pro-resolving mediators (SPMs), such as resolvins at target sites for their function.

We have shown that supplementation with specific PUFAs (e.g., EPA or DHA) leads to their incorporation into cellular membranes, and these modifications are transferred to EVs. Consequently, EVs exhibit altered lipid mediator profiles, with increased production of pro-resolving mediators that enhance their immunomodulatory potential. This highlights the possibility of engineering EV function through controlled lipid manipulation.

Our results propose that by transporting precursor PUFAs in lipid bilayer, enzymes, and even bioactive mediators, they integrate membrane lipid metabolism with systemic immunoregulation. Targeting EV lipid composition therefore represents a promising strategy to modulate inflammation and improve the efficacy of cell-based and cell-free therapies.

FT23

Limitations of cell count-dependent inflammatory indices in neutropenic sepsis: a clinical and nonlinear modeling approach

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Inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR) are widely used in sepsis but rely on intact leukocyte dynamics, potentially limiting their applicability in neutropenic patients.
We analyzed septic patients across three groups: non-oncologic, hematologic malignancy (HM) without neutropenia, and HM with neutropenia. We compared CRP, NLR, and inflammatory burden index (IBI) across groups and developed a nonlinear mathematical model to assess index behavior under immune cell depletion.
CRP levels were comparable across all groups. However, NLR was significantly reduced in neutropenic patients compared to non-oncologic ($P < 0.001$) and HM non-neutropenic patients ($P < 0.05$), with no difference between the latter two groups. Similarly, IBI was significantly lower in neutropenic patients ($P < 0.0001$ vs non-oncologic; $P < 0.05$ vs HM non-neutropenic), while remaining comparable between non-oncologic and HM non-neutropenic groups. Cell-count-dependent inflammatory indices systematically underestimate inflammatory burden in neutropenic sepsis. Our nonlinear modeling approach demonstrates that this bias arises from intrinsic mathematical constraints of ratio-based biomarkers and provides a framework for correcting index interpretation under conditions of immune cell depletion.

FT24

Acute effects of EPA on endothelial function in two murine models of hyperlipidaemia studied *in vivo* towards better understanding of a possible involvement of 5-LOX and 12/15-LOX-mediated pathways

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Background & objectives: Clinical data shows that eicosapentaenoic acid (EPA) lower cardiovascular risk, although the underlying mechanisms remain not fully explained. Our study aimed to verify whether EPA would improve endothelial function after single administration in vivo and to characterize enzymatic pathways and specialized pro-resolving mediators involved in the EPA-induced endothelial effects in two murine models of hyperlipidaemia.

Methods and results: Murine models used in the study included: APOE*3Leiden E3L.CETP mice featured by endothelial dysfunction development along with hyperlipidaemia and ageing without atherosclerosis as well as ApoE/LDLr-/- mice featured by endothelial dysfunction and atherosclerotic plaques formation. Single EPA administration in both E3L.CETP and ApoE/LDLr-/- mice induced a significant improvement in endothelial function as evidence by magnetic resonance imaging in vivo. Interestingly, administration of lipoxygenase (LOX) modulator such as acetyl-11-keto-β-boswellic acid (AKBA) abolished EPA-mediated vascular response. Plasma lipid mediator profile assessed in E3L.CETP mice after EPA supplementation showed a marked increase in the biosynthesis of 18-HEPE as well as LOX-derived lipid mediators from EPA pathway, and co-administration with AKBA resulted in 12/15-LOX pathway activation not only for EPA, but also arachidonic acid (AA) and docosahexaenoic acid (DHA) pathways, while 5-LOX pathway products remained unchanged. Additionally, AKBA seemed to increase soluble epoxide hydrolase activity and non-enzymatic pathways of EPA, AA and DHA metabolism.

Pharmacological studies in ApoE/LDLr-/- revealed that inhibition of 12-LOX by ML355 significantly improved endothelial function and did not affect EPA-induced improvement of endothelial function, while 5-LOX inhibitor as zileuton abolished EPA-induced endothelial function improvement. Noteworthy, FLAP inhibition by MK886 did not affect EPA-induced vascular response.

Conclusions: Our results directly show the acute improvement of endothelial function by single administration of EPA in murine models of hyperlipidaemia independently on the presence or absence of atherosclerosis. EPA-induced improvement of endothelial function might be mediated by 5-LOX-derived RvEs independent of FLAP activity.

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Posters

P1

The association of vitamin D insufficiency/deficiency with metabolic syndrome, quality of life and depression in postmenopausal women

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Introduction: Vitamin D deficiency is common among postmenopausal women and has been linked to increased cardiometabolic risk and poorer mental health. This cross-sectional study investigated the association between vitamin D insufficiency/deficiency and metabolic syndrome (MetS) risk factors, health-related quality of life (QoL), and symptoms of depression and anxiety in postmenopausal women aged ≥50 years.
Methods: Women attending a handicraft course in Bursa, Türkiye (March 2019) were screened (n=165). Eligible participants with serum 25-hydroxyvitamin D [25(OH)D] levels <30 ng/mL were enrolled (n=150). Vitamin D status was classified as deficiency (<20 ng/mL) or insufficiency (20–<30 ng/mL). MetS was defined according to International Diabetes Federation criteria and assessed by waist circumference (WC), blood pressure (BP), fasting blood glucose, and lipid profile. QoL was evaluated using the SF-36, and psychological status was assessed with the Hospital Anxiety and Depression Scale (HADS).
Results: Overall, 78.7% of participants had vitamin D deficiency, and 21.3% had insufficiency. Compared with the insufficiency group, women with vitamin D deficiency had a higher prevalence of MetS (46.6% vs 18.8%) and significantly higher WC, BP, and fasting blood glucose, together with lower HDL cholesterol (all $P<0.05$). SF-36 subscale scores for physical functioning, vitality/energy, mental health, and general health were significantly lower in the deficiency group ($P<0.05$). HADS depression and anxiety scores were also significantly higher among women with vitamin D deficiency ($P<0.05$).
Conclusion: Among postmenopausal women with low vitamin D status, vitamin D deficiency was associated with a higher prevalence of MetS, a less favorable cardiometabolic profile, poorer QoL, and greater depressive and anxiety symptoms. These findings support the importance of monitoring and addressing vitamin D deficiency in this population.

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P2

Comprehensive analysis of GGCT genes in u's triangle *Brassica* species: insights into abiotic stress responses and potential association of BnaGGCT11/26 with seed weight

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Introduction: Glutathione homeostasis, crucial for plant growth and stress adaptation, is regulated by the enzyme γ-glutamylcyclotransferase (GGCT). As the critical component of the glutathione recycling pathway, GGCT plays a vital role in maintaining cellular redox balance under normal and stressful conditions. While the GGCT gene family has been characterized in *Arabidopsis thaliana*, its diversity, evolution, and functional roles remain unexplored in the U's triangle *Brassica* species, which includes important oilseed crops.
Methods and Results: We identified and characterized 154 putative GGCT genes in U's triangle Brassica species (*Brassica nigra*, 20; *Brassica oleracea*, 21; *Brassica rapa*, 18; *Brassica juncea*, 35; *Brassica napus*, 31; *Brassica carinata*, 29). Phylogenetic analysis grouped these GGCTs into three distinct clades, highlighting their structural and motif diversity. The diversity in cis-regulatory elements highlighted their role in growth and stress responses. Expression profiling of BnaGGCT genes revealed their differential expression patterns across the tissues at different developmental stages, such as BnaGGCT11 and BnaGGCT26, which are specifically expressed during late seed development phases. Furthermore, gene expression analysis under hormones and abiotic stresses indicated their contribution in stress responses as confirmed by eight selected BnaGGCT genes under drought and salt stresses. In addition, SNP analysis of BnaGGCT11 revealed a single-nucleotide variant that is significantly associated with seed weight and yield, potentially influencing gene function or translation efficiency.
Conclusion: Collectively, this study comprehensively identified GGCTs that enhance our understanding of the functional evolution of the GGCT gene family in U's triangle Brassica species and lay the groundwork for further research into GGCT-mediated stress responses and seed development. In particular, the seed-specific expression.

P3

Circadian rhythm in the resolution of inflammation: biological mechanisms and considerations for research and therapies

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Inflammation is a fundamental biological response to infection, injury, and tissue stress, and its timely resolution is essential for maintaining homeostasis. Increasing evidence demonstrates that the circadian rhythm—an endogenous ~24-hour biological timing system—plays a crucial regulatory role in both the initiation and resolution phases of inflammation. The circadian clock operates through interconnected transcriptional–translational feedback loops involving core clock genes such as BMAL1, CLOCK, PER, and CRY, which coordinate physiological processes across immune cells, endocrine signaling, and metabolic pathways.

Immune functions including cytokine secretion, and notably leukocyte trafficking, macrophage polarization, and the production of pro-resolving mediators exhibit strong circadian oscillations. Experimental studies have shown that clock gene dysregulation appear with increased age and disease progression and can alter macrophage activity, neutrophil recruitment, and lipid mediator synthesis, thereby prolonging inflammatory responses and delaying tissue recovery.

Integrating these considerations of temporal dynamics including age context of immune responses has important implications for research and implementation of novelty therapy approaches into clinical practice. In experimental research, circadian timing should be carefully controlled and reported, as variations in sampling time can significantly influence immune and molecular outcomes. Emerging pro-resolving therapies and targeting specify immune cell networks may demonstrate improved outcomes when administered according to circadian patterns of immune activity.

Future research should focus on integrating circadian biology with immunology, systems biology, and translational medicine to identify time-dependent biomarkers and optimize therapeutic schedules. A deeper understanding of circadian control over inflammatory resolution may lead to novel interventions aimed at restoring rhythmic immune regulation and improving outcomes in chronic inflammatory diseases

P4

Region-specific modulation of neuroinflammation by Siponimod in the subacute phase of spinal cord injury

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Introduction: Traumatic spinal cord injury (SCI) triggers a robust neuroinflammatory response that contributes to secondary tissue damage. Targeting glial activation represents a promising therapeutic strategy. Siponimod, a selective sphingosine-1-phosphate (S1P) receptor modulator, has been shown to modulate immune responses by affecting both peripheral lymphocyte migration and central glial cell activity; however, its effects during the subacute phase of SCI remain unclear.
Methods: We evaluated the impact of Siponimod on glial activation and pro-inflammatory gene expression in a rat compression model of SCI at the Th9 level (40 g, 15 minutes). Animals were divided into three groups: sham-operated controls treated with vehicle (5% DMSO), SCI animals treated with vehicle (5% DMSO), and SCI animals treated with Siponimod (2 mg/kg in 5% DMSO). Vehicle or Siponimod was administered intraperitoneally once daily for 7 days. All animals survived for 7 days post-injury, and gene expression was assessed using quantitative PCR (qPCR).
Results: SCI induced a significant increase in microglial activation (Iba1) and pro-inflammatory markers, including IL-1β, IL-6, TNF-α, and iNOS. Siponimod treatment did not uniformly suppress these mediators, as several remained elevated compared to vehicle-treated animals. However, a distinct effect was observed at the level of glial populations. While microglial activation was only partially modulated, Siponimod significantly reduced astrocytic activation (GFAP) at the lesion epicenter, in some cases below control levels.
Conclusion: These findings demonstrate that Siponimod exerts region- and cell-type-specific effects on neuroinflammation during the subacute phase of SCI. Rather than broadly suppressing inflammation, Siponimod appears to selectively modulate glial responses, highlighting its potential role in fine-tuning post-injury inflammatory processes. Ongoing analyses suggest the involvement of S1P-related signaling pathways, warranting further mechanistic investigation.

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P5

Integrated biomarker analysis of colorectal cancer: genetic, inflammatory, and macrophage profiles

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Colorectal cancer (CRC) is driven by a complex interplay between genetic mutations and the inflammatory tumor microenvironment. This study investigates the combined impact of tumor suppressor proteins, systemic inflammation, and macrophage polarization on CRC progression. We analyzed 40 CRC patients and 20 healthy controls. Plasma levels of TP53, APC, and KRAS were quantified via ELISA, while KRAS mutations were assessed using real-time PCR. In parallel, M1 (CD163) and M2 (CD68) macrophage markers were measured by ELISA to evaluate immune polarization. Routine hematology provided inflammatory indices including NLR, PLR, and MLR. CRC patients exhibited elevated TP53 and PLR levels, alongside a pronounced shift in the M1/M2 macrophage ratio, indicative of a pro-inflammatory tumor milieu. KRAS mutations, particularly G12V, were associated with both aggressive tumor behavior and heightened inflammatory/macrophage responses. Correlation analyses revealed a strong link between tumor-related protein expression, systemic inflammation, and macrophage polarization. These findings highlight a bidirectional crosstalk between genetic alterations and immune dysregulation in CRC. The integration of TP53, KRAS/APC status, inflammatory indices, and M1/M2 macrophage balance offers a novel biomarker framework for prognosis and precision therapy development.

P6

In vivo and *in vitro* investigation the regulating role of cell-death-primed MSC-derived secretome in psoriasis

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Introduction: The aim of our research is to investigate the immunoregulatory role of the extracellular vesicles (EVs) derived from mesenchymal stem cells (MSCs) "primed" by cell death in psoriasis. The central question of the project is how the self-perpetuating inflammatory microenvironment characteristic of psoriasis is established and maintained, and how it can be interrupted by targeted cellular regulation. Psoriasis is a chronic, relapsing inflammatory disease in which persistent activation of the innate and adaptive immune systems is observed. We hypothesize that endogenous danger signaling molecules (DAMPs) released from keratinocytes undergoing various forms of regulated cell death play a key role in maintaining immune activation and in the persistent functional reprogramming of leukocytes. This process may contribute to the development of a self-perpetuating inflammatory cycle.
Methods: We investigate the role of cell death-related mediators in the immunopathomechanism of psoriasis, with a particular focus on innate immune cells and T-cell polarization. Based on these, we aimed to optimize a new therapeutic approach: we aim to use the EVs of death-primed MSCs for immunomodulation. Based on our results, the immunoregulatory effect of MSCs is primarily related not to living cells, but to apoptotic cells and the vesicles they produce.
In an imiquimod-induced mouse model, we demonstrated that EVs derived from apoptotic and necroptotic MSCs reduce inflammation more effectively than vesicles derived from other forms of cell death or living cells. In this project, we will compare the composition and effects of these EVs, and investigate their effects on immune cells and T-cell responses in order to uncover the role of molecules that may be crucial in interrupting the self-perpetuating cycle of inflammation and initiating resolution.
Conclusion: Our results may provide new mechanistic insights into the pathogenesis of psoriasis and may lay the foundation for the development of an innovative, cell-free, MSC-based immunotherapy.

P7

Systemic inflammatory indices as prognostic markers in colorectal cancer: insights into immune dysregulation

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Colorectal cancer (CRC) progression is driven by systemic inflammation and impaired resolution mechanisms that promote tumor growth and immune evasion. This study evaluated the prognostic significance of three cost-effective hematological indices - the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) in 81 CRC patients compared to 42 healthy controls. Our results demonstrate that NLR, PLR, and SII are significantly elevated in CRC patients relative to controls, reflecting a systemic pro-inflammatory state. Among these, SII showed the strongest association with disease progression, highlighting its reliability in assessing integrated immune-inflammatory activation. Notably, the observed inflammatory pattern was non-linear; indices were highest in Stage 2 and Stage 4, with a moderate decline observed in Stage 3, likely reflecting complex immune modulation or therapeutic effects during intermediate disease stages. These findings support the clinical utility of accessible hematological markers in complementing conventional staging and risk stratification. While these indices provide immediate prognostic value, our ongoing prospective work involves cytokine profiling of IL-17, IL-32, and TGF-β to further elucidate the molecular mechanisms of dysregulated inflammation-resolution. Ultimately, integrating these markers into routine care facilitates a scalable strategy for the personalized management of CRC and the identification of patients who may benefit from pro-resolving therapeutic interventions.

P8

Stereochemical resolution of specialized pro-resolving mediators using chiral UHPLC-MS/MS

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Lipid mediators are bioactive compounds that play a critical role in the initiation and resolution of inflammation. Derived from omega-3 and omega-6 poly-unsaturated fatty acids, these molecules serve as key signaling components in the immune response. We currently quantify 60 distinct lipid mediators in tissues, plasma, and in vitro cell experiments using a targeted, reversed-phase UHPLC-MS/MS method. While enzymes produce lipid mediators in an enantio- and stereo-selective manner, some are produced non-enzymatically, resulting in racemic mixtures of multiple isomers which reversed-phase UHPLC-MS/MS cannot always separate. This is particularly important for specialized pro-resolving mediators (SPMs), as many of these lipid mediators exist as isomers that differ significantly in their biological activities and receptor interactions. Stereochemical resolution is therefore important to fully understand their individual roles in modulating inflammation and to strengthen in the reliability of the lipid mediators we report.
To determine the isomerism of our identified products, we have developed a chiral analytical method using UHPLC-MS/MS to separate these isomers and assess the presence of isomeric mixtures. We are applying these newly developed analytical methods to improve the lipid mediator analysis, enhancing specificity for the identification of the SPMs.

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P9

Stochastic models in biology

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Stochastic models have become an essential tool in the study of biological systems, where randomness and uncertainty play a fundamental role. By incorporating noise and probabilistic dynamics, these models provide a more realistic description of complex processes such as population dynamics, epidemic spread, and gene regulation. Frameworks based on stochastic differential equations, Markov processes, and jump processes allow for the analysis of variability, rare events, and system stability under uncertainty. This approach not only improves the understanding of biological mechanisms but also supports more accurate prediction and optimal decision-making in applications ranging from ecology to medicine.

P10

Exploring the potential of salivary lipid mediator signatures for early detection of oropharyngeal squamous cell carcinoma

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Introduction: Periodontitis, a chronic inflammatory disease of the oral cavity, has been strongly associated with oropharyngeal squamous cell carcinoma (OPSCC). Clinical observations indicate that patients with OPSCC frequently present with advanced generalized periodontitis during routine pre-treatment dental assessments, suggesting a potential overlap between the two conditions. However, not all individuals with periodontitis develop OPSCC, highlighting important biological differences. We aimed to investigate these differences from a resolution biology perspective. Saliva, being a biofluid bathing both disease sites, provides a relevant and non-invasive medium for such analysis.
Objectives: To determine differences in the salivary lipid mediator profiles between patients with periodontitis and OPSCC.
Methods: We recruited 40 participants, including age-decade and sex-matched healthy controls, patients with generalized Stage III or higher periodontitis, and patients with OPSCC of all stages, from Barts Health NHS Trust, London. Unstimulated whole saliva samples were collected following a 30-minute abstinence from food and drink. Lipid mediator profiling was performed using targeted LC-MS/MS based on established protocols. Data were analysed using both univariate and multivariate statistical approaches.
Results: Multivariate analysis did not demonstrate significant group separation and indicated potential overfitting. However, univariate analysis revealed that periodontitis patients had significantly higher levels of combined Maresin-2 and Maresin-2 n-3 DPA compared to OPSCC patients. In contrast, OPSCC samples showed relatively higher levels of pro-inflammatory prostanoids, including combined PGD2, PGE2, PGF2α, and TXB2.
Conclusion: These findings highlight a differential balance between pro-resolving and pro-inflammatory lipid mediators in periodontitis and OPSCC. The Maresin-to-prostanoid ratio may serve as a potential biomarker for distinguishing these conditions. Further studies in larger cohorts are needed to evaluate whether this could be used for stratification, and prognostication of OPSCC along with early detection.

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P11

Evaluation of different integration and signal to noise algorithms on lipid mediator identification

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Lipid mediators (LM), including specialized pro-resolving mediators and the classic eicosanoids, are crucial in modulating many biological processes as well as inflammation and its timely resolution. Liquid chromatography tandem-mass spectrometry (LC-MS/MS) is extensively used in studying these mediators in biological systems. Analysis of LC-MS/MS datasets relies on integration algorithms that are used to integrate the raw data to generate chromatograms and algorithms to calculate signal to noise (s/n) ratios. There are a range of algorithms available with different software for these analyses.

Due to the considerable differences between measurement tools and the inherently low concentrations of LM biological systems, it is crucial to assess the impact of different algorithms on LM identification.

We evaluated outcomes obtained using algorithms available in Sciex OS. Using either the AutoPeak or MQ4 algorithms for data integration and the Peak-to-Peak, Standard Deviation, and Relative Noise algorithms for calculation of s/n ratios we found that results were essentially identical between the different algorithms when using an external blank and methodologies recommended by the US Pharmacopeia to determine the noise region. Whilst s/n ratios calculated by identifying noise from the region adjacent to the peak of interest demonstrated that Standard Deviation, and Relative Noise algorithms gave similar results. Whereas the Peak-to-Peak algorithm gave s/n values that were largely lower than those calculated using methodologies recommended by the US Pharmacopeia. We also evaluated the influence of smoothing on both peak identification and s/n values. Results from these experiments demonstrated that while differences were observed for peaks with s/n values >20, smoothing had limited impact on the s/n values of low intensity peaks (i.e. s/n <8).

Overall, our findings suggest that comparison of integration algorithms showed minimal impact on s/n ratio calculations, while algorithms for calculating s/n significantly affected the outcome when an external blank is not used.

P12

Selective modulation of GABAA receptors containing the α6 subunit promotes restoration of homeostasis in a human iPSC-derived tri-cell culture model of neuroinflammation

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Introduction: Neuroinflammation is a common feature of many central nervous system (CNS) diseases, acting as either a cause or a consequence of these conditions. In addition to classical immune mechanisms, neuronal γ-aminobutyric acid (GABA) signaling has emerged as an important regulator of inflammatory processes in the CNS. GABAA receptor-mediated pathways have been associated with anti-inflammatory and homeostasis-promoting effects, highlighting specific receptor subtypes as promising pharmacological targets. Therefore, the aim of this study was to evaluate the effect of the α6GABAA receptor positive allosteric modulator DK-I-56-1 on neuroinflammation in vitro.
Method: An hiPSC-based tri-cell culture model of neuroinflammation was used, involving iCell microglia, astrocytes and glutamatergic neurons exposed to lipopolysaccharide (100 ng/ml) and interferon-γ (50 ng/ml) to stimulate an inflammatory response. DK-I-56-1 (0.3 μM) was added two hours after LPS/IFN-γ, and cultivation continued for 14 hours. Fluorescent immunocytochemical staining was performed to evaluate phenotypic characteristics, and culture supernatants were used for cytokine quantification using a multiplex bead-based immunoassay.
Results: In cultures treated with DK-I-56-1, the percentage of Iba1 positive cells (microglia) co-expressing CD86 and CCR7 was significantly reduced, while colocalization with P2Y12 increased compared to LPS/IFN-γ-stimulated controls. Co-localization analysis also showed an increase in EAAT2 signal within the GFAP-positive (astrocytic) area, along with a decrease in co-localization with S100B and vimentin in the treatment group compared to LPS/IFN-γ-stimulated cultures. Additionally, the increase in β III-tubulin-positive area in DK-I-56-1-treated cultures compared to LPS/IFN-γ-stimulated cultures suggests improved neuronal integrity and neurite outgrowth following treatment. Consistent with these cellular changes, a significant reduction in pro-inflammatory cytokine levels (TNF-α, IL-8, IL-6, and GM-CSF) was observed in DK-I-56-1-treated compared to LPS/IFN-γ-stimulated cultures.
Conclusion: Our findings indicate that selective α6 GABAA receptor modulation promotes restoration of CNS homeostasis, as evidenced by reduced inflammatory signaling, a shift toward less reactive astrocyte and microglial phenotypes, and improved neuronal structure.

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P13

Development and validation of a high sensitivity method for the identification and quantitation of specialized pro-resolving mediators and classical eicosanoids

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Lipid mediators, including specialized pro-resolving mediators and classical eicosanoids, are integral to both the onset and resolution of inflammatory responses. Generated via stereoselective oxygenation of C20 and C22 polyunsaturated fatty acids by dedicated enzymes predominantly of cyclooxygenase (COX), lipoxygenase (LOX) and cytochrome P450s (CYP) families, many species are highly potent and endogenously present in very low concentrations. Thus, it is essential to develop sensitive and robust methodologies for the identification and quantitation of these species in biological samples to further our understanding of their biology and role in disease pathogenesis. Here in we developed a sensitive and versatile RP-HPLC MS/MS method for simultaneous analysis of 39 lipid mediator species.

We employed automated reverse-phase C18 Solid Phase Extraction (SPE) with a fractioning step for independent recovery of peptide-conjugated mediators. We employed RP-HPLC for separation of both double-bond isomeric and diastereomeric mediator species, and independently optimised negative and positive sMRM methods allowed for sensitive profiling of both non- and peptide-conjugated mediator subsets. The quantitative analytical method was developed using linear 10-point analyte-to-IS area ratio calibration curves to enable robust comparison between samples, which were validated in both solvent and a surrogate plasma matrix. Matrix effect experiments demonstrated significant ion suppression effects common to ESI-based analysis in complex biological matrices, the method nevertheless exhibiting LLOQs in the region of 0.01 pg and 0.1 pg in phase and plasma matrix respectively. Intra-and interday validation experiments at low, medium, and high concentrations indicated good precision and accuracy, with the relative standard deviations (RSD) ranging from 5-12% and accuracies from 14-20%. Stability experiments indicated the majority of the studied mediators exhibit reasonable stability under storage conditions typical of LC-MS/MS workflows (in extracted plasma matrix, 4 oC, 72 hrs), with some mediators most mediators displaying remarkable stability up to 21 days.

P14

HSP90 inhibitor-loaded nanoparticles show antifibrotic effects in cardiac fibroblasts and reduce systemic inflammation

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Introduction: Cardiac fibrosis is a pathological process driving adverse cardiac remodelling and progression to heart failure, characterised by excessive extracellular matrix deposition following injury. Fibrosis also reflects a defective resolution of post-injury inflammation. The primary effectors of fibrosis are myofibroblasts, which also contribute to its progression by secreting inflammatory mediators. HSP90 inhibitors, such as Alvespimycin (17-DMAG), a derivative of the antibiotic geldanamycin, exhibit anti-fibrotic activity. HSP90 inhibitors modulate TGF-β signalling by disrupting the chaperone's function and destabilising its receptor complex, reducing fibrosis progression. Despite advances in cardiovascular research, the molecular mechanisms underlying fibrotic remodelling remain incompletely understood, and effective therapeutic strategies remain to be developed.
Methods: Nanoparticles (NPs) encapsulating the 17-DMAG were synthesised and conjugated with various fibrosis-homing peptides that recognise extracellular matrix (ECM) components. Antifibrotic activity was evaluated in vitro in primary mouse cardiac fibroblasts activated with TGF-β1 and treated with free or NPs-encapsulated drug. Cardiac fibrosis was induced in C57BL/6 mice through a two-week angiotensin II infusion using implanted osmotic pumps. After identifying the best targeting peptide for optimal accumulation in the fibrotic heart, the therapeutic efficacy of the targeted NPs was assessed.
Results: Fibronectin-targeted NPs significantly reduced ECM markers (periostin, collagen III) in fibroblasts, confirming antifibrotic efficacy. α-SMA expression remained unchanged, consistent with its variable relevance in fibrosis. In vivo, fibronectin-targeted NPs preferentially accumulated in the heart and reduced the fibrotic pathways. Also, they mitigate inflammation by reducing plasma levels of pro-inflammatory cytokines (e.g., TGF-β, IL-6, and IL-1α).
Conclusion: Fibronectin-targeted nanoparticles delivering 17-DMAG reduced fibrosis markers in cultured cardiac fibroblasts and in vivo, confirming antifibrotic efficacy. Also, TGF-β was significantly reduced in the plasma of mice, suggesting a shift toward the resolution phase and potential tissue repair.

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P15

Lipid emulsions affect lipid mediator secretion from primary human macrophages in vitro

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Introduction: Lipid emulsions are an essential part of total parenteral nutrition. However, emulsions rich in n-6 polyunsaturated fatty acids (PUFAs) have been associated with inflammatory side effects. Emulsions rich in n-3 PUFAs made from fish-oil reduce these side effects but they are not environmentally sustainable. A new plant-based formulation, Vegaven, rich in the n-3 PUFA stearidonic acid, has been developed and has shown beneficial effects in mice and piglets. One possible mechanism for the beneficial effects of Vegaven could be the generation of lipid mediators produced by macrophages from the supplied n-3 and n-6 PUFAs. We therefore measured the lipid mediator secretome of human macrophages treated with different lipid emulsions.

Methods: Primary human monocyte derived macrophages were cultured in vitro under serum free conditions and in the presence of either Vegaven, a fish-oil based n-3 rich emulsion, or a n-6 rich emulsion. Macrophages were then polarized to M1 and M2 in the absence of emulsions and the lipid mediator profiles were analyzed in the cell supernatants by UHPLC-MS/MS analysis.

Results: The supernatant of Vegaven treated macrophages contained lower levels of DHA, EPA and arachidonic acid derived lipid mediators compared to the n-3 rich fish oil emulsion, while having increased levels of ALA derived lipid mediators. In contrast, Vegaven treatment led to higher levels of EPA derived lipid mediators in comparison to the n-6 rich emulsion.

Conclusion: These results indicate that the supplied lipid emulsions affect the lipid mediator secretome of macrophages in accordance with the supplied PUFAs. In addition, they show that supplementation with Vegaven increases the levels of EPA derived lipid mediators secreted from macrophages, indicating the conversion of shorter chain n-3 PUFAs to EPA which then serves as a precursor for anti-inflammatory and pro-resolving lipid mediator production.

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P16

Production of specialized pro-resolving mediators and their signaling is altered in a cystic fibrosis mouse model

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Introduction: Cystic fibrosis is characterized by an altered mucociliary clearance driving inflammation and airway tissue degradation. The inflammatory response is exacerbated by bacterial infections leading to respiratory failure and death. The biosynthesis of several Specilaized Proresolving Mediators (SPM) is decreased in CF (Karp, 2004, Ringholz 2014, Shum, 2022). This alteration, more pronounced in women, may contribute to persistent inflammation. In this study, we explored the resolution biology in a murine model of CF, integrating SPM biosynthesis and function, immune cell responses and sex differences.
Methods: We use Scnn1b transgenic mice overexpressing the ENaC causing mucus dehydration and inflammation as described in the airway of CF patients. Resolution effectors are evaluated at homeostasis and after intranasal administration of Pseudomonas aeruginosa LPS. Cells population are analyzed with flow cytometry in bronchoalveolar lavages (BAL) as well as lung tissue. Mucus secretion is evaluated in BALs and lung SPMs content is quantified by LC-MS/MS.
Results: As previously reported (Mall, 2004), BAL from Tg mice displays an inflammatory signature with an increased neutrophils and alveolar macrophages counts and mucus accumulation. Moreover, preliminary data suggests that differentiating and interstitial macrophages from Tg mice express lower levels of ChemR23. The lipidomic analysis of the lungs showed a decreased SPM biosynthesis in Tg mice which is more pronounced in female and is consistent with increased 5-HETE and decreased 12-HETE. LPS administration to mice induces an acute inflammatory response, characterized by persistence of neutrophils in the BAL of Tg mice 72 post-challenge.
Conclusion: These data confirm the inflamed phenotype of Scnn1b Tg mice, suggest defective resolution during inflammatory challenge, and indicate a worse profile in females. They provide a basis to assess the therapeutic potential of SPM administration in this CF model.

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P17

Targeting Nucleolin in myocardial infarction: a promising therapeutic strategy to promote inflammation resolution

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Introduction: A prolonged inflammatory response after myocardial infarction (MI) can lead to adverse cardiac remodeling, fibrosis, and progression to heart failure. Acute inflammation predominates at 2 days post-MI and endogenous SPMs are insufficient to promote resolution of inflammation. Nucleolin (NCL) expression is dynamically upregulated under ischemic conditions and can be redistributed to the cell surface, representing a promising target for nanoparticle-mediated SPMs delivery to the injured myocardium.
Objectives: To investigate the potential of NCL as a molecular target for targeted delivery of SPMs using nanoparticles to enhance inflammation resolution and limit tissue damage in the myocardium following MI.
Methods: Lipid nanoemulsions (LN) were synthesized and functionalized with an NCL-targeting peptide. Fluorescent NCL-targeted (NCL-LN) and non-targeted (LN) nanoemulsions were intravenously administered to C57BL/6 mice post-MI to track biodistribution, and organ fluorescence was measured ex vivo. Resident and infiltrating cells, as well as LN uptake, were analyzed by flow cytometry after enzymatic digestion of left ventricular tissue. SPM receptor expression on cardiac fibroblasts isolated from C57BL/6 mice was assessed by flow cytometry to evaluate their potential responsiveness to SPM therapy after MI.
Results: LN with a hydrodynamic diameter of ~150 nm were prepared and functionalized with an NCL-targeting peptide at ~15 µg/µmol lipid. Although LN accumulated more in the infarcted heart, NCL-targeted nanoparticles were specifically taken up by endothelial cells within the injured myocardium, demonstrating precise cellular targeting. TGF-β-activated cardiac fibroblasts exhibit higher SPM receptor expression than control cells, suggesting increased responsiveness to SPM-mediated immune modulation post-MI.
Conclusion: The data suggest that NCL-targeted lipid nanoemulsions enable precise delivery to endothelial cells in the injured heart, while activated cardiac fibroblasts can respond to SPMs, highlighting the potential of targeted SPM therapy to modulate post-MI inflammation.

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P18

Bioprospecting green seaweed lipids as promising anti-inflammatory and antioxidant ingredients

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Green seaweeds, *Codium tomentosum* and Ulva sp., are an important source of omega-3 polyunsaturated fatty acids (n-3 PUFAs). These fatty acids are mainly found in esterified forms within polar lipids, namely phospholipids and glycolipids, which have been reported to exhibit anti-inflammatory and antioxidant properties, with promising nutritional and functional benefits for use as ingredients in cosmetics and nutricosmetics applications. In vitro assays were performed for the bioprospecting of lipids from *Ulva* sp. and *C. tomentosum* using RAW 264.7 macrophages and the KeratinoSens™ assay.

Co-treatment with lipids from *Ulva* sp. or *C. tomentosum* reduced nitrite (•NO) production from 23.5 ± 1.68 µg/mL to 18.5 ± 1.66 µg/mL at 25 µg/mL, respectively, and from 23.5 ± 1.68 µg/mL to 15.1 ± 1.10 µg/mL and to 16.0 ± 2.66 µg/mL at 50 µg/mL, respectively, in lipopolysaccharide (LPS)-stimulated RAW 264.7 cells in a dose-dependent manner. In the absence of LPS, *C. tomentosum* induced a slight increase in NO production at both 25 and 50 µg/mL. Regarding the KeratinoSens™ assay, lipids from *Ulva* sp. induced only a slight fold increase in luciferase activity for the lowest concentration tested (1.23-fold induction), while lipids from *C. tomentosum* induced fold changes at both 25 and 50 µg/mL (1.55 and 1.52, respectively).

This suggests that both seaweeds may activate the Nrf2 pathway, although at different extents, contributing to antioxidant and anti-inflammatory effects. These findings support the potential use of seaweed-derived lipids for the development of targeted applications aimed at modulating inflammatory processes and promoting health benefits, particularly as ingredients in cosmetic and pharmaceutical industries.

P19

Accumulation of HSP90 inhibitors in the heart, when delivered via fibronectin-targeted nanoparticles, may involve contributions from neutrophils

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Introduction: Cardiac fibrosis is characterized by excessive extracellular matrix (ECM) deposition and inflammatory cell recruitment, leading to myocardial dysfunction. HSP90 supports pro-fibrotic signaling via the TGF-β/SMAD3 pathway, making it a therapeutic target, while circulating immune cells infiltrate injured myocardium and may influence nanoparticle biodistribution. We aimed to develop fibronectin-targeted lipid nanoparticles for the selective delivery of HSP90 inhibitors to the fibrotic myocardium and investigate their interactions with circulating immune cells.
Methods: Nanoparticles (~200 nm; ζ-potential −40 mV) encapsulating HSP90 inhibitors were prepared via oil-water emulsification and sonication, and fibronectin-binding peptides were conjugated using maleimide-thiol chemistry. Biodistribution and immune cell uptake were assessed in an Ang II-induced cardiac fibrosis model using near-infrared imaging and flow cytometry, while TGF-β1-activated cardiac fibroblasts were treated with free or nanoparticle-encapsulated inhibitors to evaluate anti-fibrotic responses by qRT-PCR.
Results: Ang II treatment elevated circulating $CD11b^+$ myeloid cells and neutrophils, indicating systemic immune activation, and caused capillary obstruction, tissue damage, and neutrophil elastase (NE) deposition in the heart. Fibronectin-targeted nanoparticles accumulated preferentially in the heart compared with untargeted nanoparticles. Using flow cytometry, we observed an enhanced uptake of fibronectin-targeted nanoparticles by circulating immune cells, predominantly neutrophils. Functionally, fibronectin-targeted nanoparticles delivering HSP90 inhibitors to activated fibroblasts suppressed fibronectin and collagen III expression, demonstrating a therapeutic effect in attenuating cardiac hypertrophy.
Conclusion: These findings suggest that fibronectin-targeted nanoparticles enhance cardiac specificity and anti-fibrotic effects, with circulating neutrophils potentially facilitating their delivery.

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P20

Favouring anti-inflammatory and pro-resolving features of lung microbiota can ease the burden of chronic inflammatory lung diseases

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Introduction: In healthy lung microbiota has a crucial role in host protection by regulating innate and adaptive lung immunity. But chronic inflammatory lung diseases (e.g. asthma, COPD, PF) are featured by changed lung microbiota, known as dysbiosis. Lung dysbiosis correlates with disease severity and exacerbations, which are associated with morbidity and mortality. Current anti-inflammatory therapy is based on corticosteroids, which may be inefficient in lung inflammation suppression and cannot restore impaired and lost lung tissue. Thus, there is a need to develop a novel, safe and effective therapy that will eliminate disease symptoms and stimulate repair of damaged lung tissue. Lactic acid bacteria (LAB) are recognized by their immunomodulatory and health-promoting effects and are signified as probiotics.
Methods: Immunomodulatory ability of selected LAB was analyzed in human bronchial epithelial cells (BEAS-2B) exposed to LAB strains prior to stimulation with LPS using qRT-PCR method for measuring expression of the genes Il-1β, Il-6 and Il-8.
Results: Significant decrease of at least two analyzed pro-inflammatory genes was detected when BEAS-2B cells were exposed to Lactobacillus plantarum BGPKM22, Lb. paracasei BGAR88-2 and Streptococcus thermophilus BGKMJ1-36. On the contrary, significant increase of Il-6 was detected when BEAS-2B cells were exposed to Lb. plantarum BGAN8, while Il-1β and Il-6 were increased when the cells were exposed to Lb. helveticus BGRA43. Herein, it was shown that LAB exhibit anti-inflammatory or pro-inflammatory effects in interaction with BEAS-2B cells. The strain BGAN8 showed an increase of Il-6 expression, which is a pleiotropic cytokine also characterized by anti-inflammatory, pro-resolving and regenerating properties. Since LAB belong to lung commensals, the composition of lung microbiota determines its state
Conclusion: This opens up the possibility for enrichment of lung microbiota with probiotic strains that can reduce inflammation and stimulate resolution and regeneration of lung tissue, which may be employed in prevention or treatment in chronic inflammatory lung diseases.

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P21

Resolvin D5 reprograms cancer–CD8+ T cell crosstalk to restore antitumor immunity

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The tumor microenvironment (TME) sustains chronic, non-resolving inflammation that promotes dysfunctional crosstalk between cancer cells and CD8+ T cells, ultimately driving T cell exhaustion and loss of antitumor immunity. Although immune checkpoint blockade can partially reinvigorate exhausted CD8+ T cells, most patients do not achieve durable benefit, highlighting the need for new approaches that actively restore immune function and reprogram the inflammatory TME. Specialized pro-resolving mediators hold potent immunomodulatory properties, but their potential to rescue antitumor immunity remains incompletely understood.

Here, using preclinical models of head and neck cancer, we investigated resolvin D5 (RvD5) as a strategy to restore CD8+ T cell-mediated tumor control.

In vitro, RvD5 disrupted the altered crosstalk between cancer cells and CD8+ T cells by relieving CD8 T cells from exhaustion. This immune reprogramming was accompanied by altered tumor cell behavior, resulting in cell cycle arrest and reduced proliferation in both in vitro systems and zebrafish models. In tumor-bearing mice, systemic administration of RvD5 reduced tumor growth and prolonged survival in a CD8+ T cell-dependent manner. Mechanistically, single-cell RNA sequencing showed that RvD5 induces a transcriptional program in CD8+ T cells consistent with enhanced immunomodulatory and antitumor capacity. In parallel, RvD5 remodeled the TME by reducing key pro-tumorigenic chemokines, supporting the concept that engagement of resolution programs can counteract cancer-associated inflammation and restore effective immune surveillance. Notably, RvD5 also synergized with anti-PD-1 therapy in preclinical models.

Together, these findings identify RvD5 as a pro-resolving immunoregulatory mediator that restores CD8+ T cell function and reshapes the TME toward an immune-permissive state. Our results support the emerging concept that activation of resolution pathways may represent a novel therapeutic strategy to enhance cancer immunotherapy.

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P22

The role of IFN-β in regulating the metabolic syndrome induced by high fat diet (HFD) and modulated by the STING biased agonist BiST 2.1

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Interferons (IFNs) are a family of cytokines with critical roles in inflammation, immunoregulation, and tumor surveillance. Type I IFNs, including IFN-β, are produced by diverse immune and stromal cells through various signaling pathways, including the activation of stimulator of IFN genes (STING). Previous studies showed that IFN-β overexpression in diet-induced obesity improved glucose homeostasis, restored insulin sensitivity, promoted adipose thermogenesis, and limited weight gain, highlighting its therapeutic potential in obesity-associated inflammation.

We have previously identified a biased STING agonist that induces the production of IFN-β and IL-10, but not of pro-inflammatory cytokines. Here, we found this biased STING agonist (BiST 2.1) regulates body weight gain, abdominal fat accumulation, and fatty liver appearance in a bell-shaped manner in mice fed with high-fat diet. These responses were parallel to changes in the frequency of $F4/80^{+}/CD206^{hi}$ "M2-like" macrophages in the visceral AT. Thus, biased STING activation seems to regulate obesity-associated features through the regulation of AT macrophage phenotype.

P23

Oxidized phosphatidylcholine species differentially remodel the macrophage lipidome under basal and inflammatory conditions

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Oxidized phospholipids (OxPLs) are found in physiological and several pathological conditions, and are key bioactive mediators involved in inflammation and immune regulation. However, the specific effects of oxidized forms of different phospholipids (PLs) with varying fatty acyl chains on macrophage function remain poorly understood.
In this study, we conducted an untargeted lipidomic analysis to examine how two oxidized phosphatidylcholines (OxPC) species—esterified with n-6 or n-3 fatty acyl chains, namely PC18:0/18:2 (n6-OxPC) and PC18:0/22:6 (n3-OxPC)—affect RAW264.7 macrophages under resting and lipopolysaccharide (LPS)-stimulated conditions.
Neither OxPCs promoted a pro-inflammatory phenotype in macrophages when administered without other stimuli. Under LPS stimulation, OxPCs altered the lipid profile associated with the macrophage inflammatory response, suggesting a reduction in inflammation. LPS exposure increased several alkyl-acyl phosphatidylcholine species containing saturated fatty acids compared to the non-inflammatory state. Notably, the levels of these species decreased toward baseline following treatment with both OxPCs. Other lipidomic changes induced by OxPC under LPS conditions included an increase in ceramides, particularly in n3-OxPC, which are linked to enhanced phagocytic capacity. The reduction of PC.O, PC.P, PE.O, PI.P, mainly in n-6-OxPL, may indicate the utilization of PUFA for cytokine production or, in the case of n-3-OxPL, its use as a PE.P precursor to boost antioxidant capacity. The rise in LPL, mainly in n-6-OxPC, might suggest increased oxidative stress or a lipid adaptation related to M2 macrophage polarization and anti-inflammatory processes, as these cells display higher LPL levels than M1 macrophages.
Overall, OxPCs seem to modulate immune responses by selectively amplifying or suppressing specific lipid pathways critical for macrophage phagocytosis and cytokine production and secretion. These findings support the idea that OxPLs act as regulators of macrophages, inducing either a pro-inflammatory or anti-inflammatory phenotype depending on the structure of the oxidized phospholipid, driving cellular adaptation to minimize pro-inflammatory signaling and prevent excessive tissue damage.

P24

Combining high-throughput lipidomics, metabolomics and cytokinomics to characterize the systemic inflammatory and immunometabolic landscape of patients with advanced liver disease

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Patients with advanced liver disease exhibit pronounced, unresolved systemic inflammation that is causally linked to the development of multi-organ failure, a severe condition with high short-term mortality known as acute-on-chronic liver failure (ACLF). In this study, we characterized the systemic secretome using an integrated multi-omics approach combining lipidomics, metabolomics, and cytokinomics to identify molecular signatures associated with infections, ACLF development and mortality in patients with acutely decompensated cirrhosis (ADC).

Plasma and serum samples from 766 patients with ADC were analyzed. Targeted lipidomics of immunomodulatory lipid mediators and untargeted metabolomics were performed using liquid chromatography-mass spectrometry, while cytokines, chemokines, and growth factors were quantified using multiplex bead-based immunoassays. A multiscale, multifactorial regression network model was developed to integrate the multi-omics datasets and identify features significantly associated with clinical outcomes.

Among the 291 features included in the integrated omics analysis, we identified 22 (10 lipid mediators, 7 metabolites and 5 cytokines) associated with the clinical outcome, including the pro-resolving pathway marker 15-HETE, which was negatively associated with infections; sphingosine-1-phosphate with negative association with ACLF; and 20-HETE, which was connected with both hexanoylcarnitine and acetylcarnitine, suggesting coordinated metabolic regulation with mitochondrial dysfunction.

The 20-HETE-acylcarnitines network was experimentally validated in peripheral leukocytes, where 20-HETE was shown to induce mitochondrial oxidative stress and impair mitochondrial respiration via a GPR75-Akt signaling pathway. Finally, the network features served as early predictors of ADC outcomes, a finding that was independently validated in an external cohort of 580 ADC patients. Taken together, these findings underscore the critical role of immunomodulatory lipid mediators in modulating the course of ACLF and in determining mortality risk in advanced liver disease.

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3D ZnO@Ag-based nanopatterned detection platform for SERS diagnosis of neurodegenerative diseases from in vivo samples: an innovative approach

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The spectroscopic profiling for NDs diagnosis has emerged as a nondestructive and precise instrument, with minimal sample preparation. Among them, surface enhanced-Raman spectroscopy (SERS) has become a hotspot for medical applied research, leveraging the excellent optical properties of nanomaterials to enhance the detection performance. Its main advantages refer to the ultra-high sensitivity, resistance to photobleaching and photodegradation, and low interference in water.

We have fabricated a hybrid SERS-active sensing platform able to identify and differentiate between relevant Parkinson's disease (PD) biomarkers in clinical tissue samples of mouse striatum and cortical with induced PD. The proposed assay can achieve an ultralow dopamine (DA) determination at the nM level, a short testing time (< 30 minutes), and high signal reproducibility (RSD 11%). We also assessed the sensing attributes of our in house developed SERS platform to detect DA in spiked aCSF samples, and a limit of detection (LOD) of 10 μM was achieved.

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Human model–based insights into immune-metabolic control of atherosclerosis progression and therapy response.

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Introduction: Atherosclerosis arises from the interplay between dyslipidaemia, metabolic dysfunction and chronic low-grade-inflammation. Traditionally, lipid- and glucose-lowering agents tackle lipid imbalance and glucose dysregulation. Specialised pro-resolving mediators (SPMs) endogenously orchestrate resolution of inflammation, and, recently, stable mimetics with therapeutic potential have been developed (Fig.1). Existing in vitro and in vivo models incompletely reflect human plaque biology, limiting mechanistic understanding and therapeutic innovation. The aim of this work is to develop a translational platform, combining ex vivo human carotid endarterectomy models with in vitro monocyte/macrophage/foam-cells, to investigate how these risk factors contribute to atheroprogression, identifying therapeutic targets.

Methods: Human tissues were stimulated with TNF (5ng/mL,24h) alongside SPMs for transcriptomic/proteomic analyses. Parallel in vitro studies used MCSF-driven-THP-1-derived macrophages, polarised using IL-1B, TNF, IL-10 or IL-4. Cells were exposed to SPMs, atorvastatin, or GLP-1RA (Liraglutide) with high glucose (25mM).

Downstream measurements included transcriptomic/secretomic analyses, monocyte–macrophage migration, foam-cell formation, apoptosis and metabolic profiling of glucose-challenged-cells. A minimum of three independent experiments was used for in vitro models and at least five donors for ex vivo studies. Statistical analyses used ANOVA or paired t-tests ($p<0.05$).

Results: Ex vivo plaque tissues remained responsive: TNF increased gene expression of inflammatory markers (including IL-6 and OLR1), reducing IL-18; responses counteracted by SPMs. SPMs modulated an 11-protein-secretome "signature" in TNF-treated-plaque, with Ingenuity Pathway Analysis revealing enhanced phagocytosis, while suppressing leukocyte migration. In vitro, pro-inflammatory-macrophages showed enhanced foam-cell formation and differential regulation of cholesterol-influx (OLR1) and -efflux proteins (ABCA1), modifiable by SPMs or atorvastatin. High glucose altered the monocyte/macrophage phenotype, enhancing glucose consumption and modifying inflammatory gene expression (increasing TRAIL in monocytes and CD163 in macrophages). In glucose-challenged-macrophages, SPMs increased the release of IL-1β and IL-18, whilst reducing migration. Liraglutide reduced MCP-1 and TNF expression, and IL-1β release.

Conclusions: This translational platform recapitulates key inflammatory, metabolic, lipid-handling pathways in human atheroprogression, enabling screening of emerging immune-metabolic-therapies.

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Specialized pro-resolving mediators in cystic fibrosis airway disease

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In cystic fibrosis, there is a reduction in the airway surface fluid layer (ASL). This results in abnormal ciliary beats and impaired clearance of pathogens such as the bacterium Pseudomonas aeruginosa or the filamentous fungus Aspergillus fumigatus. Repeated infections lead to persistent airway inflammation and a progressive decline in lung function. Acute inflammation is normally followed by an active resolution phase involving specialized pro-resolvent mediators (SPMs) such as lipoxins (LX), resolvins (Rv), and maresins (MaR). However, CF is characterized by impaired inflammatory resolution.