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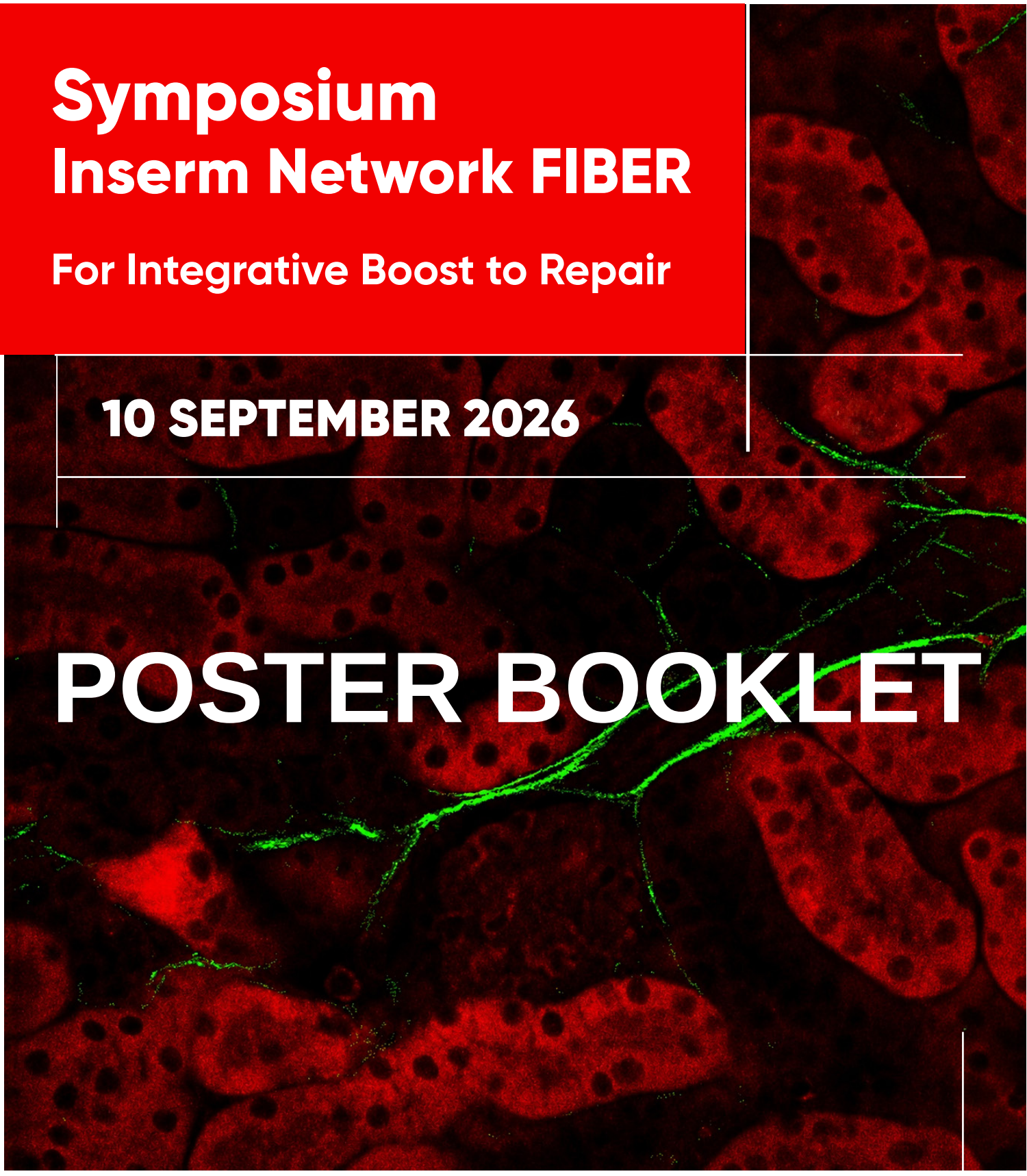

10 SEPTEMBER 2026

POSTER BOOKLET

Abstract Number	Presenting Author	Title
Topic: Chrono-Matrix		
1	Amanda Oliveira	A Weight Loss-Specific Fibrotic Response in Visceral Fat Is Driven by Defective Lysosome-Dependent Collagenolysis
Topic: Immuno-Matrix		
2	Guilhem Graveron	Uncovering endogenous pro-resolving immune-stromal programs in skin fibrosis
3	Marie Piollet	Neutrophil terminal programming in the ischemic heart drives fibrosis after myocardial infarction
4	Nicolas Perrard	Generation, viability assessment and fibrotic transformation of a novel organotypic model for cutaneous fibrosis: basis for therapeutic optimisation in systemic sclerosis
Topic: Interorgan Fibrosis		
5	Li Luo	Molecular Mechanisms Linking the Fibrotic Microenvironment to Lung Cancer Development in Idiopathic Pulmonary Fibrosis
6	Guerroumi As-sakina	Development and Characterization of Precision-Cut Mesenteric Adipose Tissue Slices as an Organotypic Model for Intestinal Fibrosis
Topic: Imaging Matrix		
7	Laura Chastagnier	Innovative Nanobody-based Approaches to Diagnose and Treat Collagen Deposition in Fibrotic Disorders through PCPE1 Targeting
Topic: FibroMarkers		
8	Méline Ricol	Investigating collagen I biosynthesis: molecular pathways and microenvironmental influences
9	Salomé Patry	Beyond crystalline silica: Engineered Stone (ES) exposure drives lung inflammation and fibrosis in 129/Sv Mice
10	Baptiste Rigoux	Legumain (asparaginyl endopeptidase) and cathepsin V participate in matrix remodeling during lung fibrosis
11	Lise Ratel	Effect of recombinant IL-33 on EMT process in colon and ileum human organoids
12	Mathilde Leboutte	The mineralocorticoid receptor in smooth muscle cells modulates gut barrier function in mice and human colonic organoids: does this predispose for intestinal fibrosis?
13	Elise Rebollo	Neutrophil Gelatinase Associated Lipocalin (NGAL) invalidation in myeloid cells did not improve inflammation but reduced fibrosis in mice with colitis
14	Sara Al Issa	Characterization of a transcriptomic signature associated to septin cytoskeleton relocalization in response to various stresses : study of its possible function in early
15	Léna E Silva	Lipidomics of extracellular vesicles from bronchoalveolar lavage identifies new target for pulmonary fibrosis
16	Divya Prabhakar Reddy	Modulation of proteoglycans expression in a bleomycin-induced pulmonary fibrosis model in mice
17	Wenrui Gao	Identification of Sfrp1 in portal fibroblasts and impact on biliary fibrosis development
18	Zhenyi Zhao	Assessing the effects of Nicotinamide Riboside (NR) combined with exercise training in heart failure with preserved ejection fraction
19	Perrine Singla	Patient-Derived Organoids Identify Epithelial Mechanisms Underlying Fibrosis in Endometriosis
20	Laura Muraine	Collagen VI is a fibrosis-associated signal disrupting muscle regeneration across distinct human myopathies
21	Mariana Amaral Raposo	Promoter-Driven Depletion of Fibrogenic Cells as a Therapeutic Strategy for Liver fibrosis
Topic: Preclinical Matrix		
22	Maéva Loriot	New therapeutic targets for hepatic fibrosis in MASLD: the SGLT2 cotransporter and the cannabinoid-1 receptor
23	Maria Bergas Buades	Modeling Fibrosis in Oculopharyngeal Muscular Dystrophy using engineered 3D human Skeletal Muscle
24	Mariia Pestriakova	Exploring the Antifibrotic Potential of the Heparan Sulfate Mimetic OTR4132 on Validated Human Precision-Cut Lung Slices (hPCLS) Model Mimicking Pulmonary
25	Karim Tazibet	Development of mouse and pig models of pulmonary fibrosis and gene inhibition testing of potential therapeutic targets
26	Florent Morfoisse	Role of Lysyl Oxidase in the pathological interplay between extracellular matrix and lymphatics in secondary lymphedema
27	Stefano Biressi	Reduced fibrosis after in vivo inhibition of complement C1 in Duchenne Muscular Dystrophy

Symposium FIBER - September 10th, 2026

Chrono-Matrix

Poster 1

A Weight Loss-Specific Fibrotic Response in Visceral Fat Is Driven by Defective Lysosome-Dependent Collagenolysis

Amanda Oliveira

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Introduction and Aim: Obesity induces profound pathological remodeling of adipose tissue (AT), including chronic inflammation and fibrosis, which contribute to metabolic dysfunction. Although weight loss improves systemic metabolism, its impact on adipose tissue remodeling and long-term tissue integrity remains unclear. We aimed to determine how visceral adipose tissue (VAT) adapts to weight loss and to identify the mechanisms limiting its recovery.

Methods: We used a murine model of diet-induced obesity followed by weight loss. Adipose tissue remodeling was assessed through histological, transcriptional and functional analyses, with a focus on extracellular matrix (ECM) dynamics and collagen turnover. Collagenolytic activity was evaluated in macrophages and progenitor cells, and pharmacological inhibition of ECM production was used to assess its contribution to fibrosis.

Results: Despite normalization of body weight and glucose homeostasis, VAT exhibited incomplete recovery following weight loss. Persistent adipocyte dysfunction and macrophage infiltration were observed. Notably, fibrosis continued to accumulate, even though transcriptional analyses showed reduced ECM production. Mechanistically, we identified impaired collagen degradation as a key driver of this paradox. Both macrophages and progenitor cells displayed defective collagenolytic activity, limiting ECM clearance. Consistent with this, inhibition of ECM synthesis reduced fibrosis during obesity development but failed to prevent fibrosis during weight loss.

Conclusion: These findings reveal a previously unrecognized, weight loss-specific fibrotic program in VAT, driven by impaired matrix degradation rather than excessive production. Our work shifts the current paradigm and identifies collagenolysis as a promising therapeutic target to restore adipose tissue function after weight loss.

Symposium FIBER - September 10th, 2026
Immuno-Matrix

Poster 2
Uncovering endogenous pro-resolving immune-stromal programs in skin fibrosis

Guilhem Graveron

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Systemic sclerosis is a chronic autoimmune disease characterized by immune dysregulation, vascular damage, and progressive fibrosis of the skin and internal organs. Although skin fibrosis can partially regress in some patients, the cellular and molecular mechanisms underlying this resolution remain poorly understood.
Fibrosis can be viewed as a maladaptive tissue repair response to chronic injury, in which persistent fibroblast activation and excessive extracellular matrix deposition lead to pathological scarring. In some experimental models of skin fibrosis, cessation of the fibrotic stimulus is followed by a spontaneous phase of tissue remodeling. This observation suggests that fibrotic tissues retain endogenous programs capable of limiting, remodeling, or resolving fibrosis. To date, most therapeutic approaches have focused on preventing matrix accumulation during the active phase of disease, whereas the mechanisms driving fibrosis resolution remain largely unexplored.
In this study, we use the hypochlorous acid (HOCl)-induced mouse model of skin fibrosis, which recapitulates several features of systemic sclerosis. To characterize the transition from active fibrosis to tissue recovery, we analyzed the skin at peak fibrosis, corresponding to cessation of the fibrotic stimulus, and at multiple time points thereafter to follow the phase of spontaneous remodeling. Using an integrative approach combining single-cell RNA sequencing, flow cytometry, conventional histology, and imaging mass cytometry, we reveal major time-dependent immune-stromal remodeling. The fibrotic phase is associated with profound reshaping of the myeloid compartment, marked by recruitment of monocyte-derived macrophages and progressive replacement of tissue-resident macrophages. In parallel, the stromal compartment displays marked dynamics, with loss of homeostatic $Pi16^{+}$fibroblasts at peak fibrosis, emergence of specialized fibroblast states, remodeling of vascular mural populations including pericytes and vascular smooth muscle cells, and progressive reappearance of $Pi16^{+}$fibroblasts during tissue recovery.
Altogether, these results suggest that skin fibrosis resolution does not simply reflect passive extinction of inflammation, but instead involves coordinated reorganization of immune and stromal compartments. This project aims to shift the therapeutic paradigm from inhibiting matrix accumulation toward identifying endogenous pro-resolving programs, which may open new perspectives for systemic sclerosis and other chronic fibrotic diseases.

Symposium FIBER - September 10th, 2026
Immuno-Matrix

Poster 3
Neutrophil terminal programming in the ischemic heart drives fibrosis after myocardial infarction

Marie Piollet

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Following myocardial infarction (MI), the heart undergoes massive neutrophil infiltration characterized by the emergence of distinct subsets, notably a SiglecF+ population that accumulates according to specific temporal dynamics. The mechanisms governing cardiac neutrophil heterogeneity and the functional impact of this diversity on tissue repair following MI remain to be elucidated. Using single-cell RNA-sequencing of neutrophils in the heart and peripheral organs of infarcted mice, we show that while acquisition of the SiglecF+ state only occurs in the ischemic heart tissue, MI primes neutrophils in the periphery to acquire Siglecf and to upregulate receptors for TGFβ and GM-CSF that drive acquisition of the SiglecF+ state. Ly6G targeting in vivo shifted cardiac neutrophils towards the SiglecF+ state at day 3 post-MI, induced the emergence of reprogrammed SiglecF+Ly6Glo and Retnlghi neutrophil states at day 5, and was associated with increased fibrosis of the infarct border zone. Mechanistically, Ly6G targeting reshaped the cardiac immune landscape with increased recruitment of pro-fibrotic γδ T cells and monocytes, and SiglecF+ neutrophils exerted direct pro-fibrotic effects on fibroblasts in a co-culture system. Altogether, our results indicate that peripheral neutrophil priming combined with their terminal programming towards a SiglecF+ state in the ischemic heart drives cardiac fibrosis after MI.

Symposium FIBER - September 10th, 2026
Immuno-Matrix

Poster 4

Generation, viability assessment and fibrotic transformation of a novel organotypic model for cutaneous fibrosis: basis for therapeutic optimisation in systemic sclerosis

Nicolas Perrard

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Background
Systemic sclerosis (SSc) is a chronic inflammatory disease characterized by vasculopathy, impaired immune response, and progressive fibrosis of multiple organs, which may ultimately lead to organ dysfunction. Despite significant progress in understanding the pathophysiology of fibrotic processes, the lack of a curative treatment for fibrosis in SSc is partly linked to the absence of experimental models capable of recapitulating the complexity of the pathophysiological mechanisms underlying cutaneous fibrosis in SSc.
We describe here a novel model of cutaneous fibrosis using murine Precision Cut Skin Slices (mPCSS), which aims to be readily reproducible and to recapitulate SSc pathophysiology.
Methods
mPCSS were generated from BALB/c mice skin using a semi-automated vibrating microtome (VF-300OZ - Precisionary Instruments) and maintained in supplemented Dulbecco's Modified Eagle Medium.
Viability was assessed using ATP quantification in slices and the presence of LDH in culture media, while architecture was assessed by histology.
Fibrotic transformation of mPCSS was performed using a sequential stimulation strategy comprising a first vascular/ischemic stimulus (inherent to the PCSS generation process itself), followed by a second inflammatory stimulus (TNF-α/IL-1β) and a third pro-fibrotic stimulus (TGF-β) added to the culture media.
Results
mPCSS maintain preserved viability for up to 7 days of culture, as evidenced by stable intracellular ATP concentrations, reflecting cellular metabolic activity. A significant decline in ATP levels was observed from day 8 of culture onwards, with an inverse correlation between mean daily ATP quantification and LDH detection ($r = -0.76$, $p = 0.03$, non-parametric Spearman correlation). Histological analyses confirmed the preservation of murine skin architecture. Progressive epithelial desquamation was observed from day 6 of culture, suggestive of selective keratinocyte impairment, alongside progressive disorganization of the overall skin architecture.
RT-qPCR analysis revealed a significant increase in the transcription of inflammatory genes at days 2 and 4 of stimulation, as well as a significant upregulation of Fn1 transcription (encoding fibronectin) following TGF-β addition. Non-sequential co-administration of all three cytokines did not appear to induce significant fibrosis. The significant upregulation of Fn1 transcription was confirmed in a second independent experiment in a dose-dependent manner using increasing TGF-β concentrations.
Conclusion

This work will enable exploration of key pathophysiological mechanisms of fibrosis using innovative organotypic models of murine skin. The knowledge generated will facilitate translation to human disease, advancing precision medicine approaches and support the development of innovative combined therapeutic strategies in SSc. Ultimately, this research could pave the way for more effective therapeutic strategies for patients with chronic inflammatory and fibrotic disorders.

Symposium FIBER - September 10th, 2026
Interorgan fibrosis

Poster 5
Molecular Mechanisms Linking the Fibrotic Microenvironment to Lung Cancer Development in Idiopathic Pulmonary Fibrosis

Li Luo

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Background: Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal lung disease associated with a markedly increased risk of lung cancer (LC). The mechanisms by which the fibrotic microenvironment promotes carcinogenesis remain poorly understood.
Methods: We established an inducible tdTomato,KrasLSL-G12D mouse model combining pulmonary fibrosis and lung cancer. Lung fibrosis was induced in tdTomato,KrasLSL-G12D mice by intratracheal bleomycin (bleo) instillation, with fibrosis established within two weeks; saline (SAL) instillation served as a sham control. At day 14 after bleo or saline treatment, Ad-Cre was administered via the endotracheal route to activate the KrasLSL-G12D allele and the tdTomato reporter to initiate tumorigenesis ("PF+LC" group). Saline-treated tdTomato/KrasLSL-G12D mice given Ad-Cre developed only limited epithelial changes ("LC" group). The tdTomato,Kras+/+ mice treated with bleo or saline and then Ad-Cre served as "PF" and "SAL" control groups, respectively. Mice were analyzed at short-term (day 28) and long-term (day 104) time points. Tomato+ cells were detected and characterized by immunohistochemistry (IHC). Immune cells were analyzed using IHC and FACS. Bulk RNA-seq transcriptome analysis was performed at day 104.
Results: the PF+LC mice displayed greater lung injury, increased TTF1^{+}/Tomato^{+}epithelial lesions at both time points, and enhanced immune infiltration (CD45+, CD3+ by IHC), but decreased NK cell recruitment in both the bronchoalveolar lavage fluid and lung tissue by FACS compared with the PF or LC alone groups at day 28. The enhanced tumorigenesis observed in the PF+LC animals was associated with increased expression of PGE2 receptors (Ptger1 and Ptger2) at both time points. Analyzing the bulk RNA-seq data at day 104, the parenchyma and immune signatures were investigated. It was observed that the basal/squamous metaplasia markers Sox2 and Krt14 (confirmed by qPCR and IHC) were upregulated in PF+LC mice, along with EGFR (Areg, Ereg) and FGFR (Fgf9) pathway ligands (confirmed by qPCR). As for the immune signature, transcriptomic profiling revealed a divergent landscape characterized by a "cold" T lymphocyte suppressed axis alongside an active tumor/myeloid/plasmocyte axis.
Conclusions: Our findings strongly suggest that PF enhances carcinogenesis in vivo from an early stage, with a shift toward squamous tumorigenesis at late time points associated with immune reshaping compared to mice with either cancer or lung fibrosis alone. The role of PGE2/PTGER and EGFR signaling pathways in this model of pulmonary fibrosis-associated lung carcinogenesis will be further investigated.

Symposium FIBER - September 10th, 2026
Interorgan fibrosis

Poster 6
Development and Characterization of Precision-Cut Mesenteric Adipose Tissue Slices as an Organotypic Model for Intestinal Fibrosis

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Introduction: Mesenteric adipose tissue, commonly referred to as creeping fat, is a hallmark feature of inflammatory bowel disease (IBD) and has been associated with active disease since the 1930s. Creeping fat correlates positively with transmural inflammation, intestinal fibrosis, and stricture formation. Adipose tissue is now widely recognized as an active immunometabolic organ that contributes to inflammation and fibrosis in several pathological conditions, including obesity, diabetes, systemic sclerosis, and pulmonary fibrosis. Despite these associations, the mechanisms by which mesenteric adipose tissue promotes intestinal fibrogenesis remain poorly understood.
The present study aimed to optimize existing protocols to develop and characterize a precision-cut adipose tissue slice (PCATS) model for the study of mesenteric adipose tissue in a fibrotic setting. By preserving the native cellular composition and extracellular matrix architecture, the PCATS model could provide a physiologically relevant platform to investigate the contribution of mesenteric adipose tissue to intestinal fibrosis.
Methods: Mesenteric adipose tissue was collected from patients with IBD and non-IBD controls within 6 hours after surgery. Whole adipose tissue was embedded in 5% agarose and sectioned into 500 µm slices using a Compresstome vibrating microtome. PCATS were maintained in culture for up to 5 days. Samples were collected on days 0 to 5 for RNA extraction, histological and morphological assessment, immunohistochemical characterization and cellular composition analysis. Viability and cytotoxicity assays were also assessed using culture supernatants.
Results: PCATS remained viable throughout the culture period. Cytotoxicity increased by day 5 but did not exceed levels observed in the high-control condition. Tissue morphology was preserved, with no detectable alteration attributable to either the sectioning procedure or the duration of culture. Hypoxic regions were observed in a subset of PCATS after 2 days in culture, notably, these areas were localized at the periphery rather than the core of the slices, suggesting that hypoxia may not be related to tissue thickness.
Conclusion: This study demonstrates that, by preserving the native cellular diversity, tissue architecture, and extracellular matrix, precision-cut adipose tissue slices (PCATS) provide a valuable experimental platform for investigating adipose tissue-driven mechanisms of intestinal fibrosis and, ultimately, for supporting the development of novel anti-fibrotic therapies for patients with inflammatory bowel disease.

Symposium FIBER - September 10th, 2026
Imaging Matrix

Poster 7
Innovative Nanobody-based Approaches to Diagnose and Treat Collagen Deposition in Fibrotic Disorders through PCPE1 Targeting

Laura Chastagnier

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Introduction & Aim: Fibrosis is a pathological process defined by the abnormal accumulation of extracellular matrix, primarily fibrillar collagens, leading to organ dysfunction. With fibrotic disorders accounting for up to 35% of global mortality (2019)1, the lack of effective early diagnostics and treatments is a major public health challenge. Understanding fibrosis mechanisms and developing specific therapeutic and diagnostic tools is critical.
This study introduces nanobodies-single-chain antibody fragments-targeting PCPE1 (Procollagen C-proteinase enhancer 1), a potent enhancer of BMP1/tolloid-like proteinases (BTPs), which is key in collagen biosynthesis. PCPE1 is upregulated in most fibrotic conditions, correlates with tissue collagen levels, and is specific to collagen biosynthesis. Previously, we engineered the first generation of anti-PCPE1 nanobodies to inhibit its interaction with procollagens2. Here, we further characterize their theranostic potential in vitro and in cellular fibrosis models.
Methods: Nanobodies were produced in bacteria or mammalian cells. Their activity on procollagen maturation was assessed in vitro via cleavage assays of mini-procollagens by BMP-1 in the presence of PCPE1. Fluorescent versions were generated using sortase-mediated coupling.
Fibrosis models were developed using Human Dermal Fibroblasts (HDF), aiming to increase procollagen processing, collagen deposition, and PCPE1 overexpression. These were measured by Western Blot (procollagen I and C-propeptide), collagen I immunostaining, TEM analysis of fibril ultrastructure, and ELISA (PCPE1). A profibrotic cocktail was optimized using a Design of Experiment (DoE) approach to mimic fibrosis-initiating molecular signaling. The cocktail was tested in 2D HDF cultures and a 3D self-organized long-term HDF model (14-21 days).
Results: From an initial pool of 25 nanobodies, two combinations of covalently-linked nanobodies targeting PCPE1 (diabodies D1 and D3) were selected. They exhibit sub-nanomolar affinity for PCPE1, high stability (≥6 days in culture supernatants), and no cytotoxicity. They completely abolish PCPE1-stimulated mini-procollagen cleavage in vitro.
A fibrosis model based on the profibrotic cocktail achieved significantly increased collagen-I-rich ECM neosynthesis and PCPE1 secretion in 2D and 3D HDF cultures. Fluorescently labeled nanobodies efficiently detected PCPE-1-rich fibrotic areas in cellular models, confirming their diagnostic potential.
Conclusion: The DoE-optimized profibrotic cocktail provides insight into the biochemical factors driving fibrosis and PCPE1 overexpression. The 2D/3D models proved suitable for evaluating PCPE1 inhibitors and PCPE-1 imaging tools. The nanobodies demonstrate high affinity, specificity, stability, and biocompatibility, offering strong theranostic potential for early fibrotic lesion detection and fibrosis progression prevention.
References:
1 Mutsaers, H.A.M., et al. J Transl Med. 2023
2 Lagoutte P et al. J Mol Biol. 2024

Poster 8

Investigating collagen I biosynthesis: molecular pathways and microenvironmental influences

Méline Ricol

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The common hallmark of fibrotic diseases is the dysregulation of collagen biosynthesis. Collagen is synthesized through a complex and multistep process and its production can be triggered by diverse stimuli. Among them, ascorbic acid (AA) is a key factor of the microenvironment that sustains collagen secretion. Additionally, in healthy and pathological healing, including fibrosis, oxygen levels are also critical factors regulating collagen biosynthesis. We analysed the effects of these two factors on collagen synthesis and investigated whether their effects are solely explained by their ability to promote collagen proline hydroxylation.
The mechanisms induced by AA and hypoxia (1% O2), alone or in combination, were compared using primary human dermal fibroblasts. The various steps of collagen biosynthesis and collagen levels in the different cellular compartments (intracellular compartment, supernatants and extracellular matrix) were analyzed by RT-qPCR, hydroxyproline quantification, western-blot and various imaging modalities. Quantitative proteomics was also used to reveal new regulatory pathways.
We observed increased collagen deposition by both stimuli, with an additive effect when combined. However, neither AA nor hypoxia significantly induced collagen I gene transcription. In contrast, through different mechanisms, both promoted the 4-hydroxylation of collagen proline residues. Surprisingly, hypoxia had a stronger effect on this step than AA, despite stronger effects of AA on collagen secretion. This unexpected result challenges the belief that AA-induced collagen proline hydroxylation is sufficient to explain its impact on collagen secretion and raises the possibility of an additional AA-specific mechanism triggering collagen secretion. Indeed, further analyses revealed that the CXCL12/CXCR4 axis is a key pathway in the regulation of AA-induced collagen synthesis.
Our results show that distinct mechanisms are involved in collagen deposition by fibroblasts depending on the microenvironmental factors and provide new insights into how they can be manipulated in therapeutic or tissue engineering applications.

Symposium FIBER - September 10th, 2026
FibroMarkers

Poster 9
Beyond crystalline silica: Engineered Stone (ES) exposure drives lung inflammation and fibrosis in 129/Sv Mice

Salomé Patry

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Exposure to crystalline silica (SiO_2), a major component of the Earth's crust, is a well-established risk factor for silicosis and autoimmune diseases. More recently, engineered stone (ES), widely used in kitchen and bathroom benchtops, has emerged as a significant occupational hazard due to its high silica content combined with resins and metals that may enhance toxicity. Although epidemiological studies report rapid onset of silicosis and autoimmune manifestations in exposed workers, the underlying pathogenic mechanisms remain poorly understood.
This study aimed 1) to characterize ES particles by comparing older formulations (ES M2, ES M4) with newer ones (ES Grind, ES Dust), presumed to contain lower silica content, and 2) to compare the effects of repeated exposures to these particles on pulmonary inflammation and fibrosis with those of reference crystalline silica (DQ12), in autoimmune-prone 129/Sv mice.
Physicochemical characterization of each sample using Scanning Electron Microscopy, granulometry, X-Ray Diffraction and Fluorescence, and Mid InfraRed spectroscopy revealed that ES particles exhibit marked heterogeneity compared to DQ12.This includes broader size distributions with an increased nanoparticle fraction, irregular and fractured morphologies, and a complex mineralogical and chemical composition combining crystalline and amorphous phases, organic components, and heterogeneous silanol populations with altered surface accessibility.
Mice received two oropharyngeal instillations (2 × 1.5 mg) two weeks apart and were sacrificed after 16 weeks. Histological assessment (Ashcroft score and Sirius Red staining quantification) demonstrated significant lung fibrosis in both SiO_2 and ES-exposed groups. RT-qPCR and ELISA analysis of lung tissue and BAL fluids respectively, revealed an increased expression of fibrotic markers (Col1a1, Fn1, Tgfβ and Tnc), matrix remodeling genes (Mmp9 and Timp1), and a broad panel of inflammatory mediators (Cxcl10, Cxcl4, Il-10, Il-6, Tnfα, Il-13, Kc, Mpo, Ccl2, S100a8/9 and Il-1β), with more pronounced responses observed for SiO_2 and older ES samples than new ones.
Altogether, these findings indicate that, despite having a lower silica content, ES particles can still induce inflammatory and profibrotic responses (particularly the older formulations), likely driven by their complex surface chemistry and structural heterogeneity. This work underscores the importance of considering particle physicochemical properties beyond silica content alone, to better evaluate their health effects and to improve occupational health risk assessment.

Symposium FIBER - September 10th, 2026
FibroMarkers

Poster 10
Legumain (asparaginyl endopeptidase) and cathepsin V participate in matrix remodeling during lung fibrosis.

Baptiste Rigoux

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Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal lung disease characterized by irreversible fibrous thickening in the interstitial tissue. Pathogenesis involves injury to alveolar epithelial cells, triggering TGF-β1-mediated differentiation of fibroblasts into myofibroblasts. These myofibroblasts produce excessive extracellular matrix (ECM) components, leading to dysregulated tissue remodeling in fibrotic foci associated with an altered proteolytic balance.
Among proteases involved, some cysteine cathepsins are potent collagenases actively contributing to ECM remodeling. During IPF, the cathepsin/cystatin (i.e., their endogenous inhibitors) balance is shifting in favor of cystatins; especially, the secretion of human Cystatin C (hCC), a recognized fibrotic biomarker fostering excessive collagen deposition.
In addition, fibronectin and elastin expression levels are altered during fibrogenesis. This prompted us to investigate the roles of Legumain (LGMN, a.k.a. asparaginyl endopeptidase) and Cathepsin V (CatV; the most potent human elastase) in ECM degradation, as well as Cystatin M/E (CysM), a dual tight-binding inhibitor of both enzymes, in the differentiation of human lung fibroblasts. Our analyses revealed elevated expression of LGMN and CysM in lung biopsies (n=26) and bronchoalveolar lavage fluids (n=18) from IPF patients, whereas CatV levels were reduced. Consistent transcriptional and translational regulations were observed in a TGF-β1-dependent myodifferentiation model using primary human lung fibroblasts. Furthermore, we evaluated the consequences of hCC and CysM overproduction on ECM accumulation and protection from proteolytic degradation.
Deciphering these molecular mechanisms suggests that the overproduction of hCC and CysM mitigates the enzymatic activities of LGMN and CatV. Consequently, impairment of the proteolytic balance during myofibrogenesis leads to the buildup of fibronectin and elastin, promoting ECM deposition and the fibrotic phenotype. Altogether, LGMN was identified as an effector of matrix remodeling, acting in concert with CatV, with a pivotal role in tissue repair.

Poster 11

Effect of recombinant IL-33 on EMT process in colon and ileum human organoids

Lise Ratel

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Background:
Inflammatory bowel diseases (IBD) are frequently complicated by intestinal fibrosis and strictures formation yet no specific therapy is currently available. Intestinal fibrosis is characterized by excessive extracellular matrix (ECM) deposition by intestinal myofibroblasts which can arise from resident fibroblasts or through epithelial-mesenchymal transition (EMT). Interleukin-33 (IL-33) is a pleiotropic alarmin released by epithelial, endothelial and stromal cells following tissue injury. Depending on receptor engagement, IL-33 signaling through ST2 (suppressor of tumorigenicity 2) promotes inflammation, whereas through RAGE (receptor for advanced glycation end-products) has been implicated in tissue repair. Colonic epithelial expression of IL-33 and ST2 is increased in IBD patients compared to healthy controls. In other fibrotic diseases, IL-33 has been shown to promote EMT, including increased vimentin expression in endometrial epithelial cells, suggesting a potential pro-fibrotic role. However, the contribution of IL-33 to intestinal fibrosis remains poorly understood. We hypothesized that IL-33 promotes IBD-associated intestinal fibrosis by inducing EMT and therefore evaluated the effects of IL-33 on EMT process on human colonic and ileal organoids.
Methods:
Human ileal and colonic organoids were established from biopsies of healthy donors and cultured in 60% Matrigel with expansion medium lacking (EM+/-A83-01) to promotes epithelial remodeling. EMT was induced by TNF-α (10 ng/mL) and TGF-ß1 (2 ng/mL) treatments for 4 days. Ileal and colon organoids were treated with IL-33 (10 ng/mL) in 3 steps: 24h before EMT induction - during EMT induction - after the EMT induction for 24h. Expression of the EMT- and fibrosis-related genes ACTA2 (α-SMA), VIM (Vimentin) and COL1A1 (COL1A1) was quantified by RT-qPCR.
Results:
Treatment with TNF-αand TGF-ß1 significantly increased the expression of ACTA2 ($p<0.001$), VIM ($p<0.05$) and COL1A1 ($p<0.01$) in human colon organoids whereas no significant changes were observed in ileal organoids. IL-33 treatment administered before, during or after EMT induction significantly reduced the expression of ACTA2 ($p<0.001$), VIM ($p<0.05$) and COL1A1 ($p<0.01$) in colonic organoids but had no effect in ileal organoids.
Conclusion:
IL-33 reduced EMT-associated gene expression in human colonic organoids but not in ileal organoids, suggesting a region-specific protective role against intestinal fibrosis. Further experiments are needed to decipher the underlying mechanisms, including the relative contribution of ST2 and RAGE-mediated signaling to the anti-EMT effects of IL-33.
Disclosure: The authors have no conflict of interest to disclose.

Poster 12

The mineralocorticoid receptor in smooth muscle cells modulates gut barrier function in mice and human colonic organoids: does this predispose for intestinal fibrosis?

Mathilde Leboutte

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Background: Intestinal fibrosis is a key therapeutic challenge in the management of inflammatory bowel diseases (IBD) due to the lack of anti-fibrotic therapies. Recently, we reported that genetic deletion of mineralocorticoid receptor (MR) in smooth muscle cells (SMCs) alleviated intestinal fibrosis in a preclinical mouse model. IBD is characterized by impaired intestinal barrier function, and many patients develop fibrotic strictures. Now, we aimed to investigate the cellular and molecular interactions promoted by SMCs-expressed MR on gut barrier.
Methods: Mice with tamoxifen-inducible overexpression of MR in SMC were used. Control mice did not express SMA-CreERT2, and therefore had native expression of MR. Ussing chambers were used to assess gut barrier function in colonic tissue by transepithelial electrical resistance (TEER) and passage of 457Da Lucifer Yellow. Primary human colonic SMC (HCoSMC) were exposed for 24 h with or without aldosterone (10 nM), washed, and conditioned was harvested after an additional 24 h culture without aldosterone medium (HCoSMC-CMALDO and HCoSMC-CMCON, respectively). Intestinal epithelial cells (Caco2) were polarized on transwell insert for 21 days and TEER was analyzed when treated with variable amounts of HCoSMC-CM at the basolateral side for 24 h. Human crypt-derived colon organoids were treated with HCoSMC-CM for 48 hours. Organoids integrity was monitored by acquiring images. Barrier function-related gene expression was assessed by RT-qPCR (TJP1, MUC2). As additional control, colon organoids and polarized Caco2 monolayer were treated with equivalent amounts of HCoSMC culture medium (media_HCoSMC).
Results: SMC MR overexpression decreased colon TEER in mice ($p<0.01$), whereas it increased Lucifer Yellow levels passage ($p<0.05$). On polarized Caco2 monolayer, CM from aldosterone-treated HCoSMC decreased TEER compared to media_HCoSMC ($p=0.04$), but not CM from untreated HCoSMC. CM_HCoSMC or media_HCoSMC did not exert cytotoxic effects on colon organoids. CM from HCoSMC increased mRNA expression of TJP1 and MUC2 in colon organoid compared to media_HCoSMC ($p(ANOVA)=0.0417$), particularly CM from aldosterone-treated HCoSMC increased MUC2 mRNA expression ($p=0.04$).
Conclusion: SMC-specific MR overexpression impairs colonic barrier integrity in mice. Moreover, MR activation in SMC impairs Caco-2 intestinal epithelial barrier function through secreted factors. Still, beneficial effects of secreted factors from SMC were observed on barrier function-related gene expression in human colonic organoids, particularly after aldosterone pre-exposure. Further studies are needed to elucidate the involvement of SMC in controlling gut barrier function, and the specific role of SMC-expressed MR.

Acknowledgments: This work was supported by European Crohn's and Colitis Organization pioneer award.

Poster 13

Neutrophil Gelatinase Associated Lipocalin (NGAL) invalidation in myeloid cells did not improve inflammation but reduced fibrosis in mice with colitis.

Elise Rebollo

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Inflammatory bowel diseases (IBD) are frequently complicated by intestinal fibrosis. As there is no specific therapy to prevent or inhibit intestinal fibrosis, it thus constitutes a major treatment challenge. We previously demonstrated the proof of concept of the benefit of pharmacological MRA in experimental intestinal fibrosis through Neutrophil Gelatinase Associated Lipocalin (NGAL). We now hypothesize that myeloid NGAL may promote the transition from inflammation to intestinal fibrosis by modulation of macrophage plasticity. We aimed to investigate whether myeloid NGAL deletion prevents colitis development in mice.
Chronic colitis was induced by 1% dextran sodium sulfate (DSS) in male and female myeloid NGAL knock-out mice (male: MyNGAL KO, n=18, WT n=16; female: MyNGAL KO = 12, WT n=9). Inflammation was assessed by body weight, fecal calprotectin and NGAL levels. Fibrosis was assessed by qPCR analysis and histology. The cecal microbiota of male mice was characterized by 16S rRNA gene sequencing and short chain fatty acids were measured.
Male mice treated with DSS exhibited significantly lower body weight at the end of each DSS cycle ($p<0.01$). By contrast, female body weight was not impacted by DSS-induced colitis or myeloid NGAL invalidation. Genetic NGAL deletion in myeloid cell increased colitis-induced weight loss of male mice ($p<0.05$). MyNGAL invalidation in male and female mice did not significantly impact fecal calprotectin and NGAL concentrations. MyNGAL invalidation reduced DSS-induced mRNA expression of fibrotic markers such as Smad2, Smad3, fibronectin 1, and NFkB ($p<0,05$ for all) in male mice with chronic DSS-induced colitis. MyNGAL invalidation did not impact histological score in male and female mice. MyNGAL invalidation resulted in a significant difference in beta diversity analysis in microbiota communities in male mice ($p<0.01$). It also increased isobutyrate production ($p<0.05$), restored Pseumonodota phylum level ($p<0.05$) and decreased Sutterellaceae ($p<0.01$) and Muribaculaceae($p<0.05$) in male mice with colitis.
Here, we show that genetic myeloid NGAL invalidation reduced body weight loss and fibrosis markers in male mice with chronic DSS-induced colitis but did not impact colon inflammation. We also reported that myeloid NGAL invalidation is linked with gut microbiota modifications. Intestinal fibrosis is an unmet medical need, and the repositioning of fibrosis targets already available in other medical applications may also open new therapeutic avenues in IBD.
This work was supported by the Agence Nationale de la Recherche (ANR-23-CE14-0003) (to RML, PG and FJ). ER was supported by a PhD grant from La Fondation de la Recherche Médicale.

Symposium FIBER - September 10th, 2026
FibroMarkers

Poster 14
Characterization of a transcriptomic signature associated to septin cytoskeleton relocalization in response to various stresses : study of its possible function in early fibrosis.

Sara Al Issa

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Previous work from our laboratory showed that resistance to paclitaxel chemotherapy can be mediated by the rapid relocalization of septins cytoskeleton from actin stress fibers to microtubules, in MDA-MB-231 cervix cancer cells. This drastic cytoskeletal remodeling appears as a general stress response, since it also occurs in HHL16 hepatocyte cell line, either upon paclitaxel or lipid overload treatment but also when cultured on soft extracellular matrix (ECM). In all stresses, actin stress fibers are thinner and relocalize at the cell cortex, with an associated mechanotransduction disruption, hallmarked by cytoplasmic retention of the transcriptional regulator YAP.
By transcriptomic analysis, we identified a signature of 7 genes, that were more than two-fold up-regulated upon septin relocalization in hepatocytes. Since some of them are related to fibrosis in the literature, this suggests in the context of early stress response/adaptation, a new role of septin-mediated cytoskeleton remodeling in early fibrosis control. One important actor in that response may be the hyaluronan glycosaminoglycan.
Keywords
Cytoskeleton, septin relocalization, mechanotransduction, transcriptional adaptation, gene signature, hyaluronan

Symposium FIBER - September 10th, 2026

FibroMarkers

Poster 15

Lipidomics of extracellular vesicles from bronchoalveolar lavage identifies new target for pulmonary fibrosis.

Léna E Silva

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Background: Idiopathic pulmonary fibrosis (IPF) is a progressive and lethal lung disease. Impaired cellular communication may play a key role and is potentially mediated by lipid nanostructures termed extracellular vesicles (EVs) whose accumulate within the IPF lung. Those vesicles exacerbate fibrosis mechanisms. The contribution of EV-associated lipids to the pro-fibrotic activity of these vesicles remains unclear. We aimed to identify a fibrotic-EV lipidome in experimental pulmonary fibrosis, identify metabolism enzymes related to these lipids, and develop new tools to monitor disease progression.

Methods: EVs were isolated from bronchoalveolar lavage fluid (BALF) of mice exposed to bleomycin or control NaCl. Lipid profile was analyzed by high-resolution lipidomics. Mice were monitored by in vivo PET/CT using [18F]-choline to assess choline kinase activity and pulmonary radioactivity was quantified by gamma counting.

Results: BALF-EVs from bleomycin-treated mice have a distinct lipidomic profile, with 61 lipid species increased at 14 days post-bleomycin compared to NaCl controls. Levels of specific EV-lipids correlated with mouse lung function impairment. Those alterations came along with the dysregulation of phosphatidylcholine metabolism-linked enzymes, which were upregulated in IPF patients. In vivo, [18F]-choline lung uptake doubled in mice following bleomycin exposure compared to controls ($p=0.002$), correlated with CT-based fibrosis quantification ($r=0.66$, $p=0.022$), and decreased after nintedanib treatment.

Conclusions: Pulmonary EVs display a fibrosis-specific lipidomic fingerprint associated with phosphatidylcholine metabolism and lung function decline. [18F]-choline PET emerges as a promising non-invasive biomarker to monitor pulmonary fibrosis.

Poster 16

Modulation of proteoglycans expression in a bleomycin-induced pulmonary fibrosis model in mice.

Divya Prabhakar Reddy

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BACKGROUND
Bleomycin-induced pulmonary fibrosis in mice is characterized by a remodeling of extracellular matrix (ECM), with collagen deposition, leading to progressive disruption of lung architecture and respiratory function. Glycosaminoglycans (GAGs) are sulfated and negatively charged structures forming hydrated gel by retaining water, influencing tissue biomechanics, cell-matrix interactions, inflammatory responses and growth factor signaling. Dysregulation of GAGs metabolism and proteoglycans (PGs) expression may modify these properties contributing to prolonged tissue remodeling, thus remained to be investigated.
OBJECTIVE
The aim was to establish a cartography of GAGs and PGs in mice lung injured by bleomycin.
METHODS
Transcriptomic analysis of public RNA sequencing dataset, for bleomycin (BLM) induced fibrosis and control mouse lungs were analysed for differential gene expression. Hallmark, gene ontology - molecular function and cnet analysis were performed to identify enriched pathways. For histological validation, pulmonary fibrosis was induced in male mice (C57Bl/6JRj) by intratracheal instillation of BLM (3.5 UI/g), lungs were collected after 21 days of treatment. Haematoxylin and eosin staining was used for morphological analysis and Alcian blue for GAGs accumulation. Additionally, the distribution of differentially regulated proteoglycans, aggrecan (ACAN), versican (VCAN) and biglycan (BGN) was assessed by immunohistochemistry.
RESULTS
Our analysis revealed significant transcriptional changes in BLM-induced fibrotic mouse lung tissue. Differential gene expression analysis showed increased expression of ECM remodelling genes, including Vcan, Acan, Bgn, Fn1, Col1a1, Col5a1, Adamts4, Has2, Timp1 and Mmp12. Hallmark enrichment analysis further demonstrated the activation of key profibrotic pathways including epithelial-mesenchymal transition, inflammatory response, TNFα/NF-κB signalling and hypoxia. Additionally, gene ontology molecular function analysis revealed significant enrichment in ECM binding, PG, GAGs and heparin binding functions as well as protease regulation, highlighting coordinated remodelling of the fibrotic extracellular microenvironment. These results were further validated experimentally by histological analysis. GAGs accumulation in fibrotic lesions was observed through Alcian blue staining. Immunohistochemical analyses revealed an increased expression of VCAN, ACAN and BGN. VCAN and ACAN were predominantly localized within the interstitium, macrophage-rich regions and fibrotic lesions. In contrast BGN exhibiting a network-like distribution surrounding the perivascular compartment while also accumulating within fibrotic areas.
CONCLUSION
Our findings linking transcriptomic analysis to tissue-level validation demonstrate the critical role of GAGs and PG alterations in addition to classical collagen deposition in reshaping the fibrotic ECM during pulmonary fibrosis. These findings provide new insights into ECM biology during fibrosis and support further investigation of PGs as potential biomarkers and therapeutic targets in fibrotic lung disease.

Poster 17

Identification of Sfrp1 in portal fibroblasts and impact on biliary fibrosis development

Wenrui Gao

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Background: Liver fibrosis results from the accumulation of extracellular matrix produced by myofibroblasts (MFs). In biliary disease, fibrosis arises in the portal area from MFs originating either from portal fibroblasts (PFs) or hepatic stellate cells (HSCs). The aim of our work is to identify the specific role of MFs derived from PFs or HSCs in biliary fibrosis.
Methods: Mesenchymal cells were obtained from the bilio-vascular tree of the Abcb4 KO mouse model of biliary fibrosis and the CCl4 model of non-biliary fibrosis after enrichment by FACS by depleting cells expressing EpCAM, CD31, CD45 and CD11b. Mesenchymal cells underwent scRNAseq and resulting data were analyzed with Seurat v5. Fibrogenic cells (HSCs and PFs) were annotated as quiescent or myofibroblastic based on known markers in homeostatic and fibrotic settings. A differential gene expression analysis was performed to identify genes that could discriminate PFs from HSCs.
Results: Portal mesenchymal cells were isolated from Abcb4 KO mice and of CCl4-injected mice with an equivalent amount of liver fibrosis, as ascertained by Sirius red staining and Col1a1 gene expression. Within the scRNAseq data, we first identified fibrogenic cell populations from biliary and non-biliary fibrosis, respectively, and then merged and further annotated them as 8 clusters of MFs and 12 clusters of qPFs and/or qHSCs. Uniform Manifold Approximation and Projection (UMAP) visualization showed distinct projections between fibrogenic cell populations from biliary and non-biliary fibrosis, indicating specific cellular processes involvement. Gene expression analysis identified 12,294 differentially expressed genes (DEGs) between the PF and HSC lineages. Among DEGs, four genes were evidenced that were expressed in PF cells (pct.PF > 50%) and which expression was significantly higher ($p < 0.01$, logFC > 1.8) than in HSCs. Among these four genes, Sfrp1 showed an increased gene expression proportional to fibrotic tissue accumulation in Abcb4 KO and DDC-fed mice, as ascertained on whole liver by RT-qPCR.
Conclusion: By combining cell isolation and scRNAseq analysis, we show a specific involvement of PFs in the portal space during biliary fibrosis, while HSCs are solicited in non-biliary fibrosis. Furthermore, we identified Sfrp1 as a specific marker of the PF lineage that will allow us to better understand the specific involvement of these cells in liver fibrosis.

Poster 18

Assessing the effects of Nicotinamide Riboside (NR) combined with exercise training in heart failure with preserved ejection fraction

Zhenyi Zhao

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Impaired cardiac energy metabolism, particularly nicotinamide adenine dinucleotide (NAD^+) depletion and mitochondrial dysfunction, is one of a key features of HFpEF. Nicotinamide riboside (NR), a NAD^+precursor, and exercise are both known to modulate NAD^+-dependent mitochondrial axis, potentially through enhancing NAD^+salvage, while limiting excessive NAD^+consumption through suppression of CD38 and poly (ADP-ribose) polymerases (PARPs) activity.[1] Angiotensin II/phenylephrine (Ang II/PE) infusion in C57BL/6J (B6J) mice has been established as a non-obese hypertensive model of HFpEF, a phenotype often observed in post-menopausal women. [3]

Objective

We aimed to investigate the effects of NR and exercise on cardiac metabolism and function in ovariectomized B6J female mice with AngII/PE infusion.

Materials & Method

Ovariectomized B6J female mice (8-10 weeks old) were implanted with osmotic minipumps for continuous infusion for 3 and 4 weeks. filled with saline (control group) or AngII /PE (HFpEF group). 2 additional HFpEF groups were injected subcutaneously with NR. One this group was additionally subjected to acceleration training on treadmill (ATT). Cardiac function was assessed by echocardiography. Cardiomyocyte fibrosis was evaluated using Sirius Red staining. Gene expression of markers related to hypertrophy, fibrosis, and NAD^+signaling pathways were analyzed by qRT-PCR, and NAD levels were measured using alcohol dehydrogenase cycling assay.

Result

With 3 and 4 weeks of ANG II/PE infusion, NR combined with exercise increased fractional shortening and reduced left ventricular filling volume, without improving cardiac output or reducing cardiac hypertrophy in HFpEF. Notably, ATT, but not NR alone, partially restored mitochondrial respiratory capacity, particularly at complexes II and IV. At the molecular level, NR alone and NR+ATT increased NAD level and reduced CD38 expression, and NR alone further reduced PARPs activity. Moreover, both treatments markedly reduced cardiac fibrosis along with the expression of fibrosis-associated collagen genes.

Conclusion

NR restored myocardial NAD^+homeostasis through modulation of NAD^+consumption pathways, while NR+ATT partially improved mitochondrial respiratory capacity. Despite attenuated fibrosis and improved metabolic remodeling, these interventions did not significantly improve cardiac function, suggesting that longer treatment duration may be required to reverse established hypertensive HFpEF.

[1] Mericskay M . et.al Nat Rev Cardiol. 2025
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Symposium FIBER - September 10th, 2026
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Poster 19
Patient-Derived Organoids Identify Epithelial Mechanisms Underlying Fibrosis in Endometriosis

Perrine Singla

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Endometriosis is a chronic hormone-dependent inflammatory gynecological disease that severely impacts patients' quality of life. Despite the anatomical and clinical heterogeneity of endometriosis, , fibrosis is a common hallmark of endometriotic lesions and is thought to contribute to pain and disease progression. Understanding the cellular and molecular mechanisms underlying fibrotic remodeling is therefore essential to identify new therapeutic targets.
To address the heterogeneity of the disease while distinguishing lesion-specific alterations from those already present in the eutopic endometrium, we generated patient-derived organoids from paired eutopic endometrium and endometriotic lesions and compared their transcriptomic profiles. Using RNA sequencing of patient-derived endometrial and endometriotic organoids, we identified differentially expressed genes associated with extracellular matrix (ECM) organization and matrisome remodeling. Single-cell RNA sequencing further revealed distinct epithelial cell populations displaying a pro-fibrotic transcriptional signature and enriched for ECM-related genes. A single-cell atlas of matched eutopic endometrium and endometriotic lesions across the menstrual cycle is currently being generated to further investigate these mechanisms in patient tissues .
Together, these findings establish patient-derived organoids as a robust platform for dissecting fibrosis-associated mechanisms in endometriosis and identify epithelial pathways involved in extracellular matrix remodeling that may represent novel therapeutic targets.

Poster 20

Collagen VI is a fibrosis-associated signal disrupting muscle regeneration across distinct human myopathies

Laura Muraine

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Muscle fibrosis is a major driver of progression in diverse myopathies, yet the conserved molecular mediators of this process in humans remain poorly defined. Here, we identify collagen VI as a common regeneration-impairing extracellular matrix (ECM) component across three distinct human myopathies: Duchenne Muscular Dystrophy (DMD), Oculopharyngeal Muscular Dystrophy (OPMD), and Inclusion Body Myositis (IBM). Proteomic profiling of fibrotic biopsies reveals consistent upregulation of collagen VI and laminin γ1, alongside disease-specific alterations. Fibroadipogenic progenitors (FAPs) are the predominant source of these ECM components, including collagen VI and laminin γ1. Functionally, xenotransplantation of patient-derived FAPs into regenerating mouse muscle induces localized collagen deposition, myofiber atrophy, and depletion of $Pax7^{+}$muscle stem cells. Mechanistic assays demonstrate that FAP-derived collagen VI is sufficient to impair myogenic fusion, while silencing COL6 in patient FAPs restores fusion capacity, directly linking pathological collagen VI deposition to regeneration failure. Our findings uncover collagen VI as a conserved effector of fibrosis and stem cell niche disruption in human myopathies, positioning it as a potential therapeutic target across genetically and clinically distinct muscle diseases.

Symposium FIBER - September 10th, 2026
FibroMarkers

Poster 21
Promoter-Driven Depletion of Fibrogenic Cells as a Therapeutic Strategy for Liver fibrosis

Mariana Amaral Raposo

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Confidential Abstract

Symposium FIBER - September 10th, 2026
Preclinical matrix

Poster 22
New therapeutic targets for hepatic fibrosis in MASLD: the SGLT2 cotransporter and the cannabinoid-1 receptor

Maéva Loriot

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Introduction: Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) is the leading cause of chronic liver disease worldwide, affecting ~30% of the population. It is highly prevalent in individuals with obesity or Type 2 Diabetes (T2D). The pathophysiology is complex, progressing from steatosis (hepatic fat accumulation) to fibrosis (excessive collagen deposition), driven by insulin resistance and chronic inflammation. Current drug treatments are not optimal and can cause side effects, particularly gastrointestinal ones. However, some evidence suggests that sodium/glucose cotransporter 2 (SGLT2) inhibitors, beyond their glucose-lowering effects, lead to improvements in hepatic steatosis and fibrosis. In parallel, numerous preclinical studies have demonstrated the anti-MASLD potential of cannabinoid-1 receptor (CB1R) blockade. This study aimed to assess whether a poly-pharmacological approach combining SGLT2 inhibition and CB1 receptor antagonism could represent an effective strategy to limit hepatic fibrosis.
Methods: C57Bl/6J mice were fed a Western Diet (WD) and high fructose corn syrup water to induce obesity, insulin resistance, and MASLD for 20 weeks. Control mice were fed a standard diet and classic water. For 28 days, mice received either a vehicle, the CB1 receptor antagonist (zevaquenabant), the SGLT2 inhibitor (empagliflozin), or a combination of the two, at doses of 3 mg/kg or 10 mg/kg for each compound. Metabolic parameters, liver histology, and gene expression were evaluated.
Results: WD-fed mice developed significant weight gain, hyperglycemia, insulin resistance and hepatic damage, including severe steatosis and fibrosis. Combination treatment markedly reduced hepatic steatosis by decreasing the size and number of lipid droplets, as well as hepatic triglyceride content and the expression of lipogenic genes (Acc1, Fasn). Gene expression of inflammatory markers (Cd68, Clec4f, Tnf, Il1b) were reduced, indicating attenuated liver inflammation. Finally, combination treatment reduced fibrosis progression as demonstrated by Sirius red staining and fibrotic gene expression (Tgfb1, Col1a1, Col1a2, Col3a1). RNA sequencing analyses revealed a reduction in inflammation through decreased MHC class II antigen presentation. There was also a downregulation of collagen formation, extracellular matrix organization, the RHO GTPase cycle and the VEGF and PDGF signaling pathways. The higher treatment dose (10 mg/kg) produced better results for most parameters, highlighting dose-dependent effect.
Conclusion: Combined SGLT2 inhibition and CB1 receptor antagonism reduced steatosis, inflammation, and fibrogenesis while modulating multiple pathways implicated in MASLD pathogenesis. These findings highlight complementary mechanisms that may enhance therapeutic

efficacy when targeted simultaneously. Together, they support the development of poly-pharmacological strategies to address the complex metabolic and molecular drivers of MASLD.

Poster 23

Modeling Fibrosis in Oculopharyngeal Muscular Dystrophy using engineered 3D human Skeletal Muscle

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Introduction
Muscle fibrosis is characterized by the excessive accumulation of extracellular matrix (ECM) components around muscle fibers, leading to impaired muscle function. In skeletal muscle, fibro-adipogenic progenitors (FAPs) are the primary source of ECM proteins and key drivers of fibrosis in myopathies such as Oculopharyngeal muscular dystrophy (OPMD), a late-onset, slowly progressive genetic disorder affecting the pharyngeal and eyelid muscles. Despite its clinical impact, no treatment is currently available to reverse fibrosis in OPMD.
Methods
We have established 2D and 3D human co-culture models combining both myoblasts and FAPs to explore cell communication between these two cell types and identify anti-fibrotic compounds active on FAPs.
Results
In 2D co-cultures using myoblasts and FAPs, we previously demonstrated the positive effect of Bosentan, a specific inhibitor of the EDNRB receptor, in preventing exacerbated ECM deposition by OPMD FAPs (Bensalah et al JCSM 2022), and we are now extending our analysis to a range of known anti-fibrotic molecules as well as to additional candidates identified through an in-house OPMD omics dataset. In parallel, we have generated 3D skeletal muscle organoids combining human primary myoblasts and FAPs. These constructs form multinucleated myofibers with a well-structured sarcomeric organization. Furthermore, the 3D co-culture system recapitulates essential features found in fibrotic muscles from OPMD patients, including increased FAPs proliferation, enhanced ECM deposition and an increased number of Pax7+ satellite cells.
Conclusion
Together, these complementary 2D and 3D systems provide a promising platform to study human skeletal muscle fibrosis and evaluate potential anti-fibrotic therapeutic candidates.

Symposium FIBER - September 10th, 2026
Preclinical matrix

Poster 24
Exploring the Antifibrotic Potential of the Heparan Sulfate Mimetic OTR4132 on Validated Human Precision-Cut Lung Slices (hPCLS) Model Mimicking Pulmonary Diseases

Mariia Pestriakova

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Most acute pulmonary injuries are characterized by diffuse alveolar damage (DAD). DAD is an acute nonspecific reaction of the lung, observed commonly in a wide range of infectious diseases (e.g. acute respiratory distress syndrome, SARS-COVID-19), and various other conditions (e.g. xenobiotics, environment, burns). DAD is characterized by scarring and stiffening of lung tissue and may lead to severe loss of lung function such as idiopathic pulmonary fibrosis.
DAD causes remodeling of the extracellular matrix (ECM), impairing gas exchange and leading to respiratory distress. In this context, matrix metalloproteinases (MMP) and endoglycanases (e.g. heparanases) are released. MMP mediate the shedding of heparan sulfate (HS) proteoglycans, while heparanases degrade HS chains directly. Together, these processes disrupt the endothelial glycocalyx, impair vascular function, and promote lung edema and neutrophil adhesion.
Some HS mimetics (HSM), known as ReGeneraTing Agents (RGTA®), are synthetic polysaccharides that can promote ECM remodeling by restoring the glycan-based scaffold lost following tissue injury. RGTA® ability to restore the ECM is due to its structural and functional similarities to HS, as well as its resistance to heparanases. In altered ECM, RGTA® bind to growth factors, protecting them from enzymatic degradation and increasing their bioavailability, to promote tissue repair.
To evaluate the effect of this matrix therapy on the slowing of the progression from DAD to lung fibrosis, we used an ex vivo human precision-cut lung slices (hPCLS) model. This model has two key advantages: it preserves the native three-dimensional architecture of the lung and retains all major lung cell types. These characteristics make hPCLS an ideal system for investigating lung diseases and for assessing the safety, efficacy, and toxicity of novel therapies.
After confirming that RGTA® OTR4132 was non-toxic in the hPCLS model, the slices were exposed to a profibrotic cocktail (PFC) known to induce a cytokine storm and lead to fibrosis. Three concentrations of OTR4132 were then tested, with nintedanib used as a positive antifibrotic control. Model validation was achieved through histological staining (HE, Alcian blue, MT, PAS), followed by proteomic analysis.
Proteomic analysis revealed that PFC induced the upregulation of collagens, proinflammatory cytokines, and proteoglycans, which was attenuated by nintedanib. Not only did OTR4132 modulated these markers, but it also affected proteins involved in ECM remodeling (MMP-1, MMP-

9, MMP-12), TGF-β signaling inhibition (BCAR1), and inflammation and angiogenesis (IBP7, ANGP2, VEGFR1).
Overall, these results support the antifibrotic activity of OTR4132 in a validated hPCLS model.

Poster 25

Development of mouse and pig models of pulmonary fibrosis and gene inhibition testing of potential therapeutic targets

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Background
Idiopathic pulmonary fibrosis is a rare, severe and progressive interstitial lung disease characterized by irreversible fibrotic remodeling. Current antifibrotic treatments slow disease progression but neither halt nor reverse fibrosis. Existing experimental models also have important limitations, particularly in preserving native lung architecture and cell-cell interactions. Precision-cut lung slices (PCLS) provide a promising ex-vivo platform that maintains the complexity of lung tissue. This study aimed to establish an adult ex-vivo fibrosis model using mouse and pig PCLS, identify early overexpressed genes, and evaluate their therapeutic targeting using antisense oligonucleotides (ASOs).
Methods
PCLS were prepared from whole C57BL/6 mouse lungs (250µm) and pig lung punches ((400µm). After 24 hours of culture, slices were exposed daily for five days to a fibrotic cocktail containing TGF-β1, PDGF-AB, TNF-α, lysophosphatidic acid, IL-1β, IL-13 and cadmium. Fibrosis was assessed by Masson's staining using the modified Ashcroft score. Sirius Red staining, immunofluorescence for α-SMA, fibronectin and COL1A1, and TaqMan RT-qPCR were used to evaluate extracellular matrix deposition and pro-fibrotic genes expression (Tgf-β1, Acta2 and Col1a1). Three early candidate genes previously identified in a mouse embryonic lung fibrosis model (Lcn2, Saa3 and Serpina3g) were analyzed after 16 hours of treatment. When overexpressed, genes were targeted with Morpholino ASOs (2µM) added directly to the culture medium. Statistical analysis were performed using non-parametric tests.
Results
The profibrotic cocktail reproducibly induced moderate fibrosis in both mouse and pig PCLS, demonstrated by increased Ashcroft scores and extracellular matrix deposition. In mouse PCLS, Lcn2 was upregulated (fold change=2.6, n=11), Saa3 showed a trend towards increased expression, and Serpina3g was unchanged. None of these genes was detected in pig PCLS. Lcn2 inhibition with a Morpholino ASO reduced the Ashcroft score, Col1a1 expression and Sirius Red staining compared with the Muc5ac control ASO, whereas Saa3 inhibition did not attenuate fibrosis.
Conclusion
This study established a reproducible pharmacologically induced PCLS model that recapitulates key early fibrotic changes while preserving native lung architecture, providing a relevant ex-vivo platform for mechanistic and therapeutic studies. Within this model, Lcn2 emerged as a promising early therapeutic target, as its inhibition attenuated fibrotic responses. Further studies are warranted to confirm target inhibition at the protein level, elucidate the underlying mechanisms, and evaluate this strategy in human PCLS and in vivo models.

Poster 26

Role of Lysyl Oxidase in the pathological interplay between extracellular matrix and lymphatics in secondary lymphedema

Florent Morfoisse

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Secondary lymphedema (LD) is characterized by lymphatic vessel dysfunction and profound alterations of the tissue microenvironment, particularly through pathological extracellular matrix (ECM) remodeling. During lymphedema progression, lymphatic endothelial cells (LECs) are exposed to a highly fibrotic microenvironment that contributes to persistent tissue dysfunction and lymphatic vessel impairment. In LD, fibrosis primarily affects the dermis, leading to significant tissue stiffening. This stiffening is largely determined by collagen fiber density and organization, mainly involving fibrillar collagens such as type I collagen, which undergo collagen crosslinking (CCL). CCL is regulated by enzymes including lysyl oxidase (LOX) and transglutaminases, as well as by non-enzymatic glycation. This study aims to elucidate the molecular mechanisms underlying ECM remodeling in lymphedema and its impact on lymphatic function.
To address this question, we employed a multifaceted approach combining immunostaining, bulk RNA sequencing, and single-cell RNA sequencing analyses using both patient samples and a murine model of lymphedema. Our findings revealed a significant upregulation of LOX in lymphedematous tissues. LOX overexpression correlated with increased collagen deposition, fiber reorganization, and ECM stiffening in both human samples and a murine LD model. Importantly, inhibition of LOX activity led to a marked reduction in lymphedema severity, characterized by decreased fibrosis and partial restoration of lymphatic vessel function.
Single-cell RNA sequencing identified a distinct fibroblast subpopulation responsible for LOX-mediated ECM remodeling, suggesting a specialized role for fibroblasts in lymphedema progression. These findings support the existence of Lymphedema-Associated Fibroblasts (LAFs), analogous to Cancer-Associated Fibroblasts, with specific pathological functions in disease progression.
To further confirm the key role of fibroblast-derived LOX in LD-associated fibrosis, we generated a fibroblast-specific LOX conditional knockout mouse model using a Col1a2-Cre; Loxfl/fl strategy. LOX-deficient mice exhibited reduced lymphedema development, associated with a strong decrease in collagen accumulation and crosslinking compared with WT littermates. These results further demonstrate that targeting fibroblast-derived LOX may represent a promising therapeutic strategy to limit fibrosis in LD.
Overall, this study provides novel insights into the role of ECM remodeling in lymphedema pathophysiology and identifies LOX as a central regulator of fibrosis and lymphatic dysfunction. Our findings highlight the therapeutic potential of targeting ECM remodeling to preserve lymphatic vessel integrity and function.

Symposium FIBER - September 10th, 2026
Preclinical matrix

Poster 27
Reduced fibrosis after in vivo inhibition of complement C1 in Duchenne Muscular Dystrophy

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In the muscles of Duchenne Muscular Dystrophy (DMD) patients, muscle fibers progressively undergo necrosis and are substituted by fibrotic extracellular matrix, determining a severe loss of muscular function. Recently obtained data from our laboratory demonstrate that complement C1, the complex operating upstream of the classical complement cascade, is aberrantly up-regulated in DMD patients and animal models. The C1 complex comprises multiple subunits codified by five genes: C1qa, C1qb, C1qc, C1s, and C1r. When we fractioned the cells from dystrophic muscles into the various subpopulations and evaluated the expression of the distinct complement C1 subunits, we could observe that all C1q subunits were almost exclusively expressed in macrophages, whereas C1s and C1r were preferentially induced in fibro-adipogenic progenitors (FAPs) populating the muscle interstitium. Importantly, we observed that the pharmacological inhibition of the enzymatic subunits of the C1 complex, C1s and C1r, counteracts the accumulation of fibrotic tissue in the fib-MDX model, an accelerated murine model of DMD. These observations suggest that a complement C1 plays a detrimental role in the progression of muscular dystrophy. Nevertheless, the effects of long-term inhibition of complement C1 in the dystrophic setting and the exact mechanisms underlying the influence of complement on dystrophic progression remain to be elucidated. To address these points, we began evaluating the effects of C1q inhibition in the muscles of MDX dystrophic mice and observed a profound decrease in extracellular matrix deposition.