

Immuno-Fibrotic Crosstalk: A New Target in Rheumatology

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Rheumatic diseases frequently involve chronic inflammation leading to progressive tissue damage and fibrosis, a process that remains inadequately targeted by current immunomodulatory therapies. The EULAR 2026 session, "Decoding Immuno Fibrotic Cross Talk in Rheumatology: From Mechanisms to Decisions," will explore the intricate bidirectional communication between immune cells and fibroblasts, presenting a critical opportunity to identify novel therapeutic strategies beyond conventional immunosuppression.

KEY TAKEAWAYS

- **The Pivot:** Focus shifts from purely immune modulation to targeting the immune-fibrotic axis in rheumatic diseases.
- **The Data:** Preclinical and early clinical data indicate specific molecular targets within this crosstalk, such as TGF- β , IL-6, and specific chemokine receptors, influencing fibrotic progression.
- **The Action:** Clinicians should consider the fibrotic component in rheumatic disease progression and anticipate future therapies that concurrently address inflammation and fibrosis.

The pathogenesis of many rheumatic diseases, including systemic sclerosis, rheumatoid arthritis, and lupus nephritis, is characterised by persistent inflammation that culminates in irreversible tissue fibrosis.¹ Current therapeutic approaches primarily focus on suppressing immune responses, which often mitigates inflammation but frequently fails to halt or reverse established fibrotic changes. This clinical dilemma underscores the necessity for a deeper understanding of the mechanisms driving fibrosis in these conditions.²

Fibrosis is a pathological process involving excessive extracellular matrix (ECM) deposition by activated fibroblasts, leading to organ dysfunction. In rheumatic diseases, this process is not merely a consequence of chronic inflammation but is actively driven by complex interactions between immune cells and fibroblasts. Immune cells, such as T cells, B cells, macrophages, and mast cells, release profibrotic mediators including transforming growth factor-beta (TGF- β), interleukin-6 (IL-6), platelet-derived growth factor (PDGF), and various chemokines.³ These mediators activate fibroblasts, promoting their differentiation into myofibroblasts, which are the primary producers of ECM components like collagen. Conversely, activated fibroblasts can also influence immune cell function and recruitment, creating a self-perpetuating cycle of inflammation and fibrosis.⁴ For example, fibroblasts can present antigens, produce cytokines that modulate immune cell differentiation, and express adhesion molecules that facilitate immune cell infiltration into tissues.⁵

The clinical manifestations of fibrosis in rheumatic diseases vary significantly depending on the affected organ. In systemic sclerosis, fibrosis leads to skin thickening, vascular damage, and internal organ involvement, including the

lungs, heart, and gastrointestinal tract. In rheumatoid arthritis, synovial fibrosis contributes to joint destruction and loss of function. Lupus nephritis, a severe complication of systemic lupus erythematosus, involves renal fibrosis that can progress to end-stage renal disease. These diverse presentations highlight the systemic nature of immuno-fibrotic crosstalk and the urgent need for targeted therapies that address the underlying mechanisms of tissue damage across different patient populations. The prevalence of these fibrotic complications significantly impacts patient morbidity and mortality, underscoring the public health burden of these conditions.

The EULAR 2026 Session: Mechanisms and Decisions

The EULAR 2026 session will consolidate current knowledge regarding these immuno-fibrotic interactions. It is expected to detail specific molecular pathways and cellular populations involved in this crosstalk. Key areas of discussion will likely include the role of specific T cell subsets, such as Th17 and Treg cells, in modulating fibroblast activity, and the contribution of B cells to fibrotic processes through antibody production and cytokine release.⁶ Macrophages, particularly their M2 phenotype, are known to be potent drivers of fibrosis, secreting a range of profibrotic factors.⁷ The session will also address the emerging understanding of how innate immune cells and their products contribute to fibroblast activation and ECM remodelling.⁸

Translational research presented at the session will likely highlight potential therapeutic targets identified from these mechanistic insights. For instance, strategies aimed at neutralising profibrotic cytokines like TGF- β or IL-6, or inhibiting their signalling pathways, are under investigation.⁹ Targeting specific chemokine receptors on fibroblasts or immune cells to disrupt their recruitment and activation represents another promising avenue.¹⁰ Furthermore, approaches that aim to directly modulate fibroblast activation or promote their apoptosis are being explored.¹¹ The session will move beyond basic science to discuss the clinical implications of these findings, including the identification of biomarkers for early detection of fibrosis and the stratification of patients who may benefit most from targeted anti-fibrotic therapies. The integration of these mechanistic insights into clinical decision-making will be a central theme, guiding the development of novel therapeutic strategies that concurrently address both the inflammatory and fibrotic components of rheumatic diseases.¹²

While the session will present a comprehensive overview, it is important to acknowledge the inherent complexities and limitations in translating preclinical findings into effective clinical treatments. The heterogeneity of fibrotic processes across different rheumatic diseases and within individual patients poses a significant challenge.¹³ Furthermore, the potential for off-target effects and the need for long-term safety data for novel anti-fibrotic agents will require careful consideration. Future research will need to focus on robust clinical trials to validate these emerging targets and therapies.¹⁴ The session will also likely address the methodological challenges in assessing fibrosis progression and regression in clinical trials, including the use of imaging techniques, histological analysis, and circulating biomarkers. Establishing clear endpoints for anti-fibrotic therapies remains a critical hurdle for drug development and regulatory approval.

Readers seeking a broader understanding of rheumatological principles and current therapeutic approaches may find the Oxford Handbook of Rheumatology a valuable resource.

CLINICAL IMPLICATIONS

The increasing focus on immuno-fibrotic crosstalk at EULAR 2026 signals a necessary evolution in rheumatology. For too long, our therapeutic arsenal has been heavily weighted towards immune suppression, often leaving patients with progressive, irreversible organ damage from fibrosis. The recognition that fibrosis is not merely a passive consequence but an active, immune-driven process opens up genuinely new therapeutic avenues. Clinicians should begin to consider the fibrotic burden in their patients more explicitly, moving beyond inflammatory markers alone to assess disease progression.

This shift has significant implications for pharmaceutical development. Companies like Boehringer Ingelheim, with their existing anti-fibrotic agents in other indications, or those developing biologics targeting cytokines like IL-6 (e.g., tocilizumab from Roche/Genentech), may find new applications or develop next-generation molecules that specifically interrupt the immune-fibrotic loop. The challenge will be to develop agents that are potent enough to reverse established fibrosis without causing undue immunosuppression or other systemic side effects. The regulatory pathway for such combination-effect drugs may also require novel trial designs. Ultimately, patients stand to gain the most from this expanded understanding. For conditions like systemic sclerosis, where fibrotic complications dictate prognosis, or in rheumatoid arthritis with interstitial lung disease, therapies that can halt or even reverse fibrosis would represent a substantial improvement over current standards. This is not merely about symptom management; it is about preserving organ function and improving long-term quality of life. The prospect of moving beyond simply dampening inflammation to actively remodelling diseased tissue offers a tangible hope for those living with the most debilitating aspects of rheumatic disease.

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