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FIBROKINE™ Peptides: A Broad-Spectrum of Anti-Fibrotic Chemokine Peptides to Treat Organ Fibrosis

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Objective: Fibrotic diseases are associated with 45% of deaths in the United States but effective therapy does not exist, representing a major unmet medical need. The scope of clinical and etiological manifestations is diverse among fibrotic disorders, yet they share an underlying irritation that promotes the release of various growth factors, proteolytic enzymes, angiogenic factors, and fibrogenic cytokines/chemokines. Persistence of this process causes increased, excessive accumulation of extracellular matrix components and chronic inflammation that progressively alters the cellular and structural architecture of the tissue, decreasing functionality. With progression, these changes can eventually lead to organ dysfunction and death. It is well accepted that common fibrotic diseases such as cardiac fibrosis, scleroderma, idiopathic pulmonary fibrosis, diabetic nephropathy, liver cirrhosis, rheumatoid arthritis, atherosclerosis, and nepthritis share causative factors. Our group has recently designed and developed a class of chemokine-derived FIBROKINE™ peptides that successfully target the underlying causes of common fibrotic diseases and are capable of halting, reversing, and/or eliminating fibrosis or the underlying molecular processes causing fibrosis.

Methods: Evidence has shown the unique multifunctional role of chemokines and their ubiquitous modulation of fibrotic processes. In this study, we test our newly generated class of chemokine-derived FIBROKINE™ peptides, developed by *in silico* prediction-based functional peptide design. Our goal is to advance the mechanistic knowledge of how FIBROKINE™ peptides decrease fibrosis to improve therapy. The efficacy of several FIBROKINE™ peptides was tested via functional assays for cell motility, proliferation, apoptosis, metabolic activity, angiogenic effects, and altered gene expression and protein profiles. Our *in vitro* and *ex vivo* experimental testing systems included primary human and murine dermal fibroblasts, endothelial cells, keratinocytes, cardiac fibroblasts, and cardiomyocytes, in both direct and indirect co-cultures as well as individually.

Results: We found that FIBROKINE™ peptides acted as potent and efficient antagonists of both chemotaxis and cellular function induced by pro-fibrotic chemokines. Among the broad spectrum of cellular affects, FIBROKINE™ peptides reduced the expression of α-Smooth Muscle Actin and reduced mRNA and protein secretion levels of Collagen I, Laminin, Fibronectin, and Tenascin C in both dermal and cardiac fibroblasts after induction by pro-fibrotic TGF-β. Furthermore, FIBROKINE™ peptides inhibited the TGF-β1-mediated activation of epithelial–mesenchymal transition (EMT), in keratinocytes and dermal fibroblast co-cultures, a known feature of fibrosis. Lastly, treatment of endothelial cells with FIBROKINE™ peptides significantly inhibited VEGF-induced endothelial motility and tube formation *in vitro*, properties critical for angiogenesis.

Conclusion: Our data suggest FIBROKINE™ peptides mimic biological activities of natural chemokines on fibrosis-inducing cell types. These data further reveal the effectiveness of the anti-fibrotic design of FIBROKINE™ peptides as novel, targeted therapeutic solutions that are capable of treating fibrotic conditions through disruption of multiple disease-causing mechanisms.

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