Promedior, Inc.
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Fighting fibrosis

Promedior, a clinical-stage biotechnology company, is developing immunotherapies to treat fibrosis. The company's lead product candidate is PRM-151, a recombinant form of human pentraxin-2 formulated for intravenous injection.

Fibrosis is a leading cause of death and disability that occurs when normal healthy tissue is replaced with scar tissue. This harmful process can affect nearly all tissues and organ systems that, when advanced, leads to organ dysfunction and death. With fibrotic disorders thought to contribute to approximately 45% of all deaths in the United States, there is a significant need to prevent the initiation of fibrosis and to reverse the process where possible.

Promedior's proprietary platform is based upon pentraxin-2, a normal plasma protein that plays an important role in regulating the body's response to tissue damage and subsequent fibrosis.

Normal wound healing involves three immune response pathways that act in conjunction to promote healing: inflammation, proliferation, and resolution. In response to tissue damage, monocytes of the innate immune system are mobilized to the site of the damage (inflammation), where they differentiate into macrophages that remove damaged tissue and debris or regulate tissue repair. Some differentiate into profibrotic macrophages and fibrocytes and increase extracellular matrix deposition, which initiates scar tissue formation (proliferation)—a process that continues unless the microenvironment is sufficiently altered to mediate or resolve continuation of the process (resolution).

What is fibrosis?

Fibrosis occurs when severe or chronic injury (for example, due to trauma, inflammation, or cancer) locks macrophages into the profibrotic proliferation pathway with no resolution, creating an endless loop of aberrant scar formation. "The ongoing tissue damage caused by fibrosis continues to recruit monocytes into the fibrosis pathway leading to further fibrocyte and myofibroblast activation and sustained fibrosis, perpetuating the disease process," explained Richard Jack, Promedior's president and COO.

Pentraxin-2 signals macrophages to downregulate inflammation and proliferation, halting the persistent profibrotic cycle (**Fig. 1**). Pentraxin-2 targets sites of injury by binding specifically to both damaged tissue and Fcγ receptors on local monocytes and macrophages, directing their differentiation into proresolutive macrophages. "Pentraxin-2 intervenes in the monocyte differentiation process, directing the immune system to simultaneously turn off the fibrosis pathway and turn on a resolution pathway," said Jack. "Activating this regulatory switch tips the equilibrium, blocking matrix deposition and preventing disease progression while promoting healing and resolution of fibrosis."

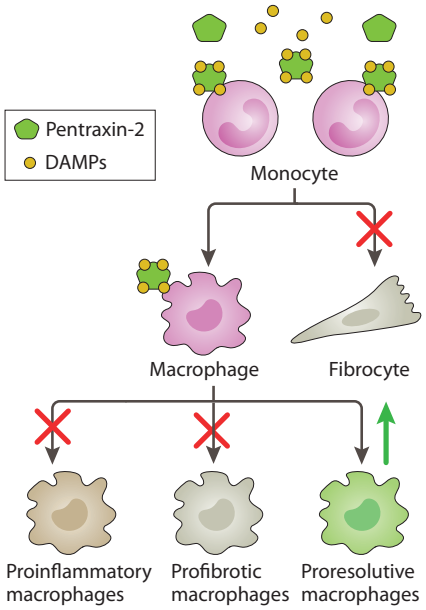

Fig. 1 | Pentraxin-2 resolutive activities in fibrotic disease. Pentraxin-2 (PTX-2) binds to danger-associated molecular patterns (DAMPs), has specificity for damaged and fibrotic tissues, and acts upstream in the fibrosis pathway. PTX-2 binds to monocyte and macrophage Fcγ receptors, blocks fibrocyte and profibrotic/proinflammatory macrophage production, and modulates the fibrotic microenvironment. PTX-2-induced microenvironmental changes prevent and reverse fibrosis by inducing proresolutive macrophages and their cytokines.

Most other experimental therapeutic approaches are not damage-specific and focus on a single downstream target, many of which are redundant. By virtue of being an endogenous protein acting upstream and targeting activity to the damaged tissue microenvironment, pentraxin-2 is more effective and likely to have fewer off-target effects.

In patients with fibrosis, the body uses more pentraxin-2 than it can manufacture, indicating the potential benefit of treating fibrosis with pentraxin-2. Preclinical studies confirm the broad potential of pentraxin-2 therapeutics in blocking the initiation and progression of fibrosis in several models of fibrotic disease and across major tissue types, including the lung, kidney, liver, bone marrow, and eye. It has also been shown to reverse established fibrosis and improve organ function in several models.

Promising results with PRM-151

Promedior's lead product candidate, PRM-151, is a recombinant form of human pentraxin-2 formulated for intravenous infusion to treat fibrotic diseases. More than 4,000 doses of PRM-151 have been administered to more than 250 patients over 6 years, and Promedior has just completed phase 2 trials in patients with idiopathic pulmonary fibrosis (IPF) and myelofibrosis (MF; which is characterized by bone marrow fibrosis), both rare and incurable fibrotic diseases. In the United States, approximately 40,000 people die each year from IPF, while more than 18,000 patients have MF. The fibrosis component of IPF leads to an irreversible decline in lung function in patients who have a median survival of around 3 years. In MF, the bone marrow is progressively replaced by scar tissue, leading to severe anemia, an enlarged spleen, clotting disorders, and hemolytic complications that can lead to death within several years of diagnosis.

PRM-151 has demonstrated significant beneficial effects in both these indications, giving hope to patients who are looking for a disease-modifying therapy. A phase 1b study in IPF showed a trend towards efficacy in lung function tests and the 6-minute walk test distance, the improvements in which are linked to better survival outcomes for patients. Results from a phase 2 study are also expected shortly. In MF, phase 2, stage 1 data show a decrease in bone marrow fibrosis in approximately half of patients given PRM-151 as well as an increased production of hemoglobin and platelets.

"Fibrosis is the common pathology of a number of serious and chronic diseases—such as IPF, MF, and nonalcoholic steatohepatitis—that have unmet patient needs," said Jack. "Our therapeutics, based on pentraxin-2, offer the potential to reverse the pathological process in fibrosis, and to significantly improve patient lives by restoring healthy organ function."

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