PharmAkea, Inc.
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Attacking fibrosis on multiple fronts

Fibrosis is characterized by the excessive or abnormal accumulation of extracellular matrix within tissue, leading to organ dysfunction and disease in a range of conditions. There is a high level of unmet need given that the limited treatments available offer only modest benefits, and new drugs are urgently needed.

PharmAkea is generating novel therapies for fibrotic diseases that offer the potential for improved efficacy and tolerability in patients either alone or in combination with existing treatments. The San Diego-based clinical-stage pharmaceutical company is developing small molecules against protein targets involved in fibroproliferative diseases. PharmAkea has developed orally available, small-molecule inhibitors of two fibrotic molecular targets: the secreted enzymes lysyl oxidase-like 2 (LOXL2) and autotaxin (ATX).

Currently, the company's portfolio includes PAT-1251, a phase 2-ready LOXL2 inhibitor for the treatment of idiopathic pulmonary, liver and kidney fibrosis, and PAT-409, a phase 1-ready ATX inhibitor for nonalcoholic steatohepatitis, primary biliary cholangitis, idiopathic pulmonary fibrosis, and scleroderma. The company is exploring strategic options including out-licensing for its two programs in fibrosis.

Poised for success

The LOXL2 enzyme increases the cross-linking of collagen and elastin, making the extracellular matrix stiffer and more resistant to degradation. This activates resident fibroblasts to become myofibroblasts, initiating a profibrotic feed-forward loop that can lead to scarring and destruction of normal tissue. LOXL2 is elevated in the serum of patients with a variety of fibrotic diseases.

Unlike previously tested monoclonal antibodies, the mechanism-based inhibitor PAT-1251 robustly inhibits the catalytic activity of LOXL2, resulting in superior antifibrotic efficacy in models of lung, liver and kidney fibrosis. Data from long-term toxicology studies and a recently completed phase 1 trial, which demonstrated that PAT-1251 is safe and well tolerated in healthy subjects, support direct entry of the small-molecule inhibitor into a phase 2 study.

ATX is a key enzyme involved in the generation of lysophosphatidic acid, a lipid implicated in a variety of fibrotic diseases that affect the liver, lung, kidney and skin. ATX inhibitors have the potential to show broader effects than compounds that selectively inhibit downstream receptors. Unlike LPA1 receptor antagonists under clinical investigation, PAT-409 has demonstrated efficacy in rodent models of nonalcoholic steatohepatitis. PAT-409 also reduced fibrosis in a rat model of inflammatory bowel disease. Investigational new drug (IND)-enabling toxicology studies have been completed, setting the stage for phase 1 trials.

"We are encouraged by our preclinical and clinical studies validating LOXL2 and ATX as key molecular targets in a wide variety of fibrotic diseases," said PharmAkea's CEO Robert Williamson. "Our two small-molecule programs are ready to be taken to the next level, paving the way for much needed therapies that will improve the clinical outcomes for countless patients worldwide."

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