Small-Molecule Therapeutic Treats Scleroderma

Fibrotic diseases account for up to 40 percent of all deaths worldwide. This includes the rare disease scleroderma, or systemic sclerosis, a chronic connective tissue disease classified as one of the autoimmune rheumatic diseases. Scleroderma is currently treated with anti-inflammatory drugs and immunosuppressants, which have major side effects and do not address an underlying cause. Despite years of research, ultimately, there are truly no effective drugs that can treat these diseases.

The Solution

University of Michigan’s Scott Larsen, Ph.D., and Richard Neubig, Ph.D., M.D., of Michigan State University, have created a novel small-molecule therapeutic that is a potential treatment for systemic sclerosis (SSc) and possibly other fibrotic diseases, including idiopathic pulmonary fibrosis, liver cirrhosis, diabetic nephropathy, etc. These diseases are caused by the transition of normal fibroblasts – cells that assist in wound healing – into myofibroblasts, which results in an excessive production of collagen throughout the body. This new therapeutic inhibits a common cell-signaling pathway, Rho/MRTF/SRF, which is induced by multiple extracellular profibrotic stimuli. In sufferers of the diseases, the compound essentially acts to switch “off” the body’s mechanism to over-produce collagen.

While SSc affects fewer than 200,000 people nationwide, its fatality rate is higher than any other rheumatic disease. There are currently no approved therapeutics for scleroderma and only two for pulmonary fibrosis, which are not very effective. This therapeutic will be positioned to be used as a once- or twice-daily oral treatment for diseases of fibrosis.
Significant Need
SSc is currently treated with anti-inflammatory drugs and immunosuppressants, which have major side effects and do not address an underlying cause. Despite years of research, ultimately, there are no truly effective agents that can treat fibrotic diseases.

Compelling Science
This compound is unique in targeting a gene transcription, specifically the common cell-signaling pathway, Rho/MRTF/SRF, which is critical for the fibroblast-myofibroblast transition. It showed single-digit nanomolar suppression of Rho-regulated SRE-Luciferase and potent inhibition of the expression of the pro-fibrotic cytokine CTGF in fibroblasts. Also, it has in vivo efficacy in a mouse skin fibrosis model to reduce both skin thickness and tissue CTGF expression.

Competitive Advantage
There is a much higher potency in vitro, lower toxicity to cells in culture, and recent work has identified a candidate molecular target, which has been a roadblock to commercial development by competitors.

MTRAC Project Key Milestones
- Drug synthesis; salt selection based on physical properties; in vitro ADME profiling; oral PK in mice; 14-day multiple dose tolerance in mice
- Oral PK in rats; non-GLP tox in rats
- Anti-fibrotic efficacy in bleo-treated mice at three doses
- Anti-fibrotic efficacy in TSK-1 mice

Overall Commercialization
- Intellectual Property
  - A provisional patent has been filed.
- Commercialization Strategy
  - Potential licensure, spin-off or acquisition.
- Regulatory Pathway
  - Pre-market review and regulation will be assigned to FDA Center for Drug Evaluation and Research (CDER); will seek Orphan Drug Status and Fast Track Designation.
- Product Launch Strategy
  - To be determined by licensee.