STATegics, Inc.
Lead PI: Juha Punnonen, MD, PhD

Organization and Team Overview

STATegics, Inc., based in Menlo Park, CA, is focused on the discovery and development of orally available cytokine receptor modulators acting through novel, allosteric sites. STATegics’ small molecules, Allomimetics, offer unique competitive advantages when compared to recombinant proteins, antibodies, peptides or oligonucleotides, particularly when bioavailability in tissues and central nervous system (CNS) is required.

STATegics has identified CNS-available small molecule erythropoietin (EPO) Allomimetics that selectively activate the tissue-protective EPO receptor. Through this mechanism, the lead compounds induce significant cytoprotective effects in primary human neurons and kidney cells \textit{in vitro} and \textit{in vivo}, without the erythropoietic activity of EPO. The compounds also demonstrate a favorable safety profile and penetrance to the brain at pharmacologically relevant concentrations, and are being investigated for treatment of PD, Friedreich’s ataxia, and acute kidney injury. In addition, STATegics has identified a proprietary thrombopoietin (TPO) Allomimetic, with best-in-class properties for the treatment of thrombocytopenia and bone marrow malignancies. STATegics’ assay technologies have demonstrated a proof-of-concept for a platform approach to screen for Allomimetics targeting other cytokine receptors with major clinical and commercial interests.

STATegics’ platform is based on inventions and know-how of the two founders, Juha Punnonen, MD, PhD and Jeffrey R. Spencer, PhD, with guidance from the late John G. Curd, MD, former CMO at Threshold Pharmaceuticals. Dr. Punnonen is a Co-Founder and Chief Executive Officer of STATegics. Prior to STATegics, he served as Vice President, R&D and Head of Biology & Pharmacology at Maxygen, Inc. (MAXY). Dr. Spencer, Senior Vice President, has over 20 years of experience in small molecule drug discovery and development. Prior to STATegics, Dr. Spencer was Senior Director and Head of Discovery Medicinal Chemistry at Celera Genomics and Axys Pharmaceuticals. Dr. James L. Miller, PhD, Director of Biology, brings over 20 years of experience in preclinical pharmacology with a focus on neurodegenerative disease, pain and autoimmune disease. Prior to joining STATegics, Dr. Miller worked at Neurex Corporation and Elan Pharmaceuticals. STATegics has assembled a strong advisory team consisting of leaders from academics and industry in CNS diseases, organ protection and small molecule drug development.

Opportunity Overview

EPO mediates both erythropoietic and tissue-protective effects, which are mediated via distinct receptors. The tissue-protective receptor, comprising an EPO receptor subunit and CD131 (common beta-chain of GM-CSF/IL-3/IL-5 receptors, CSF2RB), is present throughout the body and mediates cytoprotective, anti-apoptotic and anti-inflammatory effects. While recombinant EPO has shown efficacy in rodent models of PD and in initial clinical studies, poor penetrance across the blood-brain barrier limits the efficacy of recombinant EPO and its erythropoietic activity has prevented optimal dosing in patients. These challenges could be overcome by a CNS-available small molecule selective for the tissue-protective EPO receptor. STATegics has discovered small molecule compounds that activate the tissue-protective, heteromeric EPOR/CD131 receptor and trigger EPO-like cytoprotective effects without the erythropoietic activity of rhEPO. The lead compounds are CNS-available and provide potent neuroprotective effects in primary human and rodent neuronal cells, including primary dopaminergic neurons. The compounds have been well tolerated in mice, rats and dogs, and offer the convenience of oral ad
Details of MJFF Grant

Objective/Rationale:
The goal of the research program was to demonstrate drug-like properties and a proof-of-concept for the efficacy of EPO Allomimetic compounds in protecting dopaminergic neurons in pre-clinical models of PD.

Project Description:
As part of this research program, we scaled up the synthesis of the compounds, further characterized the mechanism of action, and evaluated the compounds' efficacy in a pre-clinical model of PD. The studies have been carried out in collaboration with Prof. Timothy J. Collier, Director of the Udall Center of Excellence in Parkinson's Disease Research at Michigan State University. A clinical candidate is being selected based on a combination of results from the experiments in cell culture, pharmacokinetics and efficacy in a pre-clinical model of PD.

Relevance to Diagnosis/Treatment of Parkinson's Disease:
Neuroprotective small molecule agonists of the tissue-protective EPOR/CD131 receptor are expected to protect against the ongoing loss of dopaminergic neurons in PD. Based on prior reports on EPO receptor biology, the compounds may also support the treatment of depression and cognitive dysfunction that associate with PD. The compounds have the potential to slow down the progression of the disease and may also repair damaged brain tissue acting as disease modifying therapies.

Anticipated Outcome:
The studies are designed such that a candidate therapeutic can be selected for more detailed development at the end of the program. Following the completion of the studies, the overall goal is to advance the selected compound into clinical studies in patients with PD.

Results and Potential Next Steps

STATegics' results to date demonstrate potent, selective activation of the tissue-protective EPOR/CD131 receptor, neuroprotective effects in vitro, favorable safety profile in vitro and in vivo, and beneficial effects in a rat model of PD.

The key results to date include:
1) Phosphorylation (activation) of the tissue-protective EPOR/CD131 receptor
2) Signaling mechanisms and gene expression profile (“gene chip”) consistent with EPOR/CD131 activation
3) Potent neuroprotective effects in primary neurons, including dopaminergic neurons, in vitro
4) No observed adverse effects in mice or rats administered three times daily up to 27 days
5) No off-target effects in a lead profiling screen, low CYP and hERG inhibition
6) Pharmacokinetic studies in rats and dogs supporting oral administration
7) Induction of a biomarker protein consistent with EPOR/CD131 activation in the brain and heart in vivo
8) Beneficial effects on behavioral outcome in rats lesioned with 6-OHDA

STATegics is interested in partnerships to support the advancement of the program into clinical development in PD.

Intellectual Property Status

STATegics' intellectual property is protected by US and international patent filings.