Medical Xpress

Cytokinetics announces fundamental research in cardiac myosin activation

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Cytokinetics, Inc. announced today the publication of preclinical research in the March 18, 2011 issue of the journal *Science* regarding the activation of cardiac myosin by an investigational drug candidate, omecamtiv mecarbil, and the potential therapeutic role that this novel mechanism may play for patients with systolic heart failure. This publication reveals, for the first time in a peer reviewed journal, the mechanism of action for omecamtiv mecarbil and the scientific rationale for directly modulating cardiac contractility as an innovative therapeutic strategy for improving cardiac performance in patients with heart failure.

"It is our honor to have Cytokinetics' novel scientific research into direct modulators of the cardiac contractile apparatus published in this prestigious journal," stated Fady I. Malik, MD, FACC, Cytokinetics' Vice President of Biology and Therapeutics and lead author of this report. "This publication summarizes the pioneering work performed by our dedicated research team that has supported the progression of our lead compound, omecamtiv mecarbil, through clinical development and now into Phase IIb clinical trials, which will be conducted by Amgen in collaboration with Cytokinetics."

The publication titled, "Cardiac Myosin Activation: A Potential Therapeutic Approach for Systolic Heart Failure," discusses the potential clinical role for therapies that directly activate cardiac myosin in the treatment of systolic heart failure. The authors recognized that decreased cardiac contractility is a central feature of systolic heart failure and that

there is a need for more safe and effective treatment options to improve cardiac contractility. Existing drugs that increase cardiac contractility do so indirectly through signaling cascades but their use is limited by their mechanism-related adverse effects. Omecamtiv mecarbil, a small-molecule, direct activator of cardiac myosin, was developed to address these limitations.

In this publication, the authors demonstrated that omecamtiv mecarbil binds to the myosin catalytic domain and acts by an allosteric mechanism to increase the transition rate of myosin into the strongly actin-bound force-generating state. Paradoxically, omecamtiv mecarbil inhibits adenosine 5'-triphosphate (ATP) turnover in the absence of actin, which suggests that it stabilizes an actin-bound conformation of myosin. In animal models, omecamtiv mecarbil increases cardiac function by increasing the duration of ejection without changing the rates of cardiac contraction. The authors concluded that cardiac myosin activation may provide a new therapeutic approach for patients with systolic heart failure.

"This ground-breaking publication underscores the quality and robustness of the science at our company which relates to the mechanics and biology of muscle function and that serves as the basis for our portfolio of drug candidates," stated Robert I. Blum, Cytokinetics' President and Chief Executive Officer. "Over several years, our promising research has now resulted in multiple first-in-class compounds that may address unmet clinical needs in a broad array of indications and medical conditions associated with impaired muscle contractility."

Development Status of Omecamtiv Mecarbil

Omecamtiv mecarbil, a novel cardiac muscle myosin activator, has been the subject of a clinical trials program comprised of multiple Phase I and Phase IIa trials conducted under Cytokinetics' sponsorship. This program

was designed to evaluate the safety, tolerability, pharmacodynamic and pharmacokinetic profiles of both intravenous and oral formulations of omecamtiv mecarbil for the potential treatment of heart failure across the continuum of care, in both hospital and outpatient settings. Two Phase IIa clinical trials of omecamtiv mecarbil from this program have been completed in patients with heart failure. In addition, five Phase I clinical trials of omecamtiv mecarbil were conducted in healthy subjects. Data from each of these trials have been reported previously.

Amgen holds an exclusive, world-wide (excluding Japan) license to omecamtiv mecarbil and related compounds, subject to specified development and commercialization participation rights of Cytokinetics. In February 2011, the company and its partner, Amgen Inc., announced plans to initiate a Phase IIb clinical trial of an intravenous formulation of omecamtiv mecarbil to evaluate its safety and efficacy in patients with left ventricular systolic dysfunction hospitalized for acute heart failure in the first half of 2011.

Provided by Cytokinetics

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