Cytokinetics Announces Publications Relating to Fast Skeletal Troponin Activation in Nemaline Myopathy

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Translational Research Suggests a New Therapeutic Approach to Rare Muscle Disease

South San Francisco, CA, June 4, 2013 - Cytokinetics, Incorporated (Nasdaq: CYTK) announced the publication of three peer-reviewed manuscripts co-authored by company scientists with a group led by Dr. Henk Granzier, Professor of Physiology, and Norville Endowed Chair, Molecular Cardiovascular Research Program, University of Arizona. These publications relate to translational research conducted by Dr. Granzier's laboratory in collaboration with Cytokinetics in which the mechanistic effects of fast skeletal troponin activation were explored in nemaline myopathy, a rare sarcomere-based disease.

Nemaline myopathy is an inherited disease that leads to skeletal muscle weakness and decreased muscle tone (hypotonia) in the muscles of the face, neck and upper limbs, and often affects the respiratory muscles. The preclinical studies described in these publications provide support for the hypothesis that CK-2066260, a fast skeletal troponin activator, may compensate in part for the defect in sarcomere calcium sensitivity found in muscle derived both from mouse models of nemaline myopathy as well as human muscle from patients with nemaline myopathy. These findings suggest that fast skeletal troponin activators may offer a promising therapeutic approach to improving muscle function in nemaline myopathy and other inherited conditions in which the calcium sensitivity of the sarcomere is abnormal.

"Our collaboration with Cytokinetics has revealed a potentially important new opportunity in the treatment of nemaline myopathy," stated Dr. Granzier. "These publications also underscore the possibility that fast skeletal troponin activation may be useful to improve muscle function in a diversity of patients with muscle disorders that relate to abnormal calcium sensitivity in the sarcomere and in whom their disease manifests as debilitating muscle weakness and persistent fatigue."

"We are very pleased to report the results of our collaboration with Dr. Granzier's group that demonstrate that fast skeletal troponin activators may have therapeutic application in primary skeletal muscle myopathies," stated Fady I. Malik, MD, PhD, FACC, Cytokinetics' Senior Vice President, Research and Early Development. "These findings suggest potential opportunities for broadening the therapeutic application of fast skeletal troponin activators and may have important implications for patients for whom treatment options are limited."

CK-2066260 is a structural analog of *tirasemtiv*, Cytokinetics' lead drug candidate arising from the company's skeletal muscle contractility program directed to neuromuscular diseases. *Tirasemtiv* selectively activates the fast skeletal troponin complex by increasing its sensitivity to calcium, thereby increasing skeletal muscle force in response to neuronal input and delaying the onset and reducing the degree of muscle fatigue. Cytokinetics is evaluating *tirasemtiv* as a potential treatment for amyotrophic lateral sclerosis (ALS) in BENEFIT-ALS (**B**linded **E**valuation of **N**euromuscular **E**ffects and **F**unctional **I**mprovement with ***T****irasemtiv* in **ALS**), an ongoing international Phase IIb clinical trial.

Publications Regarding Fast Skeletal Troponin Activation in Nemaline Myopathy

The publication titled, "Fast Skeletal Muscle Troponin Activation Increases Force of Mouse Fast Skeletal Muscle and Ameliorates Weakness Due to Nebulin-Deficiency," appeared in the February 2013 *PLOS One* journal and discusses the effects on muscle strength of fast skeletal troponin activation in mice with a complete deficiency of the sarcomeric protein, nebulin. The authors concluded that CK-20660260 increased muscle force at submaximal activation in both wild-type and nebulin deficient muscle fiber bundles and that fast skeletal troponin activation is a potential therapeutic mechanism for increasing force in nemaline myopathy and other skeletal muscle diseases characterized by diminished muscle strength.

The publication titled, "Deleting Exon 55 from the Nebulin Gene Induces Severe Muscle Weakness in a Mouse Model for Nemaline Myopathy," appeared in the May 2013 online publication of the journal *Brain*. The publication presents data from a mouse model in which only part of the nebulin gene (exon 55) is deleted in order to model a mutation frequently seen in patients with nemaline myopathy. This model allowed, for the first time, a detailed and comprehensive investigation of the impact on muscle function caused by a nebulin mutation. The results indicate that the phenotype of this mouse model recapitulates important features observed previously in patients harboring this particular mutation. Severe muscle weakness and a reduction in the calcium sensitivity of the sarcomere characterize the phenotype of both the mouse model and patients. The authors concluded that these deficits in muscle function in part could be mitigated by CK-2066260 as it augmented the response of muscle in this model to calcium.

The publication titled "Troponin Activator Augments Muscle Force in Nemaline Myopathy Patients with Nebulin Mutations," appears in the June 2013 issue of the *Journal of Medical Genetics* and highlights the ability of CK-2066260 to augment force generation at submaximal calcium levels in muscle tissue obtained from biopsies of nemaline myopathy patients with nebulin mutations. The authors found that nebulin protein concentrations were severely reduced in muscle cells from these patients compared to controls, while myofibrillar ultrastructure was largely preserved. Both maximal active tension and the calcium sensitivity of force generation were lower in patients compared to controls. CK-2066260 increased the calcium-sensitivity of muscle force generation and at sub-maximal calcium activation, the levels of force exceeded those observed in untreated control muscles. The authors concluded that fast skeletal troponin activation may be a therapeutic mechanism to augment contractile protein function in nemaline myopathy patients with nebulin mutations and with other neuromuscular diseases.

Background on Fast Skeletal Muscle Activators

Skeletal muscle contractility is driven by the sarcomere, the fundamental unit of skeletal muscle contraction. It is a highly ordered cytoskeletal structure composed of several key proteins. The first, skeletal muscle myosin, is the cytoskeletal motor protein that converts chemical energy into mechanical force through its interaction with a second protein, actin. A set of regulatory proteins, which includes tropomyosin and several types of troponin, make the actin-myosin interaction dependent on changes in intracellular calcium levels. Cytokinetics' skeletal muscle contractility program is focused to the discovery and development of small molecule skeletal sarcomere activators and leverages Cytokinetics' expertise gained from its ongoing discovery and development of cardiac sarcomere activators, including the cardiac myosin activator *omecamtiv mecarbil*, now in Phase IIb clinical development as a potential treatment for heart failure. In non-clinical models, skeletal sarcomere activators have demonstrated pharmacological activity that may lead to new therapeutic options for diseases associated with aging, muscle wasting, and neuromuscular dysfunction. The clinical effects of muscle wasting, fatigue and loss of mobility can range from decreased quality of life to, in some instances, life-threatening complications. By directly improving skeletal muscle function, a small molecule activator of the skeletal sarcomere may potentially enhance physical performance and quality of life in patients with conditions marked by muscle weakness, including neuromuscular diseases such as ALS, myasthenia

gravis, cachexia, sarcopenia and general frailty associated with aging.

Development Status of *Tirasemtiv* in ALS

Tirasemtiv (formerly CK-2017357) is currently being evaluated in BENEFIT-ALS, an international, double-blind, randomized, placebo-controlled, Phase IIb clinical trial designed to evaluate the safety, tolerability and potential efficacy of this novel drug candidate in patients with ALS. BENEFIT-ALS is designed to enroll approximately 500 patients who will first complete one week of treatment with open-label *tirasemtiv* at 125 mg twice daily. Following completion of the open-label period, patients will be randomized to receive 12 weeks of double-blind treatment with twice-daily oral ascending doses of *tirasemtiv* beginning at 125 mg twice daily and increasing weekly up to 250 mg twice daily or a dummy dose titration with placebo. Clinical assessments will take place monthly during the course of treatment; patients will also participate in follow-up evaluations one and four weeks after their final dose. The primary efficacy analysis of BENEFIT-ALS will compare the mean change from baseline in the ALS Functional Rating Scale in its revised form (ALSFRS-R) on *tirasemtiv* versus placebo. Secondary endpoints will include Maximum Voluntary Ventilation (MVV) and other measures of respiratory and skeletal muscle function. Patients taking *riluzole* at the time of enrollment and who are randomized to receive *tirasemtiv* will receive *riluzole* at a reduced dose of 50 mg daily.

About Cytokinetics

Cytokinetics is a clinical-stage biopharmaceutical company focused on the discovery and development of novel small molecule therapeutics that modulate muscle function for the potential treatment of serious diseases and medical conditions. Cytokinetics' lead drug candidate from its cardiac muscle contractility program, *omecamtiv mecarbil*, is in Phase II clinical development for the potential treatment of heart failure. Amgen Inc. holds an exclusive license worldwide (excluding Japan) to develop and commercialize *omecamtiv mecarbil* and related compounds, subject to Cytokinetics' specified development and commercialization participation rights. Cytokinetics is independently developing *tirasemtiv* and CK-2127107, both fast skeletal muscle activators, as potential treatments for diseases and medical conditions associated with aging, muscle wasting or neuromuscular dysfunction. *Tirasemtiv* is currently the subject of a Phase II clinical trials program and has been granted orphan drug designation and fast track status by the U.S. Food and Drug Administration and orphan medicinal product designation by the European Medicines Agency for the potential treatment of amyotrophic lateral sclerosis, a debilitating disease of neuromuscular impairment in which treatment with *tirasemtiv* produced potentially clinically relevant pharmacodynamic effects in Phase II trials. All of these drug candidates have arisen from Cytokinetics' muscle biology focused research activities and are directed towards the cytoskeleton. The cytoskeleton is a complex biological infrastructure that plays a fundamental role within every human cell. Additional information about Cytokinetics can be obtained at www.cytokinetics.com.

This press release contains forward-looking statements for purposes of the Private Securities Litigation Reform Act of 1995 (the "Act"). Cytokinetics disclaims any intent or obligation to update these forward-looking statements, and claims the protection of the Act's Safe Harbor for forward-looking statements. Examples of such statements include, but are not limited to, statements relating to Cytokinetics' research and development activities, including the conduct, design, enrollment, progress and results of clinical trials, the significance and utility of preclinical study and clinical trial results; and the properties and potential benefits of Cytokinetics' skeletal sarcomere activators, including tirasemtiv. Such statements are based on management's current expectations, but actual results may differ materially due to various risks and uncertainties, including, but not limited to: Cytokinetics anticipates that it will be required to conduct at least one confirmatory Phase III clinical trial of tirasemtiv in ALS patients which will require significant additional funding, and it may be unable to obtain such additional funding on acceptable terms, if at all; potential difficulties or delays in the development, testing, regulatory approvals for trial commencement, progression or product sale or manufacturing, or production of Cytokinetics' drug candidates that could slow or prevent clinical development or product approval, including risks that current and past results of clinical trials or preclinical studies may not be indicative of future clinical trials results, patient enrollment for or conduct of clinical trials may be difficult or delayed, Cytokinetics' drug candidates may have adverse side effects or inadequate therapeutic efficacy, the U.S. Food and Drug Administration or foreign regulatory agencies may delay or limit Cytokinetics' or its partners' ability to conduct clinical trials, and Cytokinetics may be unable to obtain or maintain patent or trade secret protection for its intellectual property; Amgen's decisions with respect to the design, initiation, conduct, timing and continuation of development activities for omecamtiv mecarbil; Cytokinetics may incur unanticipated research and development and other costs or be unable to obtain additional financing necessary to conduct development of its products; Cytokinetics may be unable to enter into future collaboration agreements for its drug candidates and programs on acceptable terms, if at all; standards of care may change, rendering Cytokinetics' drug candidates obsolete; competitive products or alternative therapies may be developed by others for the treatment of indications Cytokinetics' drug candidates and potential drug candidates may target; and risks and uncertainties relating to the timing and receipt of payments from its partners, including milestones and royalties on future potential product sales under Cytokinetics' collaboration agreements with such partners. For further information regarding these and other risks related to Cytokinetics' business, investors should consult Cytokinetics' filings with the Securities and Exchange Commission.

Contact:

Cytokinetics, Inc.
Joanna L. Goldstein (Investors & Media)
(650) 624-3000