Nature Neuroscience Publishes Data Demonstrating Potential Therapeutic Benefits of Karyopharm's SINE(TM) Compounds in the Treatment of Multiple Sclerosis

Research Conducted in Collaboration with Mount Sinai with Funding from the National Multiple Sclerosis Society and from the National Institute for Neurological Disorders and Stroke
Results Highlight First-in-Class SINE Compounds Reduce Disease Progression in Preclinical Multiple Sclerosis Models

NEWTON, Mass., Feb. 23, 2015 (GLOBE NEWSWIRE) -- Karyopharm Therapeutics Inc. (Nasdaq:KPTI), a clinical-stage pharmaceutical company, today announced that *Nature Neuroscience* published data showing Karyopharm's first-in-class oral Selective Inhibitor of Nuclear Export, or SINE™, compounds reduce the progression of multiple sclerosis (MS) in preclinical models. In the paper, scientists from Icahn School of Medicine at Mount Sinai and Karyopharm describe the ability of SINE exportin 1 (XPO1) inhibitors to decrease neurodegenerative symptoms and disease progression in multiple sclerosis by reducing neuronal inflammation and preventing toxic factors in the brain from attacking and destroying the neuronal myelin coating.

"Multiple sclerosis is a devastating, degenerative disease in need of continued research and innovation," said Karyopharm President and Chief Scientific Officer, Sharon Shacham, PhD, MBA. "We are honored to collaborate with Dr. Patrizia Casaccia at Mount Sinai, a recognized leader in MS research and recipient of awards from the National Institute for Neurological Disorders and Stroke, with funding provided also by the National MS Society, to explore the potential of nuclear export targeting in the treatment of MS."

While Karyopharm's lead SINE compound, oral selinexor, is in multiple registration-directed trials for hematological malignances, additional SINE compounds are being developed to treat other unmet medical needs, including inflammatory and autoimmune diseases.

"In Multiple Sclerosis, at least two events are implicated in the progression of the disease: myelin destruction and neurodegeneration. While destruction of myelin has been linked to slower axonal conduction and loss of metabolic support to neurons, it is becoming increasingly clear that the accumulation of other factors (e.g. cytokines, excitatory neurotransmitter and lipids) in the cerebrospinal fluid or brain is responsible for impairing mitochondrial function and causing neurodegenerative signs" said Dr. Patrizia Casaccia, MD, PhD, Professor in the Departments of Neuroscience, Neurology and Genetics and Genomics at Icahn School of Medicine at Mount Sinai "We had previously identified XPO1-mediated nuclear export as one of the first events preceding the occurrence of axonal damage in cultured neurons. In this study, we report the upregulation of XPO1 in MS lesions. SINE compounds are capable of reducing axonal damage in cultured neurons and to reduce the clinical progression in mouse models of MS. The key finding of this study is that treatment of mice with SINE compounds after the first signs of paralysis of the hind limbs can reduce inflammation and protect neurons, thereby slowing down the progression of the disease while allowing regenerative processes to take place."

"This is another exciting example of the breadth of opportunity for SINE compounds to help patients with limited treatment options, and demonstrates why dozens of top tier institutions, such as Mount Sinai, are actively exploring the potential for SINE compounds across multiple diseases," said Karyopharm's Chief Executive Officer, Michael G. Kauffman, MD, PhD.

Key findings from the paper, entitled "Nuclear export inhibitors avert progression in preclinical models of inflammatory demyelination" include:

- Upregulation of XPO1-mediated nuclear export in neurons in MS lesions.
- Oral administration of SINE compounds in preclinical murine models of demyelination significantly attenuated disease progression, even when started *after* the onset of paralysis.
- Efficacy was associated with decreased proliferation of immune cells, characterized by nuclear accumulation of endogenous cell cycle inhibitors, and preservation of cytoskeletal integrity even in demyelinated axons, consistent with a neuroprotective effect of the compounds.
- Neuroprotection was not limited to models of demyelination, but was also observed in other mouse models of axonal damage and detected in cultured neurons after knockdown of XPO1.
- A proteomic screen for target molecules revealed that treatment of neurons with SINE compounds prevented nuclear export of molecules associated with axonal damage while retaining transcription factors that are known to contribute to neuroprotection.

About Karyopharm Therapeutics

Karyopharm Therapeutics Inc. (Nasdaq:KPTI) is a clinical-stage pharmaceutical company focused on the discovery and development of novel first-in-class drugs directed against nuclear transport targets for the treatment of cancer and other major diseases. Karyopharm's Selective Inhibitor of Nuclear Export / SINE™ compounds function by binding with and inhibiting the nuclear export protein XPO1 (or CRM1). The inhibition of XPO1 by Karyopharm's lead drug candidate, selinexor (KPT-330), a first-in-class, oral SINE™ compound, leads to the accumulation of tumor suppressor proteins in the cell nucleus, which subsequently reinitiates and amplifies their tumor suppressor function. This is believed to lead to the selective induction of apoptosis in cancer cells, while largely sparing normal cells. Approximately 600 patients have been treated with selinexor in Phase 1 and Phase 2 clinical trials in advanced hematologic malignancies and solid tumors. Karyopharm has initiated three registration-directed clinical trials of selinexor, one in older patients with acute myeloid leukemia, one in patients with Richter's transformation and one in patients with diffuse large B-cell lymphoma (DLBCL). Karyopharm plans to initiate a single-arm trial in multiple myeloma in the first half of 2015 that is intended to be registration-directed and other potential registration-directed trials in hematological and solid tumor indications are being evaluated. Additional Phase 1 and Phase 2 studies are ongoing or currently planned, including multiple investigator-sponsored studies of selinexor in combination with one or more approved therapies. SINE™ compounds have shown biological activity in models of cancer, inflammation, autoimmune disease, certain viruses, and wound-healing. Karyopharm was founded by Dr. Sharon Shacham and is located in Newton, Massachusetts. For more information about Karyopharm, please visit www.karyopharm.com.

Forward-Looking Statements

This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the therapeutic potential of and potential clinical development plans for Karyopharm's drug candidates, including the timing of initiation of certain trials and of the reporting of data from such trials. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from the company's current expectations. For example, there can be no guarantee that any of Karyopharm's SINE™ compounds, including selinexor (KPT-330), or any other drug candidate that Karyopharm is developing will successfully complete necessary preclinical and clinical development phases or that development of any of Karyopharm's drug candidates will continue. Further, there can be no guarantee that any positive developments in Karyopharm's drug candidate portfolio will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other factors, including the following: Karyopharm's results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. Food and Drug Administration, the European Medicines Agency and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; Karyopharm's ability to obtain and maintain requisite regulatory approvals and to enroll patients in its clinical trials; unplanned cash requirements and expenditures; development of drug candidates by Karyopharm's competitors for diseases in which Karyopharm is currently developing its drug candidates; and Karyopharm's ability to obtain, maintain and enforce patent and other intellectual property protection for any drug candidates it is developing. These and other risks are described under the caption "Risk Factors" in Karyopharm's Current Report on Form 8-K filed with the Securities and Exchange Commission (SEC) on January 5, 2015, and in other filings that Karyopharm may make with theSEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Karyopharm expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

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