

Karyopharm Advancing Neuroprotective SINE(TM) Compounds in Amyotrophic Lateral Sclerosis (ALS)

- **Preclinical efficacy of SINE™ compounds validated in journal Nature publication -**
- **Presentations of ALS abstracts at upcoming AAN and SfN meetings -**
- **Collaborator grant funding supports Karyopharm's ALS research -**

NEWTON, Mass., Sept. 3, 2015 (GLOBE NEWSWIRE) -- Karyopharm Therapeutics Inc. (Nasdaq:KPTI), a clinical-stage pharmaceutical company, today reported that its SINE™ nuclear transport compounds are being evaluated for the treatment of Amyotrophic Lateral Sclerosis (ALS) and that preclinical data abstracts will be presented at two upcoming neuroscience meetings. A recent publication appearing in the journal *Nature* confirmed that nuclear transport is disrupted in a common mutation found in ALS. Given the tremendous unmet need for new treatments for ALS, Karyopharm is advancing its oral SINE™ compound KPT-350 for this indication. While Karyopharm's primary clinical focus is in advancing its lead SINE™ compound oral selinexor for human cancer, other SINE™ compounds have already shown beneficial pharmacological effects in several neurodegenerative and anti-inflammatory preclinical models, including multiple sclerosis, systemic lupus and traumatic brain injury.

The *Nature* publication entitled "The *C9orf72* repeat expansion disrupts nucleocytoplasmic transport" reported that *C9orf72*, the most common cause of familial and sporadic ALS and Frontotemporal Degeneration, results in problems with nuclear protein trafficking that affect neural function and survival. The mutation causes the affected cells to create long strands of repeating RNA, thus blocking critical pathways for nuclear transport of proteins. A first set of experiments using a fruit fly model of human ALS to screen for candidates that block brain cell death in a living organism identified a protein RanGAP, a key regulator of nucleocytoplasmic transport, that acts as a potent suppressor of neurodegeneration. Consistent with the interaction of RanGAP with XPO1 (exportin 1), the studies further showed that suppressing nuclear export of proteins also suppresses neurodegeneration. The results were validated in human stem cell derived motor neurons and autopsied brains.

In a second set of experiments, using fly and human stem cells, the addition of antisense oligonucleotides targeting *C9orf72* or small molecule inhibitors of XPO1 including one of Karyopharm's SINE™ compounds, restored proper protein nuclear localization. Importantly, this effect was sufficient to suppress neurodegeneration. This study supports the premise that nucleocytoplasmic transport defects may be a fundamental pathway for ALS that is amenable to pharmacotherapeutic intervention. The results from this publication will also be presented at the Society for Neuroscience (SfN) meeting in Chicago on October 19, 2015 by Thomas E. Lloyd, MD, Ph.D. of Johns Hopkins University.

"This valuable research reinforces that modulation of nucleocytoplasmic transport presents a potential therapeutic strategy for neurodegenerative diseases such as ALS," said Sharon Shacham, PhD, President and Chief Scientific Officer of Karyopharm. "More broadly, this work extends earlier findings in multiple sclerosis, traumatic brain injury, and auto-inflammatory disorders, further validating the vast therapeutic applicability of Karyopharm's SINE™ compounds across a broad spectrum of diseases."

In addition to the above presentation, Karyopharm's other collaborators will be presenting abstracts on the neuroprotective effects of SINE™ compounds at two upcoming neuroscience meetings this fall. Sami Barmada, MD, Ph.D. from the University of Michigan will be presenting an abstract entitled "Selective inhibition of nuclear export in amyotrophic lateral sclerosis and frontotemporal dementia" at the upcoming American Neurological Association (ANA) Meeting in Chicago on September 26, 2015 from 9:35am-11:35am. Hilary Archbold, also from the University of Michigan, will be presenting an abstract entitled "The role of nuclear export in TDP-43-mediated neurodegeneration" at the Society for Neuroscience (SfN) meeting in Chicago from October 18, 2015 from 4:00pm-5:00pm.

Karyopharm's SINE compound research efforts in ALS are being supported entirely by collaborator grant funding. The ALS Therapy Alliance is funding the in vitro research of Karyopharm's collaborator Sami Barmada, MD, Ph.D. of the University of Michigan until 2016. The goal of that grant is to investigate the mechanism of neuroprotection by SINE™ compounds and determine if they are protective in human stem cell-derived neurons from patients with ALS and FTD. Another collaborator, Ronald Klein, Ph.D. of Louisiana State University Health Sciences Center, Shreveport has been funded by the ALS Association beginning in July 2015 for two years to evaluate the therapeutic efficacy of KPT-350 in an adult onset ALS model. This in vivo research is expected to confirm whether Karyopharm's compound can ameliorate the ALS-like disease state in rats induced by gene transfer of cytoplasmic TDP-43, a major disease protein in ALS.

About Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain and spinal cord. The degeneration of nerve cells eventually causes people with ALS to lose the ability to initiate and control muscle

movement. There is no cure for the disease and few treatment options exist. Approximately 6,400 new cases of ALS are diagnosed each year in the United States. ALS usually strikes between the ages of 40 and 70 with death occurring within three-to-five years from diagnosis. Death is usually due to respiratory failure because of diminished strength in the skeletal muscles responsible for breathing. ALS affects approximately 400,000 people worldwide, with approximately 30,000 in the United States.

About KPT-350

KPT-350 is Karyopharm's orally active, brain penetrant, anti-inflammatory SINE™ XPO1 antagonist. It is an analog of SINE™ compound selinexor (KPT-330), which is being developed for the treatment of cancer. KPT-350 has been evaluated in preclinical studies in traumatic brain injury (TBI). In animal studies, the gross size of lesions resulting from TBI were dramatically reduced in rats treated with KPT-350. Furthermore, the KPT-350-induced protection at the site of the injury resulted in healthy adjacent tissue with viable neurons, which appears to indicate that KPT-350 exerted a neuroprotective effect to prevent permanent neuronal loss due to the blunt force injury. Karyopharm is evaluating SINE™ compounds, including KPT-350, in additional inflammatory, neuroprotection and autoimmune models including multiple sclerosis, ALS, TBI and systemic lupus erythematosus.

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 SINE™ compounds function by binding with and inhibiting the nuclear export protein XPO1 (or CRM1). In addition to single-agent activity against a variety of different human cancers, SINE™ compounds have also 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, 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 KPT-350 or 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 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 Quarterly Report on Form 10-Q for the quarter ended June 30, 2015, which is on file with the Securities and Exchange Commission (SEC) as of August 10, 2015, and in other filings that Karyopharm may make with the SEC 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.

CONTACT: Justin Renz

(617) 658-0574

jrenz@karyopharm.com

Gina Nugent

(617) 460-3579

nugentcomm@aol.com

Source: Karyopharm Therapeutics

<https://investors.karyopharm.com/2015-09-03-Karyopharm-Advancing-Neuroprotective-SINE-TM-Compounds-in-Amyotrophic-Lateral-Sclerosis-ALS>