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NYSCF SUPPORTED RESEARCH IDENTIFIES PROMISING COMPOUND FOR LOU GEHRIG'S DISEASE THROUGH STEM CELL SCREENING PLATFORM

A new use for stem cells identifies a promising drug target for ALS

NEW YORK, NY (April 18, 2013) – The New York Stem Cell Foundation (NYSCF) was a principal supporter of a new study published today in *Cell Stem Cell* that employed a novel stem cell-based screening method to identify a promising chemical compound for Lou Gehrig's disease, or amyotrophic lateral sclerosis (ALS). NYSCF Scientific Advisor and Medical Advisory Board Member Lee Rubin, PhD, Harvard Stem Cell Institute (HSCI) Principal Faculty member, led this study.

Using a new stem cell-based drug screening technology with the potential to reinvent and greatly reduce the cost of the way new pharmaceuticals are developed, Rubin's team has found a compound more effective in protecting human stem cell-derived neurons killed in ALS than two drugs that failed in human clinical trials after hundreds of millions of dollars had been invested in them.

The new stem cell screening technique developed by Rubin successfully predicted that the two drugs that eventually failed in the third and final stage of human testing would, in fact, fail.

"It's a deep, dark secret of drug discovery that very few drugs have been tested on human-diseased cells before being tested in a live person," said Rubin, who heads HSCI's program in translational medicine. "We were interested in the notion that we can use stem cells to correct that situation."

Rubin's model is built on an earlier proof-of-concept developed by NYSCF Senior Scientific Advisor and HSCI Principal Faculty member Kevin Eggan, PhD, who demonstrated in a NYSCF-supported study that it was possible to move a neuron-based disease into a laboratory dish using stem cells carrying the genes of patients with the disease.

"Not only does this study offer hope to patients, it validates this stem cell-based screening method to find better drugs," said Susan L. Solomon, CEO of NYSCF. "We are not mice, so why should we develop drugs on mice? Stem cell screening carries the game-changing potential to accelerate treatments."

In a paper published today in the journal *Cell Stem Cell*, Rubin lays out how he and his colleagues applied their new method of stem cell-based drug discovery to ALS. The disease is associated with the progressive death of motor neurons, which pass information between the brain and the muscles. As cells die, people with ALS experience weakness in their limbs followed by rapid paralysis and respiratory failure. The disease typically strikes later in life. Ten percent of cases are genetically predisposed, but for most patients there is no known trigger.

Rubin's lab began by first studying the disease in mice, growing billions of motor neurons from mouse embryonic stem cells, half normal and half with a genetic mutation known to cause ALS. Investigators starved the cells of nutrients and then screened five thousand drug-like molecules to find any that would keep the motor neurons alive.

Several hits were identified, but the molecule that best prolonged the life of both normal and ALS motor neurons was kenpaullone, previously known for blocking the action of an enzyme (GSK-3) that switches on and off several cellular processes, including cell growth and death. "Shockingly, this molecule keeps cells alive better than the standard culture medium that everybody keeps motor neurons in," Rubin said.

Kenpaullone proved effective in several follow-up experiments that put mouse motor neurons in situations of certain death. Neuron survival increased in the presence of the molecule whether the cells were programmed to die or placed in a toxic environment.

After further investigation, Rubin's lab discovered kenpaullone's potency comes from its ability to also inhibit HGK – an enzyme that sets off a chain of reactions that leads to motor neuron death. This enzyme was not previously known to be important in motor neurons or associated with ALS, marking the discovery of a new drug target for the disease.

"I think that stem cell screens will discover new compounds that have never been discovered before by other methods," Rubin said. "I'm excited to think that someday one of them might actually be good enough to go into the clinic."

To find out if kenpaullone works in diseased human cells, Rubin's lab exposed patient motor neurons and motor neurons grown from human embryonic stem cells to the molecule, as well as two drugs that did well in mice but failed in phase III human clinical trials for ALS. Once again, kenpaullone increased the rate of neuron survival, while one drug saw little response, and the other drug failed to keep any cells alive.

According to Rubin, before kenpaullone could be used as a drug, it would need a substantial molecular makeover to make it better able to target cells and find its way into the spinal cord so it can access motor neurons.

"This is kind of a proof of principle on the do-ability of the whole thing," he said. "I think it's possible to use this method to discover new drug targets and to prevalidate compounds on real human disease cells before putting them in the clinic."

In the meantime, Rubin's next steps will be to continue searching for better drug-like compounds that can inhibit HGK and thus enhance motor neuron survival. He believes that

the new information that comes out of this research will be useful to academia and the pharmaceutical industry.

By capitalizing on The NYSCF Global Stem Cell Array, a fully robotic automated platform that generates thousands of induced pluripotent stem (iPS) cell lines from patients' skin samples, researchers will be able to test additional chemical compounds on a diverse group of ALS patients with both familial and sporadic forms of this disease. With a large sampling of patient-derived iPS lines, this stem cell-screening method could be valuable for disease investigations.

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About the New York Stem Cell Foundation (NYSCF)
The New York Stem Cell Foundation (NYSCF) combines private philanthropy, the flexibility of a non-profit organization, and an entrepreneurial drive to enable the unrestricted pursuit of research that will accelerate development of stem cell-based treatments and cures for patients with unmet medical needs.

The Foundation has created a new model of translational research that breaks down the barriers that slow discovery and replaces silos with collaboration. The Foundation conducts research in its laboratory in New York City and supports research by stem cell scientists at other leading institutions around the world. More information is available at www.nyscf.org.