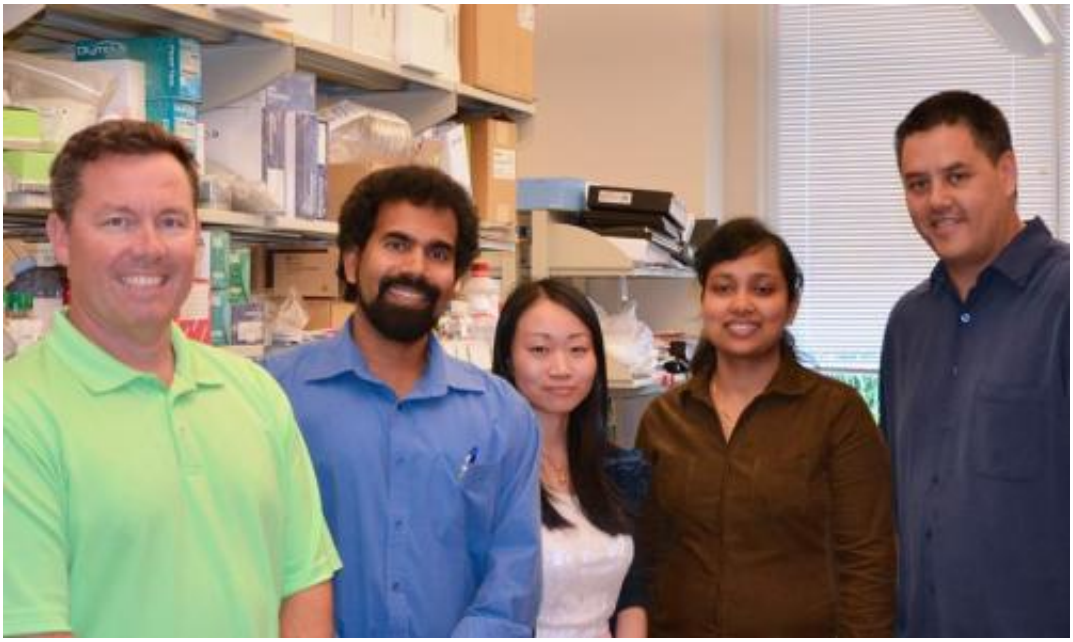
Scientists unveil new targets, test to develop treatments for memory disorder

November 12 2014



The Scripps Florida team that carried out the two studies includes (left to right) Tim Spicer, Sathya Puthanveettil, Xin-An Liu, Beena Kadakkuzha and Bruce Pascal. Credit: Photo by Trina Miles, courtesy of The Scripps Research Institute.

In a pair of related studies, scientists from the Florida campus of The Scripps Research Institute (TSRI) have identified a number of new therapeutic targets for memory disorders and have developed a new screening test to uncover compounds that may one day work against those disorders.

The two studies, one published in the journal *Proceedings of the National Academy of Sciences* (*PNAS*), the other in the journal *ASSAY and Drug Development Technologies*, could lead new approaches to some of the most problematic diseases facing a rapidly aging world population, including Alzheimer's and Huntington's diseases and dementia.

"We are actively looking at molecules critical to memory formation, so these two studies work in parallel," said Sathyanarayanan V. Puthanveettil, a TSRI biologist who led both studies. "In one study, we're reaching for a basic understanding of the process, and in the other, we're finding new ways to identify drug candidates so that we can cure these diseases."

Unlocking the 'Synaptic Proteome'

The *PNAS* study is one of the first detailed descriptions of the proteins that are transported to the synapses, which as a group are called the "synaptic proteome." Synapses are the part of a nerve cell (neuron) that passes electrochemical signals to other cells during functions such as memory storage. This new approach has the potential to advance our understanding of how synapses work, how their composition changes with learning and how brain diseases might affect them.

"We know these molecules function in the synapse, and if we can regulate their function there may be some very good therapeutic opportunities there," Puthanveettil said.

The study focuses on kinesin, a molecular motor protein that plays a role in the transport of other proteins throughout a cell.

Analyzing three kinesin complexes, the researchers found that approximately 40 to 50 percent of the protein cargos were synaptic proteins—and that the identity and location of these kinesins determine

which proteins they transport. These results reveal a previously underappreciated role of kinesins in regulating the composition of the entire synaptic proteome.

Interestingly, a bioinformatics analysis revealed the three kinesin cargo complexes examined in the study are involved in neurologic diseases. Approximately 60 cargos (out of 155) of the kinesin Kif5C are implicated in psychiatric disorders, while around 20 cargos of another kinesin Kif3A are implicated in developmental disorders.

"This shows for the first time how kinesins expressed in the same neurons can carry substantially different cargos," said Research Associate Xin-An Liu, the first author of the study. "We can use this approach to identify what molecules may be targeted for memory and in major disorders. The next step is to find how the synaptic proteome changes in neuropsychiatric diseases."

Toward New Drug Candidates

In the *ASSAY* study, Puthanveettil and his colleagues describe their new high-throughput screening test for discovering potential drug candidates based on kinesin and axonal transport for the treatment of memory disorders.

"The luminescence-based assay that we developed is highly reproducible and robust," said Puthanveetil.

Using the approach, the team screened a compound collection and identified a number of small molecules that turned on or off activity of a human kinesin.

More information: *PNAS*, "New Approach to Capture and Characterize Synaptic Proteome," include Beena Kadakkuzha, Bruce

Pascal, Caitlin Steckler, Komolitdin Akhmedov and Michael Chalmers, www.pnas.org/content/early/201 … /1401483111.abstract

ASSAY, "High-Throughput Screening for Small Molecule Modulators of Motor Protein Kinesin," include Timothy Spicer, Peter Chase, Jeffery B. Richman and Peter Hodder, online.liebertpub.com/doi/abs/10.1089/adt.2014.579

Provided by The Scripps Research Institute