MedicalXpress

New compounds could offer therapy for multitude of diseases

March 30 2015, by Anne Johnson

An international team of more than 18 research groups has demonstrated that the compounds they developed can safely prevent harmful protein aggregation in preliminary tests using animals. The findings raise hope that a new class of drugs may be on the horizon for the more than 30 diseases and conditions that involve protein aggregation, including diabetes, cancer, spinal cord injury, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS).

Proteins are necessary for almost every cellular process. However, when cell machinery doesn't clear out old proteins, they can clump, or aggregate, into toxic plaques that lead to disease.

"Diseases caused by protein aggregation affect millions of people around the world," said Gal Bitan, Ph.D., associate professor of neurology at the David Geffen School of Medicine at the University of California – Los Angeles, who will present the team's latest work at the American Society for Biochemistry and Molecular Biology (ASBMB) Annual Meeting during Experimental Biology 2015. "We hope that the new compounds will provide therapy for diseases caused by protein aggregation, many of which have no treatment at all."

The researchers call the compounds that they developed molecular tweezers because of the way they wrap around the lysine amino acid chains that make up most proteins. The compounds are unique in their ability to attack only aggregated proteins, leaving healthy proteins alone.

To develop a new drug, researchers typically screen large libraries of compounds to find ones that affect a protein involved in a disease. Bitan's team used a fundamentally different approach to develop the molecular tweezers.

"We looked at the molecular and atomic interactions of proteins to understand what leads to their abnormal clumping," Bitan said. "Then, we developed a tailored solution. So unlike many other drugs, we understand how and why our drug works."

The team is in the process of testing multiple versions of the tweezers, each with a slightly different molecular makeup. For CLR01, one of the most promising versions, the researchers have demonstrated therapeutic benefits in two rodent models of Alzheimer's disease, two fish and one mouse model of Parkinson's disease, a fish model of spinal cord injury and a mouse model of familial amyloidotic polyneuropathy, a rare disease in which protein aggregation affects the nervous system, heart and kidneys.

"Our data suggest that CLR01, or a derivative thereof, may become a drug for a number of diseases that involve protein aggregation," Bitan said. "We also found a high safety window for CLR01."

In one of the safety tests, mice receiving a daily CLR01 dose 250 times higher than the therapeutic dose for one month showed no behavioral or physiological signs of distress or damage. In fact, blood cholesterol in the mice dropped by 40 percent, a possible positive side effect of CLR01.

The researchers continue to study CLR01 in animal models of various diseases and are working to secure funding for more animal studies. The researchers are also making improvements that would allow CLR01 to be administered in a pill or capsule rather than requiring an injection.

During his presentation, Bitan will also discuss the evolutionary basis for protein aggregation.

Provided by Federation of American Societies for Experimental Biology