Purdue-designed molecule one step closer to possible Alzheimer's treatment

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(Medical Xpress)—A new molecule designed to treat Alzheimer's disease has significant promise and is potentially the safest to date, according to researchers.

Purdue University professor Arun Ghosh designed the molecule, which is a highly potent beta-secretase inhibitor with unique features that ensure it goes only to its target and does not affect healthy physiological processes, he said.

"This molecule maintains the disease-fighting properties of earlier beta-secretase inhibitors, but is much less likely to cause harmful side effects," said Ghosh, the Ian P. Rothwell Distinguished Professor of Chemistry and Medicinal Chemistry and Molecular Pharmacology. "The selectivity we achieved is unprecedented, which gives it great promise for the long-term medication required to treat Alzheimer's. Each time a treatment misses its disease target and instead interacts with a healthy cell or molecule, damage is done that we call toxicity. Even low levels of this toxicity could build up over years and years of treatment, and an Alzheimer's patient would need to be treated for the rest of his or her life."

The new molecule shows a 7,000-fold selectivity for its target enzyme, which far surpasses the benchmark of a 1,000-fold selectivity for a viable treatment molecule, and dwarfs the selectivity values in the hundreds for past beta-secretase inhibitors, he said. A paper detailing the work will be published in an upcoming Alzheimer's research issue of the

Journal of Medicinal Chemistry and is currently available online. The National Institutes of Health funded the research.

Beta-secretase inhibitors, which could allow for intervention in the early stages of Alzheimer's disease, have promise as a potential treatment. Several drugs based on this molecular target have made it to clinical trials, including one based on a molecule Ghosh designed previously. These molecules prevent the first step in a chain of events that leads to the formation of amyloid plaque in the brain, fibrous clumps of toxic proteins that are believed to cause the disease's devastating symptoms.

The National Institute on Aging estimates that 5.1 million Americans suffer from Alzheimer's disease, which leads to dementia by affecting parts of the brain that control thought, memory and language.

"Alzheimer's is a progressive disease that destroys the brain and also destroys the quality of life for those who suffer from it," Ghosh said. "It eventually robs people of their ability to recognize their own spouse or child and to complete basic tasks necessary for independence, like getting dressed. It is a truly devastating disease for those who suffer from it and for their friends and loved ones."

Earlier versions of the beta-secretase inhibitor were able to stop and even reverse the progression of amyloid plaques in tests on mice, but potency and selectivity are only two of the three pillars of a viable Alzheimer's treatment, Ghosh said. It has yet to be shown whether this molecule possesses the third pillar, the ability to be turned into an easily administered drug that passes through the blood-brain barrier.

Ghosh collaborates with Jordan Tang, the J.G. Puterbaugh Chair in Medical Research at the Oklahoma Medical Research Foundation, who in 2000 identified beta-secretase and its role in the progression of Alzheimer's. Later that year Ghosh designed his first molecule that

bound to and inhibited the activity of the enzyme. He has strived to create the needed improvements ever since.

Ghosh bypasses the usual lengthy process of trial and error in finding useful inhibitor molecules by using a structure-based design strategy. He uses the structures of the inhibitor bound to the enzyme as a guide to what molecular features are important for desirable and undesirable characteristics. Then he removes, replaces and adds molecular groups to amplify the desirable and eliminate the undesirable.

"I believe structure-based design is vital to the development of new and improved medicine," said Ghosh, who also is a member of the Purdue University Center for Cancer Research. "These strategies have the potential to eliminate enormous costs and time needed in traditional random screening protocols for drug development. Structure-based strategies allow us to design molecules that do precisely what we need them to do with fewer undesirable side effects."

Tang performed the X-ray crystallography and captured the crystal structures to reveal important insights and serve as a guide for Ghosh's designs.

"Developing inhibitors into clinically useful drugs is an evolutionary process," Tang said. "We learn what works and what doesn't along the way, and the knowledge permits us to do better in the next step. The miracles of modern medicine are built on top of excellent scientific findings. We try to do good science and know that the consequence will be a better chance for conquering diseases and improving lives."

Beta-secretase belongs to a class of enzymes called aspartyl proteases. Research into beta-secretase inhibitors faced setbacks when other aspartyl proteases similar in structure, called memapsin 1 and cathepsin D, were discovered and found to be involved in many important

physiological processes. Earlier designed beta-secretase inhibitors were found also to work against the biologically necessary enzymes.

Ghosh's team focused on developing ways to make the inhibitor more selective so that it would avoid these other, physiologically important enzymes. They compared the structures of beta-secretase and memapsin 1 as they interacted with the inhibitor to find an active area unique only to beta-secretase. Then they added a functional molecular feature that targets and interacts with the unique area, making the inhibitor more attractive to beta-secretase and less attractive to the other enzymes.

"The added feature serves as a bait on the inhibitor molecule that entices beta-secretase and also grabs onto it tightly, greatly enhancing its selectivity," he said. "This is a fundamental insight into the origins of selectivity and ways to increase it."

Ghosh said this work highlights an important purpose of academic research.

"Academic research lays out and shares the fundamentals to advance drug discovery," he said. "Advances in treatment are built upon the basic research happening at universities."

More information: Structure-Based Design of Highly Selective ß-Secretase Inhibitors: Synthesis, Biological Evaluation, and Protein-Ligand X-ray Crystal Structure, Arun K. Ghosh, Kalapala Venkatewswara Rao, Navnath D. Yadav, David D. Anderson, Navnath Gavande, Xiangping Huang, Simon Terzyan, and Jordan Tang, *Journal of Medicinal Chemistry*, 2012.

ABSTRACT
The structure-based design, synthesis, and X-ray structure of protein-ligand complexes of exceptionally potent and selective ß-secretase

inhibitors are described. The inhibitors are designed specifically to interact with S1 active site residues to provide selectivity over memapsin 1 and cathepsin D. Inhibitor 5 has exhibited exceedingly potent inhibitory activity (Ki= 17 pM) and high selectivity over BACE 2 (>7000-fold) and cathepsin D (>250000-fold). A protein-ligand crystal structure revealed important molecular insight into these selectivities. These interactions may serve as an important guide to design selectivity over the physiologically important aspartic acid proteases.

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