Hybrid molecules show promise for exploring, treating Alzheimer's

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One of the many mysteries of Alzheimer's disease is how protein-like snippets called amyloid-beta peptides, which clump together to form plaques in the brain, may cause cell death, leading to the disease's devastating symptoms of memory loss and other mental difficulties.

In order to answer that key question and develop new approaches to preventing the damage, scientists must first understand how amyloid-beta forms the telltale clumps.

University of Michigan researchers have developed new molecular tools that can be used to investigate the process. The molecules also hold promise in Alzheimer's disease treatment. The research, led by assistant professor Mi Hee Lim, was published online this week in the *Journal of the American Chemical Society*.

Though the exact mechanism for amyloid-beta clump formation isn't known, scientists do know that copper and zinc ions are somehow involved, not only in the aggregation process, but apparently also in the resulting injury. Copper, in particular, has been implicated in generating reactive oxygen species, which can cause cell damage.

One way of studying the role of metals in the process is by sopping up the metal ions with molecules called chelators and then seeing what happens when the metal ions are out of the picture. When other scientists have done this they've found that chelators, by removing metals, hamper both amyloid beta clumping and the production of those

harmful reactive oxygen species, suggesting that chelators could be useful in treating Alzheimer's disease.

However, most known chelators can't cross the blood-brain barrier, the barricade of cells that separates brain tissue from circulating blood, protecting the brain from harmful substances in the bloodstream. What's more, most chelators aren't precise enough to target only the metal ions in amyloid-beta; they're just as likely to grab and disable metals performing vital roles in other biological systems.

Lim and coworkers used a new strategy to develop "bi-functional" small molecules that not only grab metal ions, but also interact with amyloid-beta.

"The idea is simple," said Lim, who has joint appointments in the Department of Chemistry and the Life Sciences Institute. "We found molecules known for amyloid-beta recognition and then attached metal binding sites to them." In collaboration with Ayyalusamy Ramamoorthy, professor of chemistry and associate professor of biophysics, Lim then used NMR spectroscopy to confirm that the new, hybrid molecules still interacted with amyloid-beta.

In experiments in solutions with or without living cells, the researchers showed that the bi-functional molecules were able to regulate copper-induced amyloid-beta aggregation, not only disrupting the formation of clumps, but also breaking up clumps that already had formed. In fact, their molecules performed better than clioquinol, a clinically-available metal chelator that showed promise in early trials with Alzheimer's patients, but has side effects that limit its long-term use.

"Based on their small size and other properties, we believe our compounds will be able to cross the blood-brain barrier, but we want to confirm that using mouse models," Lim said. The researchers also plan

experiments to see if their new chelators are as good at preventing and breaking up amyloid-beta plaques in the brains of mice as they are in solutions and cultured cells.

More information: Journal of the American Chemical Society--- pubs.acs.org/journal/jacsat

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