

Novel compound is promising drug candidate for Alzheimer's disease

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Selective gamma-secretase inhibitor blocks substrate on amyloid precursor protein. Credit: Rensselaer Polytechnic Institute

A newly identified compound is a promising candidate for inhibiting the production of amyloids, the abnormal proteins that form toxic clumps, called fibrils, inside the brains of patients with Alzheimer's disease. As published today in the Royal Society of Chemistry's *Chemical Communications*, the compound—known as "C1"—uses a novel mechanism to efficiently prevent the enzyme gamma-secretase from producing amyloids.

Amyloid fibrils are largely composed of the peptide Amyloid beta, which is produced when enzymes, including gamma secretase, make cuts to the [amyloid precursor protein](#) found in high concentrations the membrane of brain cells. C1 is a covalent gamma-secretase inhibitor that blocks the active site on the precursor protein where gamma-secretase would bind to transform it into amyloids, rather than—as traditional enzyme inhibitors do—blocking the [active site](#) on gamma-secretase itself.

"Historically, [drug trials](#) for gamma secretase inhibitors failed because traditional enzyme inhibitors have severe side effects. They stopped all of the normal functions of gamma secretase," said Chunyu Wang, a professor of biological sciences and member of the Center for Biotechnology and Interdisciplinary Studies (CBIS) at Rensselaer Polytechnic Institute. "Our compound binds to the cleavage site of the precursor protein instead of the enzyme itself, which may avoid many problems associated with traditional enzyme inhibitors."

In 2018, with support from the Warren Alpert Foundation, Wang began screening drugs to identify a compound that targets the [amyloid](#) precursor protein substrate, which would block the activity of [gamma secretase](#) involved in amyloid production while allowing all other functions. He began the search with "in silico screening," using computer modeling to test tens of millions of compounds.

C1 was one of several candidates to emerge from that screening. As described in the paper, C1 blocks amyloid production with high efficiency when present at micromolar concentrations, both in test tubes and in cell culture. The research is pending.

C1 is a covalent inhibitor, meaning it forms a chemical bond with its target. Wang said that because of their permanent bond, covalent inhibitors are more durable than their non-covalent counterparts. Covalent inhibitors make up about one-third of the drug market, even though they have traditionally been viewed as having a higher risk of causing immune reactivity. In recent years, there is surge in the development of covalent inhibitors, as more highly specific covalent inhibitors showed excellent efficacy towards challenging drug targets.

"With a new approach to tackling the principal

pathology of Alzheimer's disease, Chunyu's work is generating a fresh roster of drug candidates with enormous promise," said Deepak Vashishth, the director of CBIS. "His works speaks to the power of the interdisciplinary culture of research at CBIS, and we are pleased with this early result."

More information: "Substrate Interaction Inhibits gamma-secretase Production of Amyloid-B peptides," *Chemical Communications* (2020).

Provided by Rensselaer Polytechnic Institute

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