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Molecular inhibitor breaks cycle that leads to Alzheimer's

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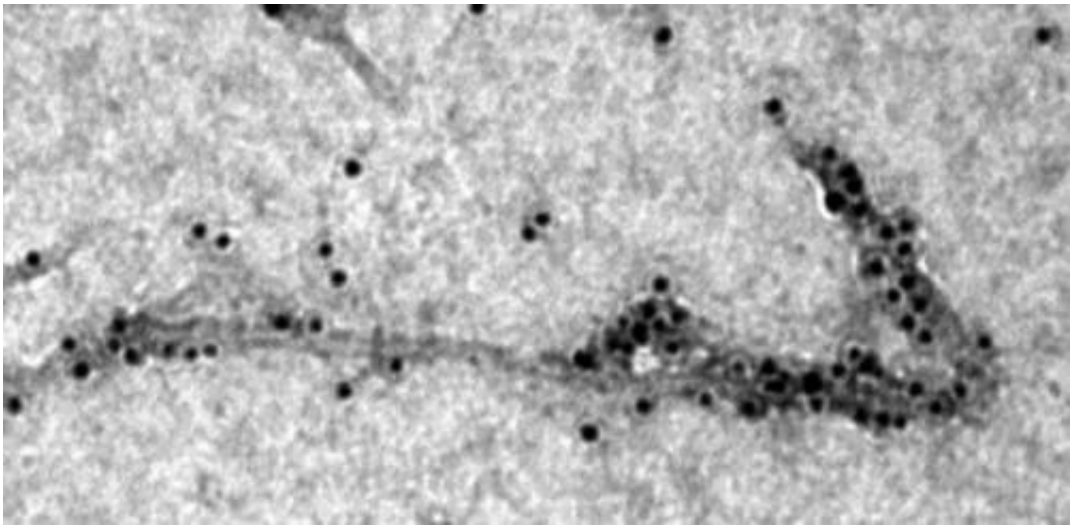

Transmission electron microscopy image showing a molecular chaperone (the black dots) binding to thread-like amyloid-beta (Aβ42). Credit: S. Cohen

A molecular chaperone has been found to inhibit a key stage in the development of Alzheimer's disease and break the toxic chain reaction that leads to the death of brain cells, a new study shows. The research provides an effective basis for searching for candidate molecules that could be used to treat the condition.

A molecule that can block the progress of Alzheimer's disease at a crucial stage in its development has been identified by researchers in a new study, raising the prospect that more such molecules may now be

found.

The report shows that a molecular chaperone, a type of molecule that occurs naturally in humans, can play the role of an "inhibitor" part-way through the molecular process that is thought to cause Alzheimer's, breaking the cycle of events that scientists believe leads to the disease.

Specifically, the molecule, called Brichos, sticks to threads made up of malfunctioning proteins, called amyloid fibrils, which are the hallmark of the disease. By doing so, it stops these threads from coming into contact with other proteins, thereby helping to avoid the formation of highly toxic clusters that enable the condition to proliferate in the brain.

This step – where fibrils made up of malfunctioning proteins assist in the formation of toxic clusters – is considered to be one of the most critical stages in the development of Alzheimer's in sufferers. By finding a molecule that prevents it from occurring, scientists have moved closer to identifying a substance that could eventually be used to treat the disease. The discovery was made possible by an overall strategy that could now be applied to find other molecules with similar capabilities, extending the range of options for future drug development.

The research was carried out by an international team comprising academics from the Department of Chemistry at the University of Cambridge, the Karolinska Institute in Stockholm, Lund University, the Swedish University of Agricultural Sciences, and Tallinn University. Their findings are reported in the journal *Nature Structural & Molecular Biology*.

Dr Samuel Cohen, a Research Fellow at St John's College, Cambridge, and a lead author of the report, said: "A great deal of work in this field has gone into understanding which microscopic processes are important in the development of Alzheimer's disease; now we are now starting to

reap the rewards of this hard work. Our study shows, for the first time, one of these critical processes being specifically inhibited, and reveals that by doing so we can prevent the toxic effects of protein aggregation that are associated with this terrible condition."

Alzheimer's disease is one of a number of conditions caused by naturally occurring protein molecules folding into the wrong shape and then sticking together – or nucleating – with other proteins to create thin filamentous structures called amyloid fibrils. Proteins perform important functions in the body by folding into a particular shape, but sometimes they can misfold, potentially kick-starting this deadly process.

Recent research, much of it by the academics behind the latest study, has however suggested a second critical step in the disease's development. After amyloid fibrils first form from misfolded proteins, they help other proteins which come into contact with them to misfold and form small clusters, called oligomers. These oligomers are highly toxic to nerve cells and are now thought to be responsible for the devastating effects of Alzheimer's disease.

This second stage, known as secondary nucleation, sets off a chain reaction which creates many more toxic oligomers, and ultimately amyloid fibrils, generating the toxic effects that eventually manifest themselves as Alzheimer's. Without the secondary nucleation process, single molecules would have to misfold and form toxic clusters unaided, which is a much slower and far less devastating process.

By studying the molecular processes by which each of these steps takes effect, the research team assembled a wealth of data that enabled them to model not only what happens during the progression of Alzheimer's disease, but also what might happen if one stage in the process was somehow switched off.

"We had reached a stage where we knew what the data should look like if we inhibited any given step in the process, including secondary nucleation," Cohen said. "Working closely with our collaborators in Sweden - who had developed groundbreaking experimental methods to monitor the process - we were able to identify a molecule that produced exactly the results that we were hoping to see in experiments."

The results indicated that the molecule, Brichos, effectively inhibits secondary nucleation. Typically, Brichos functions as a "molecular chaperone" in humans; a term given to "housekeeping" molecules that help proteins to avoid misfolding and aggregation. Lab tests, however, revealed that when this molecular chaperone encounters an amyloid fibril, it binds itself to catalytic sites on its surface. This essentially forms a coating that prevents the fibrils from assisting other proteins in misfolding and nucleating into toxic oligomers.

The research team then carried out further tests in which living mouse brain tissue was exposed to amyloid-beta, the specific protein that forms the amyloid fibrils in Alzheimer's disease. Allowing the amyloid-beta to misfold and form amyloids increased toxicity in the tissue significantly. When this happened in the presence of the molecular chaperone, however, amyloid fibrils still formed but the toxicity did not develop in the brain tissue, confirming that the molecule had suppressed the chain reaction from secondary nucleation that feeds the catastrophic production of oligomers leading to Alzheimer's disease.

By modelling what might happen if secondary nucleation is switched off and then finding a molecule that performs that function, the research team suggest that they have discovered a strategy that may lead to the identification of other molecules that could have a similar effect.

"It may not actually be too difficult to find other molecules that do this, it's just that it hasn't been clear what to look for until recently," Cohen

said. "It's striking that nature – through molecular chaperones – has evolved a similar approach to our own by focusing on very specifically inhibiting the key steps leading to Alzheimer's. A good tactic now is to search for other molecules that have this same highly targeted effect and to see if these can be used as the starting point for developing a future therapy."

More information: "A molecular chaperone breaks the catalytic cycle that generates toxic Aβ oligomers" *Nature Structural & Molecular Biology* (2015) DOI: 10.1038/nsmb.2971

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