Advancing the search for antibodies to treat Alzheimer's disease

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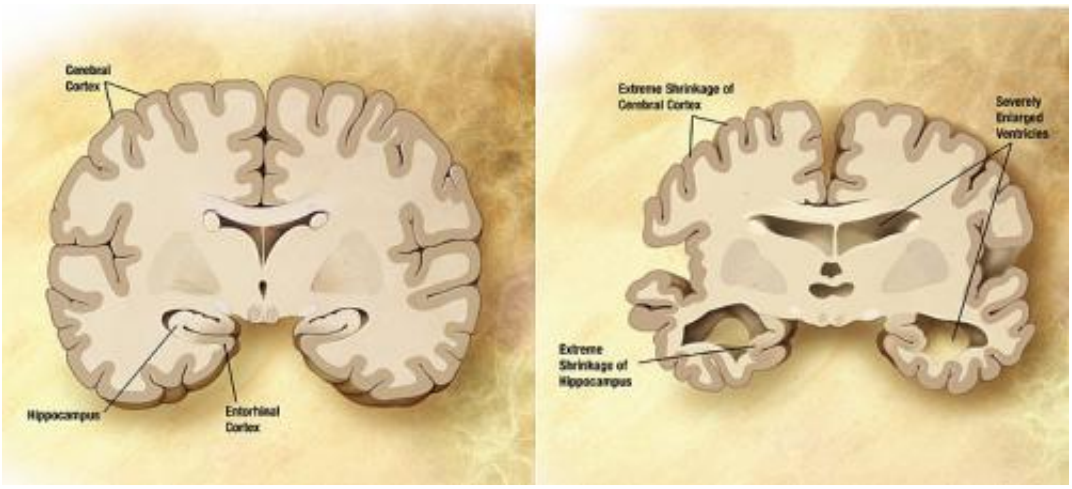

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

Two new studies published by investigators from Brigham and Women's Hospital illustrate that not all forms of amyloid-beta (Aβ) protein—the protein thought to initiate Alzheimer's disease—play an equally menacing role in the progress of the disease. Using a new way of preparing and extracting the protein as well as a new technique to search for promising drug candidates, researchers have highlighted the importance of testing and targeting different forms of Aβ. Their work may help advance the search for more precise and effective drugs to prevent or halt the progress of Alzheimer's disease.

"Many different efforts are currently underway to find treatments for Alzheimer's disease, and anti-Aβ antibodies are currently the furthest advanced. But the question remains: what are the most important forms of Aβ to target? Our study points to some interesting answers," said Dominic Walsh, Ph.D., a principal investigator in the Ann Romney Center.

Aβ protein can take forms ranging from monomers—single molecules—to twisted tangles of plaques that can pollute the brain and are large enough that they can be seen with a traditional microscope. Walsh compares monomers to single Lego bricks, which can start sticking together to form complex structures of varying sizes. The two recently published studies investigate how to find new potential therapeutics that can target the structures most likely to cause harm.

Most Alzheimer's disease studies use synthetic Aβ to approximate what conditions in the brain of an Alzheimer's patient might be like. A small number of researchers have used Aβ extracted from human brain, but the extraction process is crude. In a study published in Acta Neuropathologica in April, Walsh and colleagues developed a much gentler extraction protocol to prepare samples from subjects with Alzheimer's disease. The team found that Aβ was far more abundant in traditional crude extracts, but that the bulk of the extracted Aβ was innocuous. In contrast, much less Aβ was obtained with the gentler protocol, but in this case most of the Aβ was toxic.

In a second study published in *Nature Communications* in July, Walsh and colleagues developed a screening test to try to find potential drugs to target the toxic forms of Aβ. The new technique uses extracts of brain samples from Alzheimer's disease patients and live-cell imaging of stem-cell derived brain cells to find promising therapeutics. The team reports on 1C22, an Aβ antibody that they found could protect against toxic forms of amyloid-beta more effectively than the most clinically

advanced Alzheimer's disease therapeutics currently in clinical trials.

"We anticipate that this primary screening technique will be useful in the search to identify more potent anti-Aβ therapeutics in the future," said Walsh.

More information: Ming Jin et al, An in vitro paradigm to assess potential anti-Aβ antibodies for Alzheimer's disease, *Nature Communications* (2018). DOI: 10.1038/s41467-018-05068-w

Provided by Brigham and Women's Hospital

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