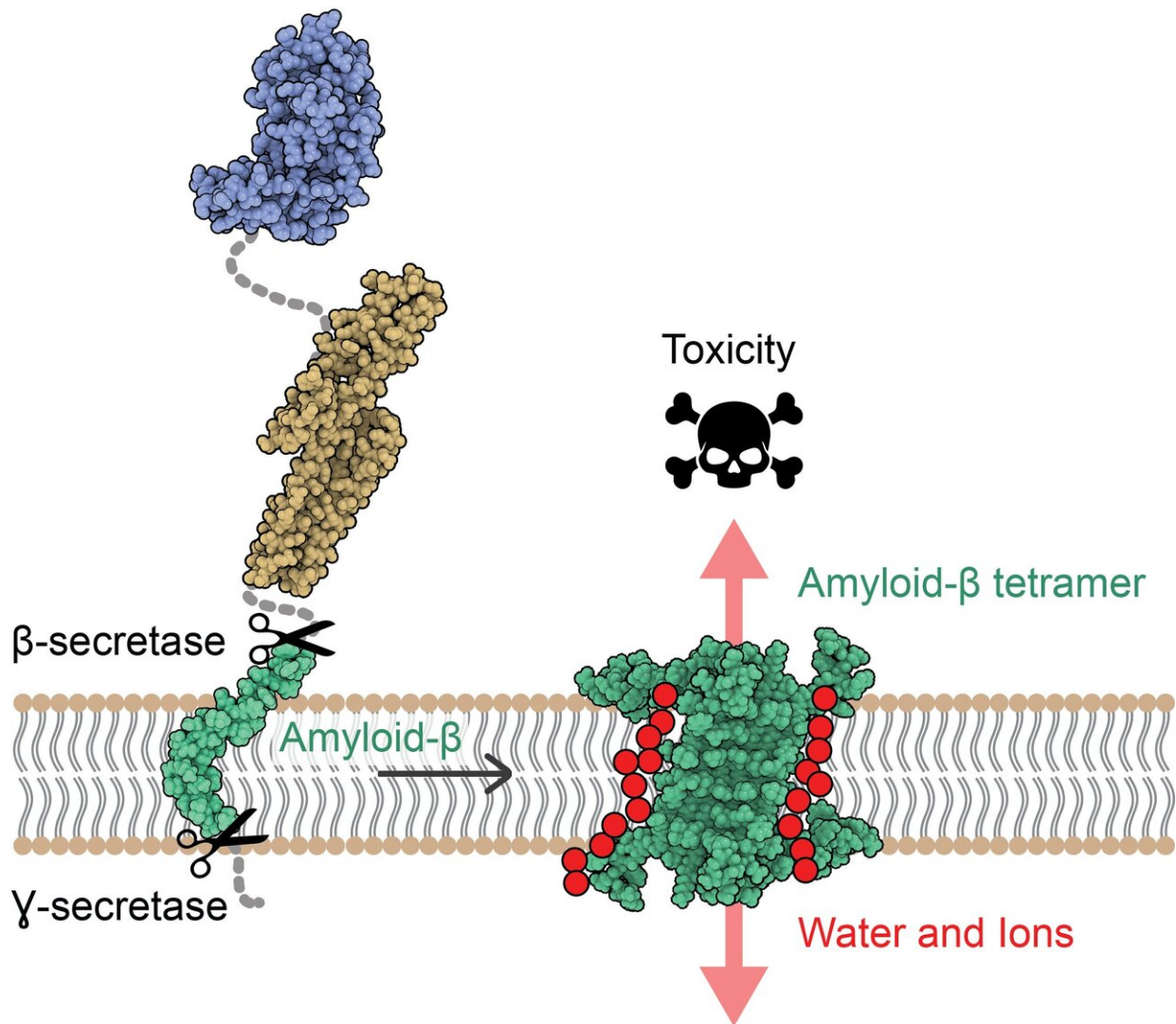


# A new mechanism of toxicity in Alzheimer's disease revealed by the 3-D structure of protein

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Amyloid Precursor Protein (APP)



The amyloid precursor protein (APP) is inserted into the cell membrane of neurons. After sequential cleavage by  $\beta$ - and  $\gamma$ -secretases, the  $A\beta$  protein (in green) is released. The membrane oligomers are formed by 4 or 8 copies of the  $A\beta$  protein. The physicochemical properties of the edges of these oligomers form a path for passage of water and ions (in red) through the membrane, thus disrupting ion cell homeostasis. Credit: Benjamin Bardiaux.

The brains of people suffering from Alzheimer's disease (AD) are slowly and inescapably being depleted of neurons, which leads to the characteristic loss of memory and cognitive function associated with this condition. However, the cause of neuronal death is still unknown. The treatments available are aimed at slowing down the development of dementia and only help to improve quality of life for short periods. Therefore, treatments to cure AD are an unmet medical need.

Researchers led by Natalia Carulla, IRB Barcelona Alumni, former group leader at the Institut Européen de Chimie et Biologie (IECB) in Bordeaux, and currently project manager at Grup CIEF have revealed for the first time the atomic structure of amyloid-beta ( $A\beta$ ) [protein assemblies](#). The knowledge of this structure reveals a new mechanism of toxicity for these assemblies, with the capacity to disrupt the neuronal [membrane](#), allowing water and ions to pass through it and causing the death of these cells. Several studies have proposed that the interaction of the  $A\beta$  [protein](#) with the neuronal membrane is responsible for the neuronal death observed in AD. However, the  $A\beta$  protein is a difficult therapeutic target because it is "sticky" and self-assembles, adopting distinct shapes and sizes.

"Knowing the features that characterize these protein ensembles, such as the number of molecules that make them and the shape they adopt, is crucial to design effective therapeutic strategies that target the forms of

A $\beta$  ensembles responsible for the neurotoxicity in AD," Carulla explains.

## **An in vitro approach to ensure stable A $\beta$ forms**

To tackle the instability of the conformations, the team first studied the A $\beta$  protein in vitro—in simplified model systems that mimic the neuronal membrane—to develop conditions to prepare stable A $\beta$  forms of uniform composition and shape. Once the compositions had been identified, they studied their structure and mode of neurotoxicity, establishing a 3-D arrangement of all the atoms making up the A $\beta$  ensemble.

"Our study suggests that some A $\beta$  associations can perforate the membrane of neurons, alter their osmotic equilibrium, and consequently trigger their death," say Sonia Ciudad and Eduard Puig, first authors of the paper. Ciudad is an IRB Barcelona Alumni, currently R&D scientist at Biokit, a Werfen Company; Puig is now a postdoctoral fellow in the Research Unit on Asymmetric Synthesis at IRB Barcelona.

## **Targeting membrane pores to avoid neurotoxicity**

This study has highlighted two A $\beta$  protein ensembles, one formed by four A $\beta$  proteins and the other by eight, whose arrangement has the capacity to disrupt cell membrane, proposing them as candidates for causing neurodegeneration in AD.

Further work should focus on approaches to prevent the formation of this ensemble, thus preventing membrane disruption. Currently, the drug discovery pipeline in this field does not include any drug targeting membrane-associated A $\beta$  assemblies, so this finding could be a significant breakthrough in the treatment of AD.

**More information:** Sonia Ciudad et al, A $\beta$ (1-42) tetramer and octamer structures reveal edge conductivity pores as a mechanism for membrane damage, *Nature Communications* (2020). [DOI: 10.1038/s41467-020-16566-1](https://doi.org/10.1038/s41467-020-16566-1)

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