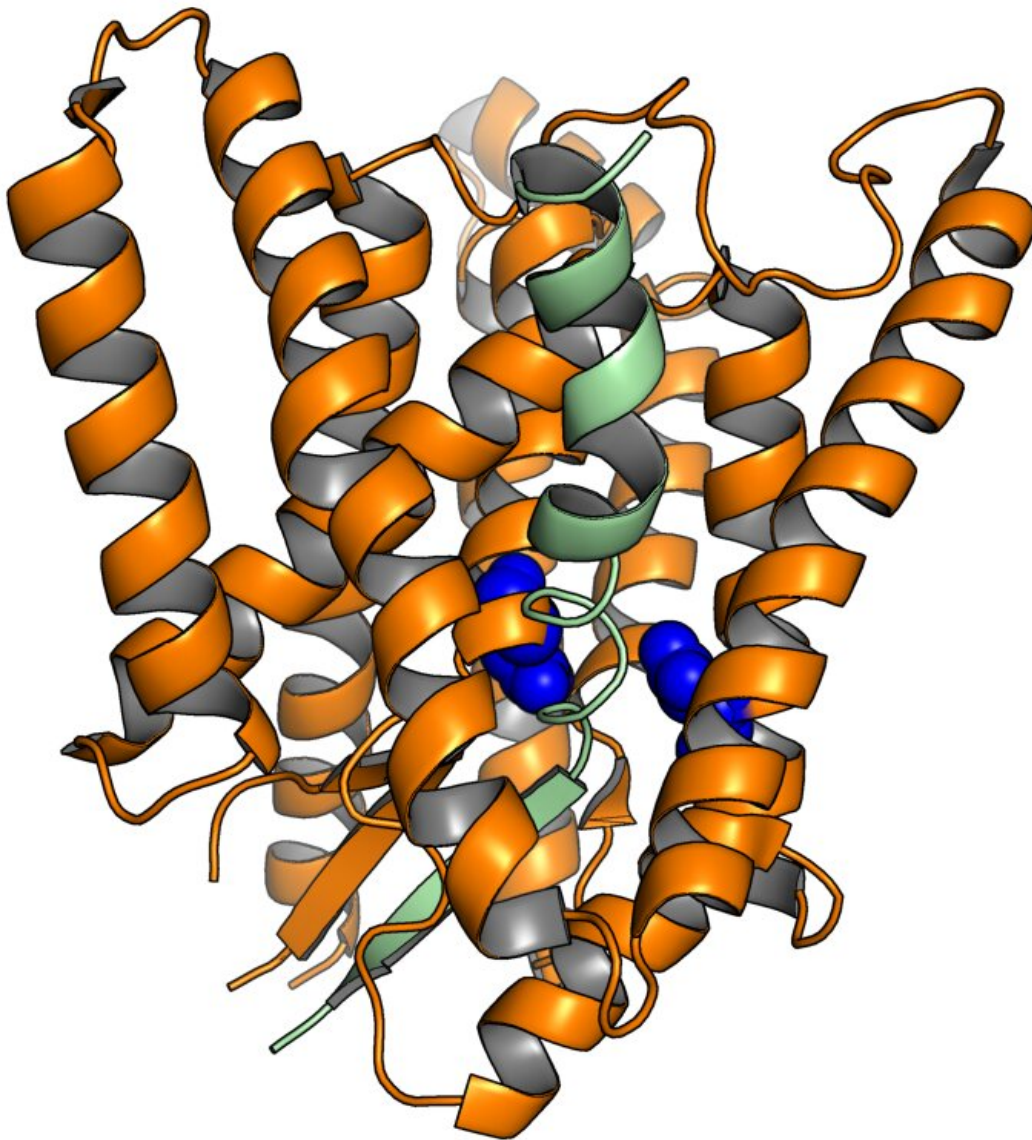


# Alzheimer-linked enzyme complex 'buckles up' for safe trip through the cell

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A research team led by Wim Annaert (VIB-KU Leuven) uncovered the early assembly of gamma-secretase, a protein complex linked to numerous cellular processes including the development of Alzheimer's disease. In a first step, two dimeric subcomplexes are formed, which independently exit the ER and only afterwards assemble into a four-subunit complex. This 'buckle up' mechanism is thought to prevent premature assembly and activity. The new insights are very relevant, as gamma-secretase is an important potential therapeutic target for Alzheimer's and other conditions.

## **An enzyme complex involved in plaque production**

Gamma-secretase is best known as the enzyme that cleaves the [amyloid precursor protein](#), generating a small peptide called amyloid beta, the main constituent of the plaques found in the brains of people affected by Alzheimer's disease. Ever since the discovery of its implication in disease, gamma-secretase has been studied and tested as a potential therapeutic target, but its role in the body is much broader than producing amyloid.

We now know that gamma-secretase is a complex made up of four components, two of which have multiple homologues, resulting in variety of complexes with distinct subcellular distributions, providing a basis for substrate selectivity. All four gamma-secretase components are transmembrane proteins that are co-translationally inserted into the endoplasmic reticulum (ER). But how these four subunits get assembled in such stable enzyme complexes remained unknown until now.

## Dissecting the assembly line

The Annaert lab at the VIB-KU Leuven Center for Brain & Disease Research is specialized in membrane trafficking and has a long track record of studying the gamma-secretase complex. By combining biochemistry and high-resolution imaging, they have now uncovered the early steps of the gamma-secretase assembly process.

"To dissect the assembly steps, we used a method developed by Randy Schekman of UC Berkeley (who won the Noble Prize in Medicine in 2013), and with whom we collaborated on this endeavor. This approach unveiled that in fact dimers of two out of the four subunits are formed in the ER, in this way preventing the premature breakdown of individual subunits," says Wim Annaert. "These dimers only get fully assembled into gamma-secretase complexes shortly thereafter, between ER-exit and their transition to the Golgi complex."

Only fully assembled complexes are transported through the Golgi onto their final destination in different cellular compartments.

Interestingly, the dimer assembly signature remains visible in the high-resolution structure of gamma-secretase, suggesting a 'buckle up model' for dimer assembly: one side of the dimers act as 'buckles', while the other side functions as the belt through interactions keeping the full complex in place.

"This 'buckle up' mechanism could prevent the untimely processing of substrates," says Annaert. "Given the broad range of substrates and pathways controlled by gamma-secretase -from developmental processes to cancer and Alzheimer, the precise tuning of this assembly process allows for further spatiotemporal regulation of gamma-secretase activity."

The insights are extremely relevant, as problems during complex assembly may also have a significant impact on the many physiological and pathological processes regulated by [gamma-secretase](#).

**More information:** Rosanne Wouters et al, Assembly of  $\gamma$ -secretase occurs through stable dimers after exit from the endoplasmic reticulum, *Journal of Cell Biology* (2021). [DOI: 10.1083/jcb.201911104](https://doi.org/10.1083/jcb.201911104)

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