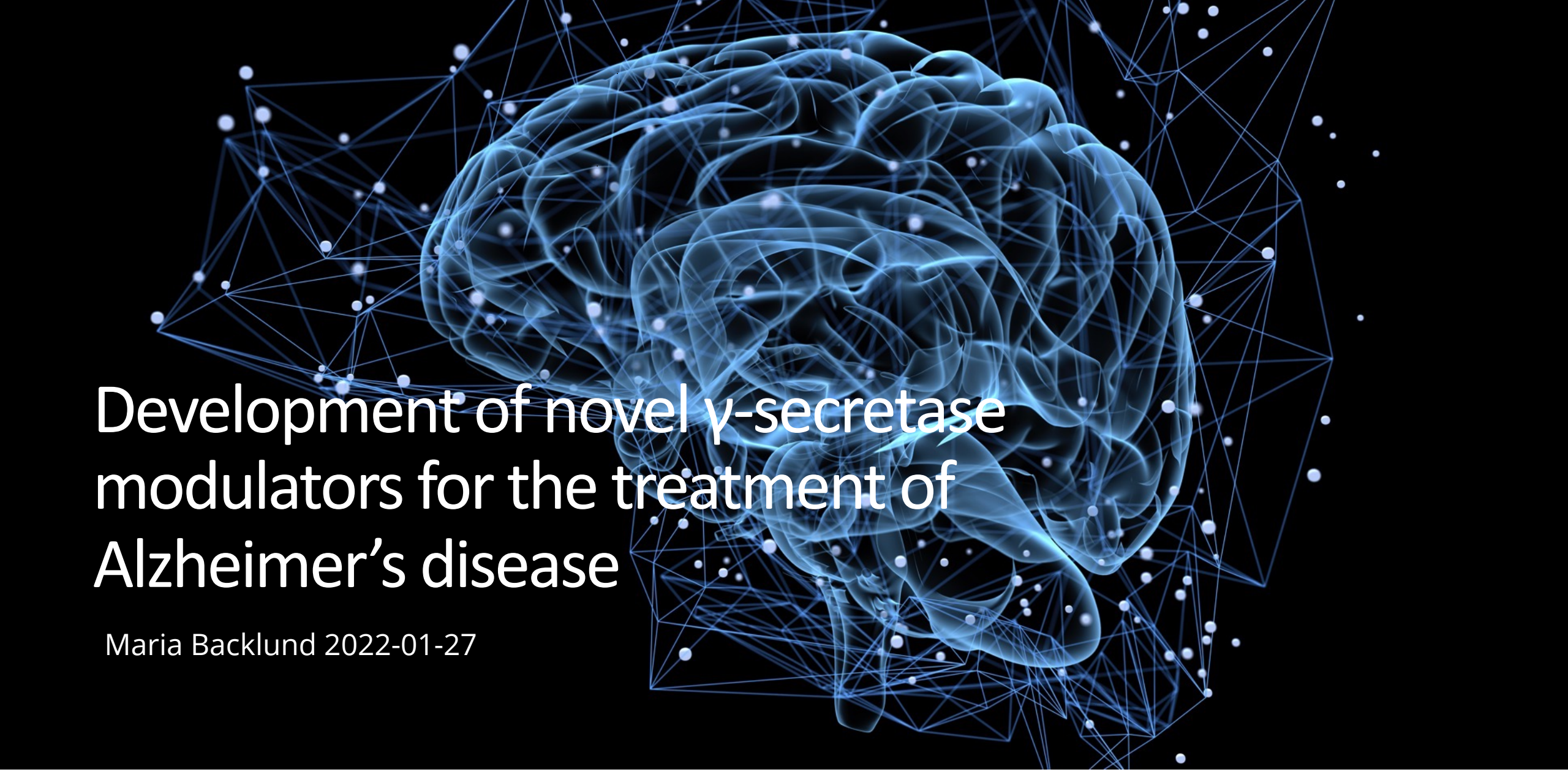


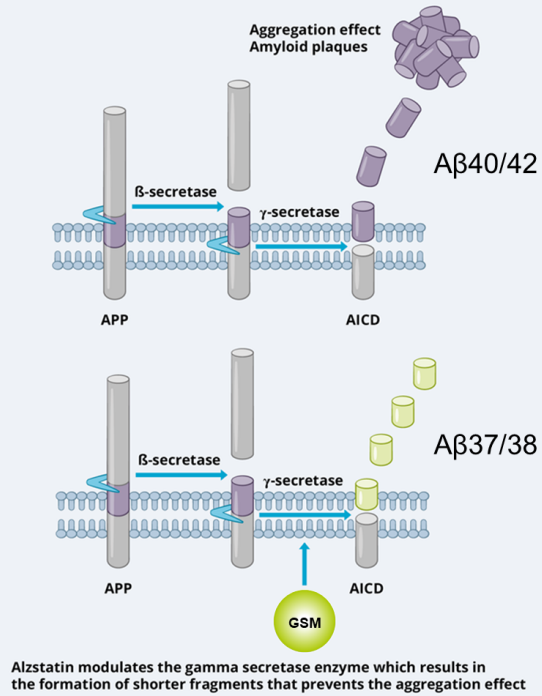
# Development of novel γ-secretase modulators for the treatment of Alzheimer's disease

Maria Backlund 2022-01-27

AlzeCure

# Development of novel γ-secretase modulators for the treatment of Alzheimer's disease

Maria Backlund, Märta Dahlström, Veronica Lidell, Sanja Juric, Magnus M. Halldin, Pontus Forsell, Johan Sandin, and Gunnar Nordvall.




Alzstatin modulates the gamma secretase enzyme which results in the formation of shorter fragments that prevents the aggregation effect

- Aggregation of the Aβ42 peptide results in amyloid plaque formation, a process that plays a pivotal role in early Alzheimer's disease (AD) pathogenesis.
- γ-secretase modulators (GSMs) are a novel class of compounds that alters the cleavage of amyloid precursor protein (APP) to less amyloidogenic peptides.
- GSMs exhibit several key features that make them suitable for the treatment of pre-symptomatic AD.
  - they reduce amyloidogenic Aβ42 production, while stimulating the formation of the shorter, less amyloidogenic peptides Aβ37 and Aβ38.
  - they modulate without affecting the total γ-secretase activity, thus sparing the γ-secretase-mediated processing of other substrates, such as Notch.

In this work, we set out to explore the in vitro and in vivo effect of AC-0027875, a novel potent GSM, on brain Aβ42 reduction in cells and animals as well as to assess its pharmacokinetic properties.

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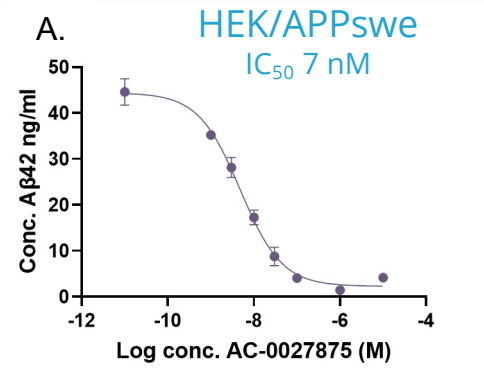
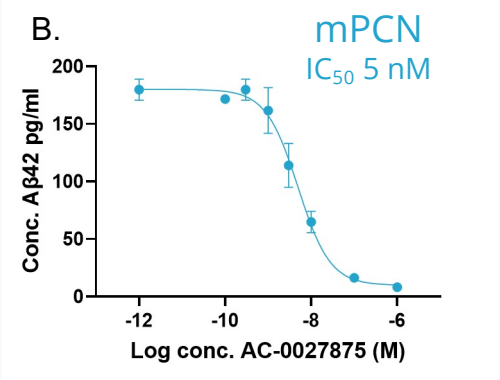
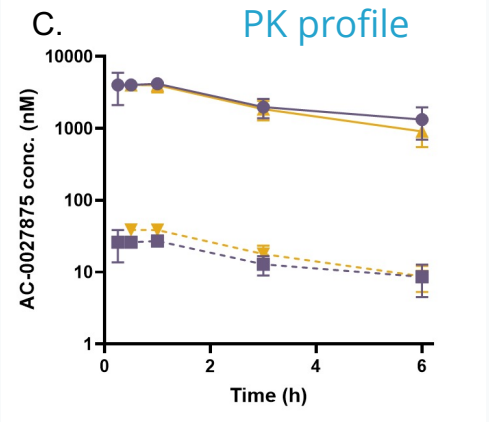
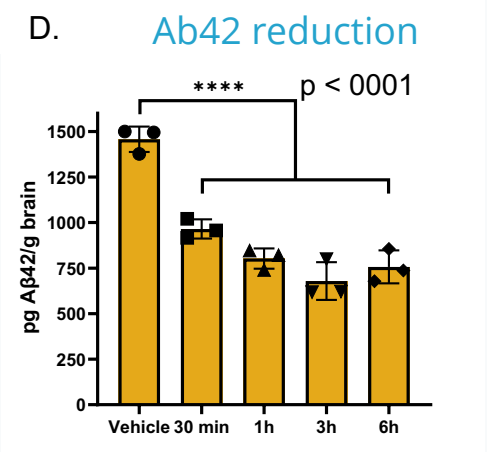



HEK APP/swe cells (A) and mPCN (B) were treated with different concentrations of AC-0027875. The amount of Aβ42 formed were analyzed using ELISA.




C57BL/6J mice were treated with a single oral dose of 60 µmol/kg AC-0027875 and plasma and brain were collected. In (C) the PK profile of AC-0027875 is shown (Mean±SD). Solid and dotted lines are total and free concentration in plasma (purple) and brain tissue (orange), respectively. In (D) brain tissue levels of Aβ42 is shown. The amount of Aβ42 is significantly reduced in all treatment groups as compared to vehicle group (Mean±SD, One-way ANOVA).

- AC-0027875 efficiently reduced Aβ42 production in HEK/APPswe cells and in mouse primary cortical neurons.
- High mouse plasma and brain tissue exposure of AC-0027875 was obtained after oral administration, with the free plasma and brain tissue exposure well above the in vitro IC50´s.
- In line with the high brain tissue exposure, AC-0027875 efficiently lowered Aβ42 in the brain with a rapid onset and a long-lasting effect.

In summary, our data suggest that GSMs such as AC-0027875 are a highly promising anti-amyloidogenic therapy for the treatment of early AD. Additional studies to fully characterize AC-0027875 in vivo are in progress.

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