May 17, 2023

Alzstatin®

A preventive treatment against Alzheimer's

- Background & Evolution

Johan Sandin, PhD, CSO, AlzeCure Pharma

AlzeCure

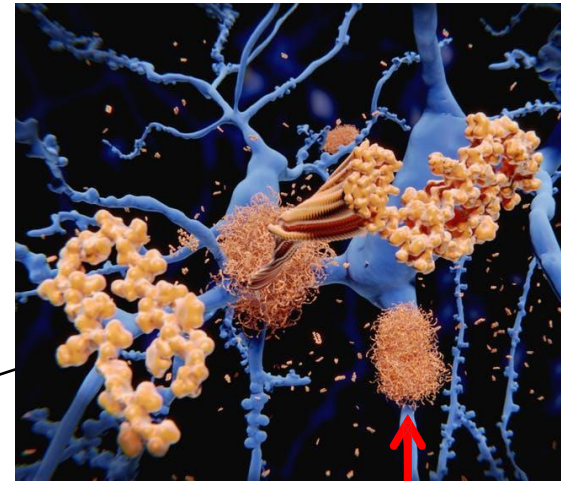# Amyloid plaques – a key hallmark of Alzheimer's

Healthy brain   Alzheimer's brain

Amyloid plaques – a key hallmark of Alzheimer's

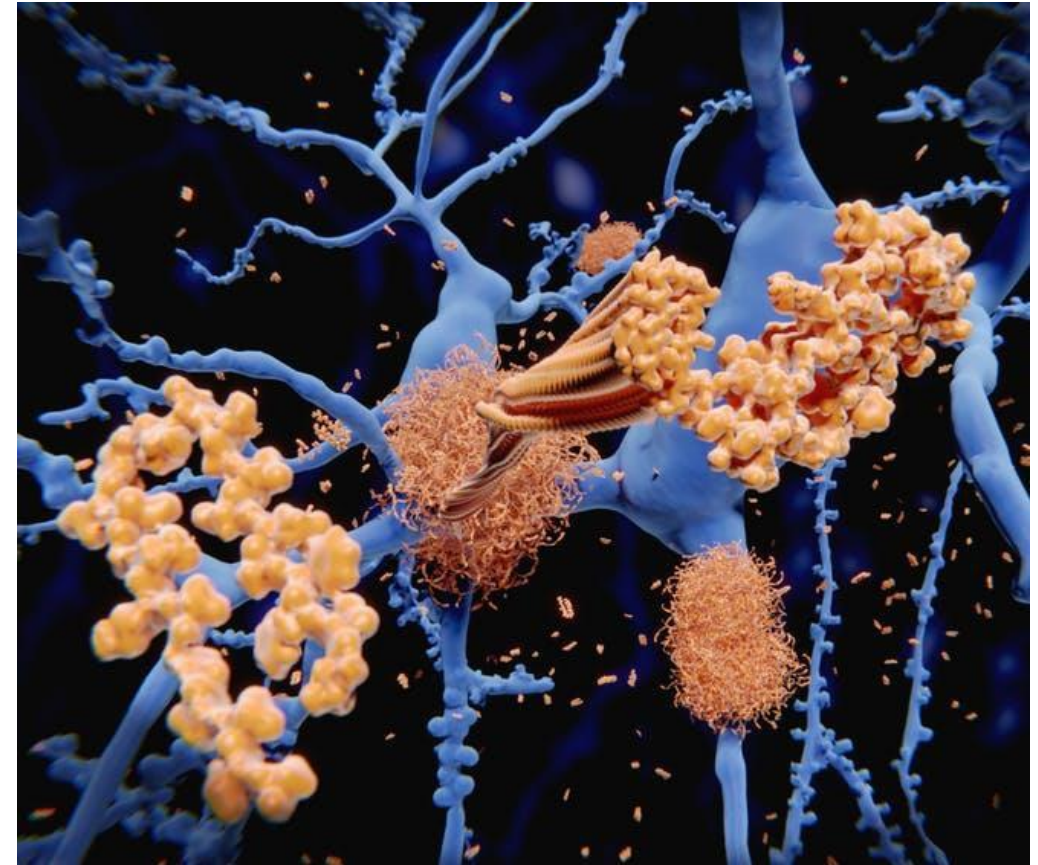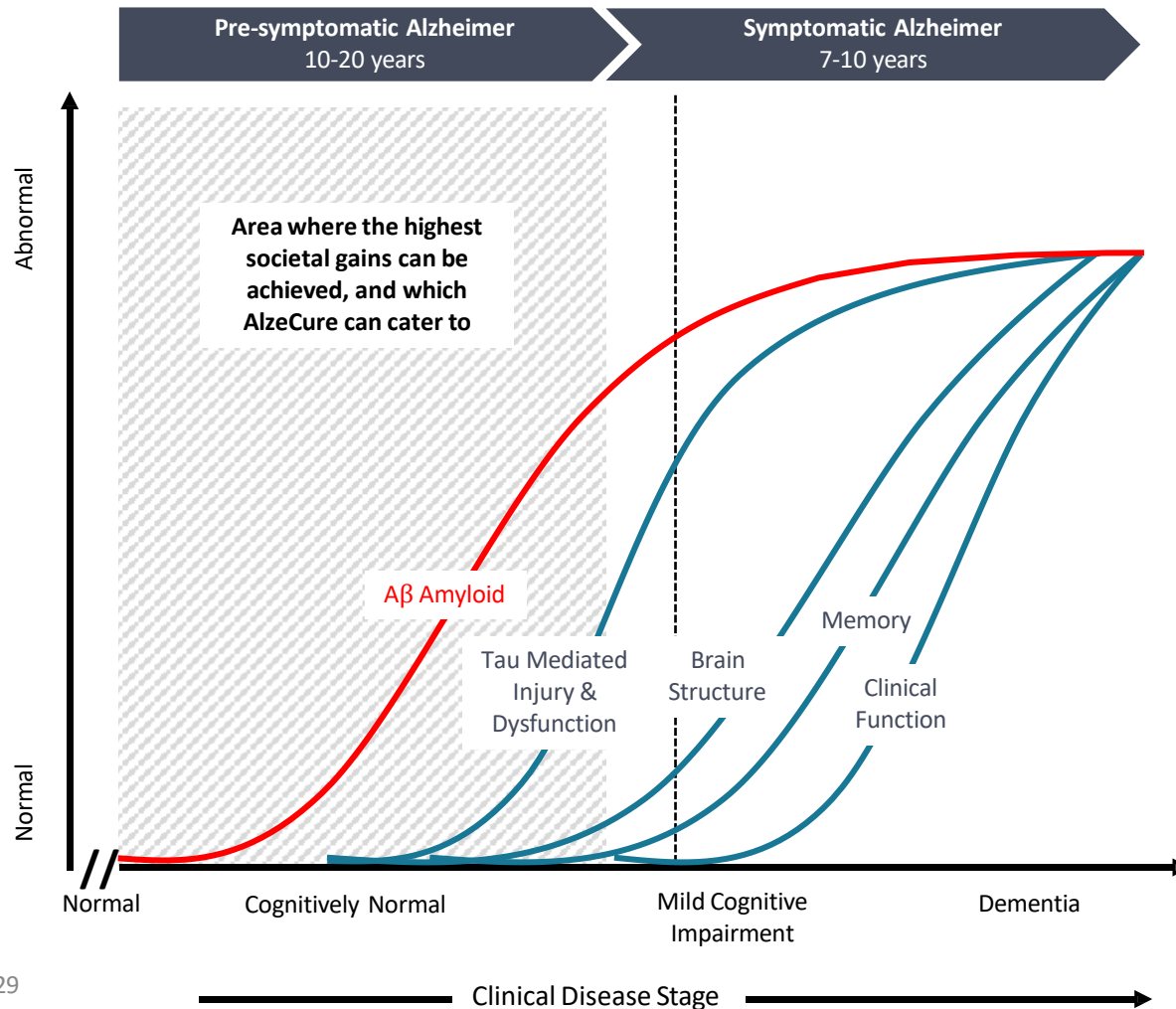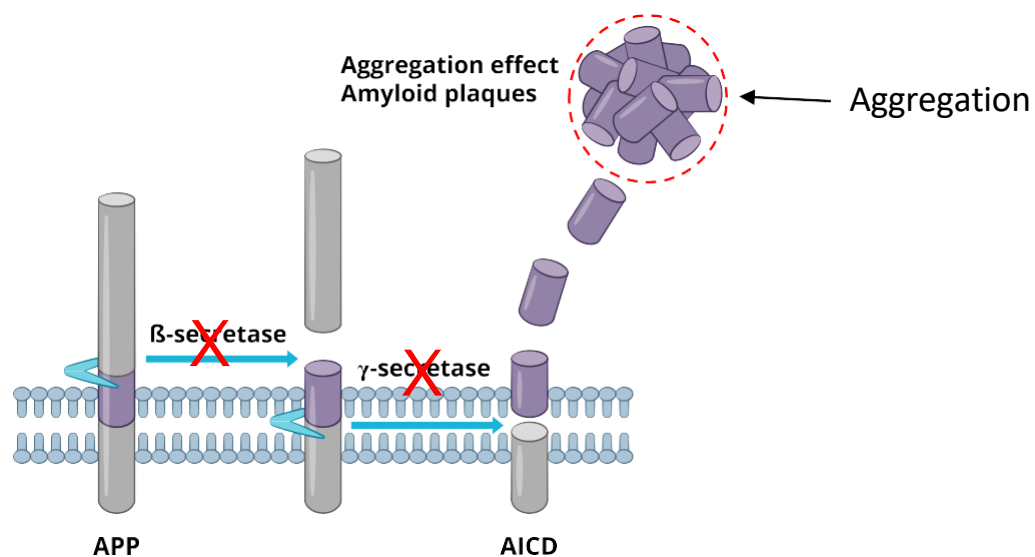Healthy brain   Alzheimer's brain

Aβ amyloid

Preventing or delaying Alzheimer's – reducing toxic Aβ42 production

ALZHEIMER'S DISEASE PROGRESSION

Pre-symptomatic Alzheimer
10-20 years

Symptomatic Alzheimer
7-10 years

Abnormal

Area where the highest societal gains can be achieved, and which AlzeCure can cater to

Aβ Amyloid

Tau Mediated Injury & Dysfunction

Brain Structure

Memory

Clinical Function

Normal

Normal

Cognitively Normal

Mild Cognitive Impairment

Dementia

Clinical Disease Stage

Preventing or delaying Alzheimer's – reducing toxic Aβ42 production

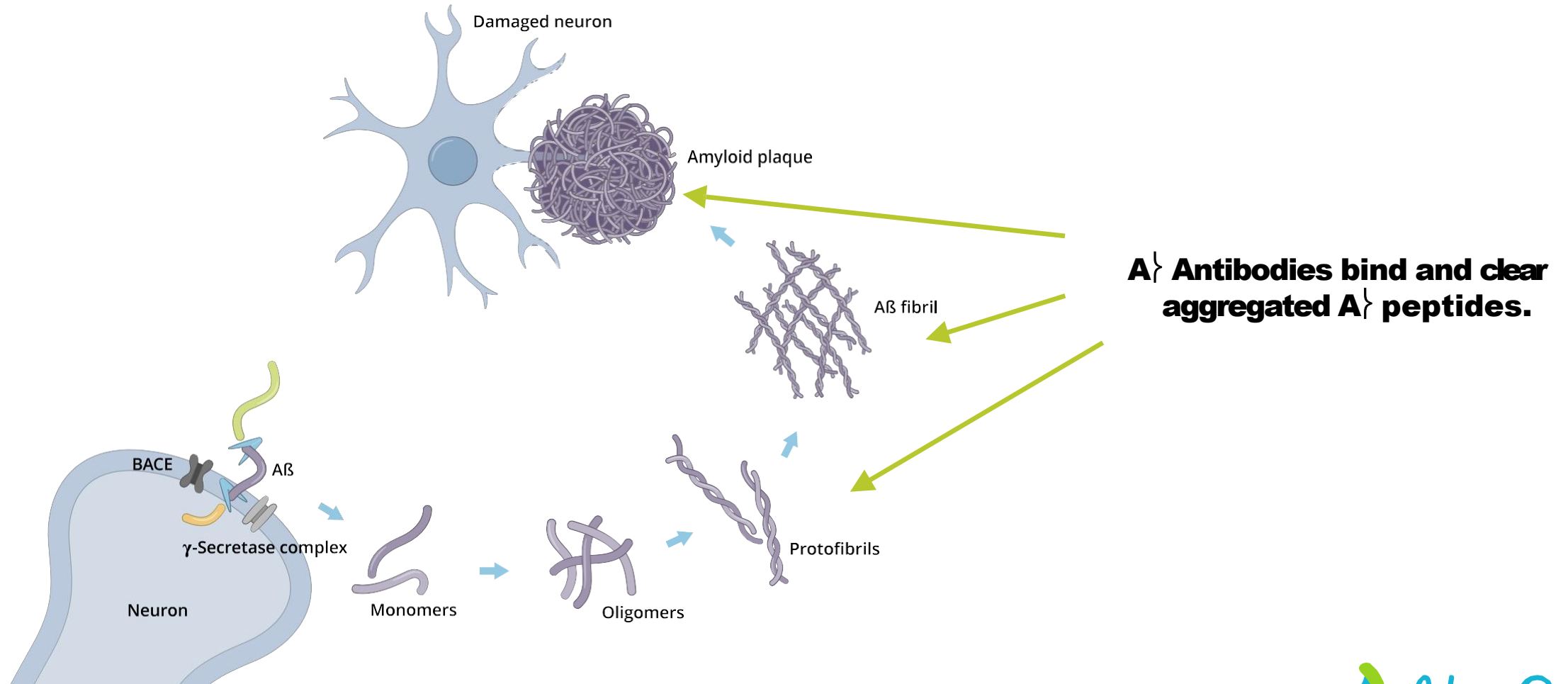**Aggregation effect Amyloid plaques** ← Aggregation

Aβ42 - main culprit in Alzheimer progression

Alzstatin® *modulates* the enzyme, alter its cleaving pattern and thereby **limits the aggregation**
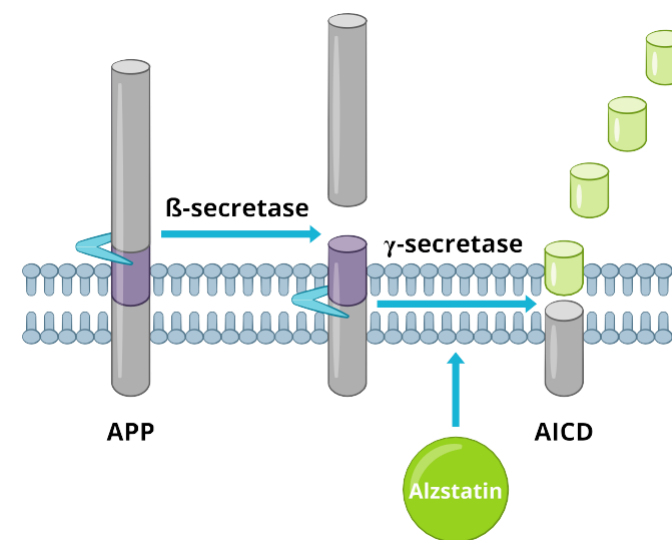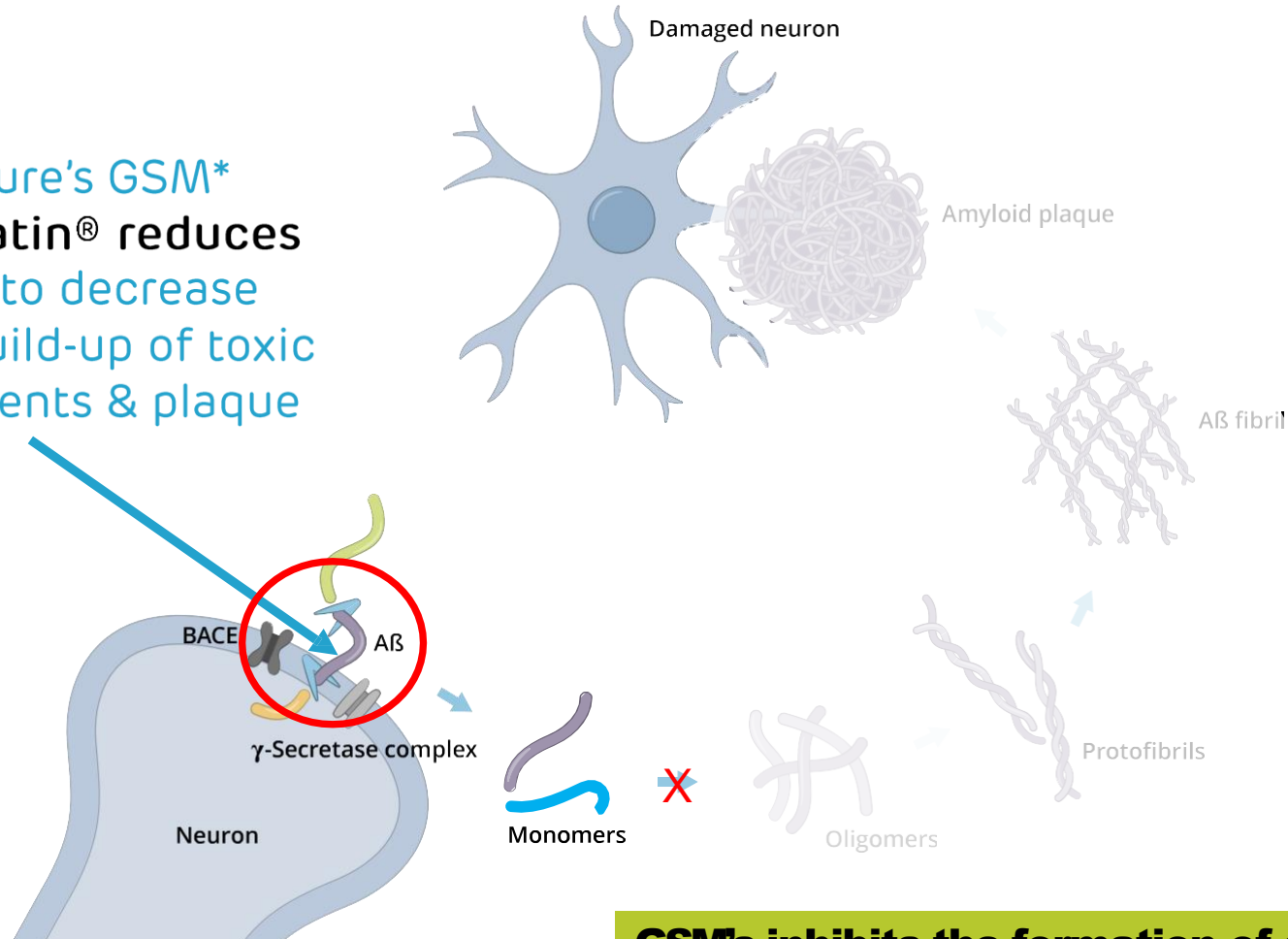
Alzstatin® **targets the gamma-secretase** *as a* **modulator** *- does* **not** *block enzyme activity*

The Amyloid Cascade - Generates toxic & damaging fragments, including plaques, destroying neurons & brain structures

Damaged neuron

Amyloid plaque

Aß fibril

Aβ Antibodies bind and clear aggregated Aβ peptides.

BACE

Aß

γ-Secretase complex

Neuron

Monomers

Oligomers

Protofibrils

AlzeCure

The Amyloid Cascade - Generates toxic & damaging fragments, including plaques, destroying neurons & brain structures

Damaged neuron

AlzeCure's GSM*
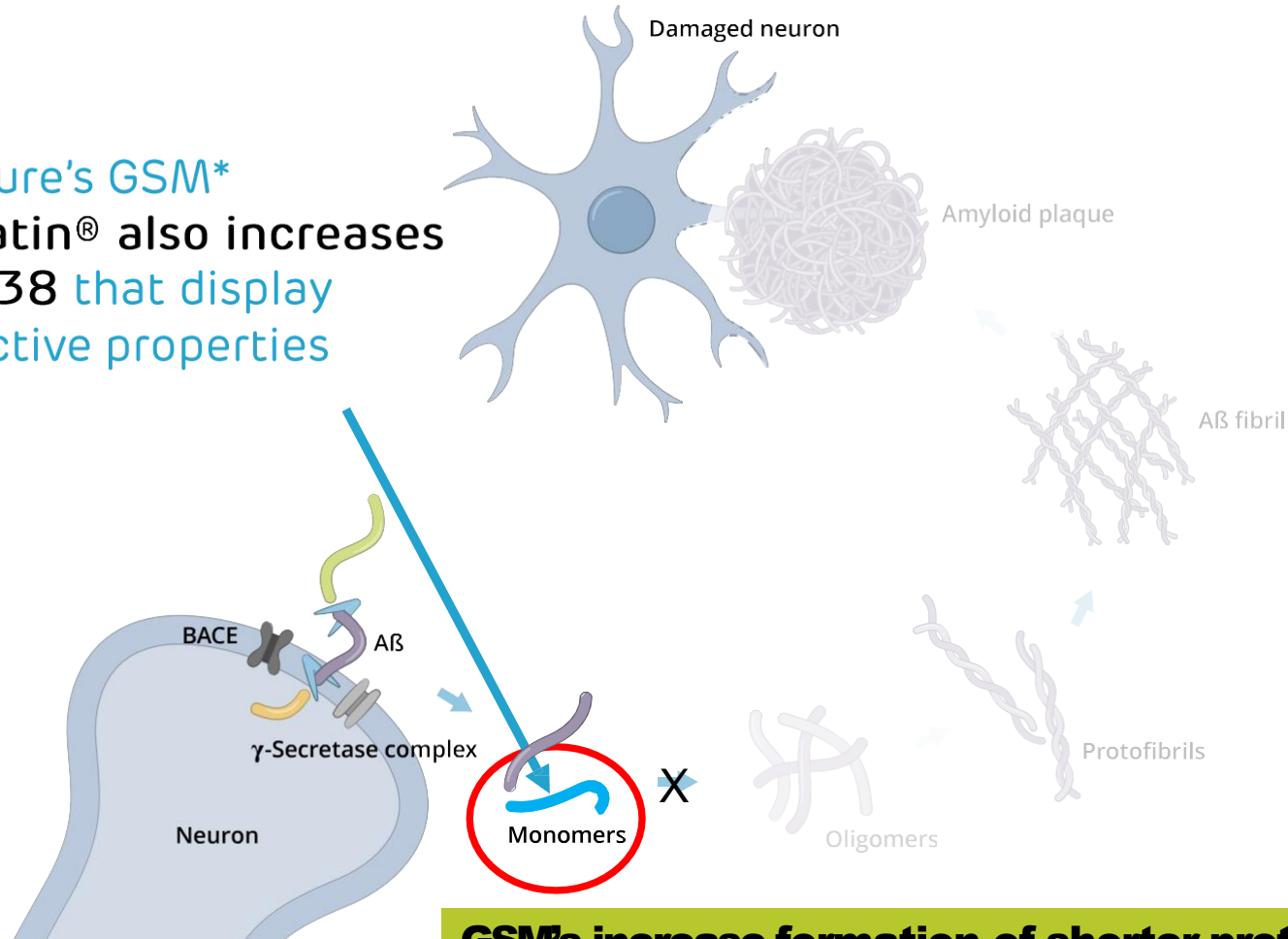**Alzstatin® reduces Aβ42** to decrease the build-up of toxic fragments & plaque

Amyloid plaque

Aß fibril

BACE

Aß

γ-Secretase complex

Protofibrils

Neuron

Monomers

X

Oligomers

GSM's inhibits the formation of all Aß aggregates

*) GSM = Gamma Secretase Modulator

The Amyloid Cascade - Generates toxic & damaging fragments, including plaques, destroying neurons & brain structures

Damaged neuron

Amyloid plaque

Aß fibril

Protofibrils

AlzeCure's GSM*
Alzstatin® also increases Aβ37/38 that display protective properties

BACE

Aß

γ-Secretase complex

Neuron

Monomers

Oligomers

X

GSM's increase formation of shorter protective Aβ fragments

*) GSM = Gamma Secretase Modulator

Recent data show that shorter Aβ peptides could have advantageous effects

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

Identification of the Aβ37/42 peptide ratio in CSF as an improved Aβ biomarker for Alzheimer's disease

Lei Liu, Bianca M. Lauro, Amy He, Hyo Lee, Sanjay Bhattarai, Michael S. Wolfe, David A. Bennett, Celeste M. Karch, Tracy Young-Pearse, Dominantly Inherited Alzheimer Network (DIAN), Dennis J. Selkoe ✉

First published: 12 March 2022 | https://doi.org/10.1002/alz.12646 | Citations: 1

Read the full text >

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Abstract

Introduction

Identifying CSF-based biomarkers for the β-amyloidosis that initiates Alzheimer's disease (AD) could provide inexpensive and dynamic tests to distinguish AD from normal aging and predict future cognitive decline.

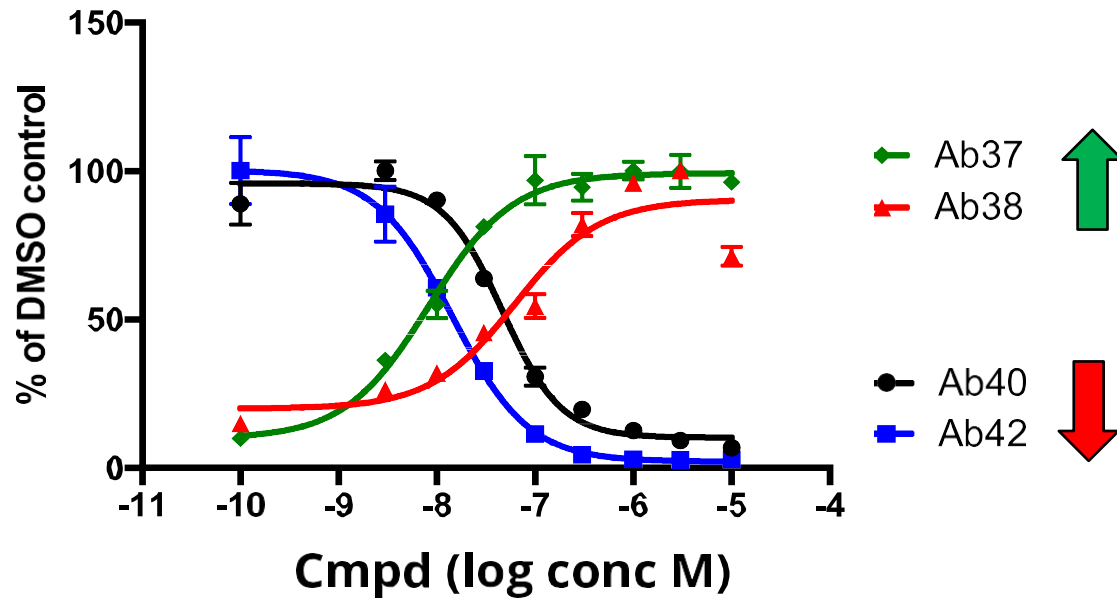...ith Risk of Alzheimer

PhD,
euroimaging Initiative

Correspondence
Mr. Cullen
nicholas.cullen@med.lu.se

...loid (Aβ) species
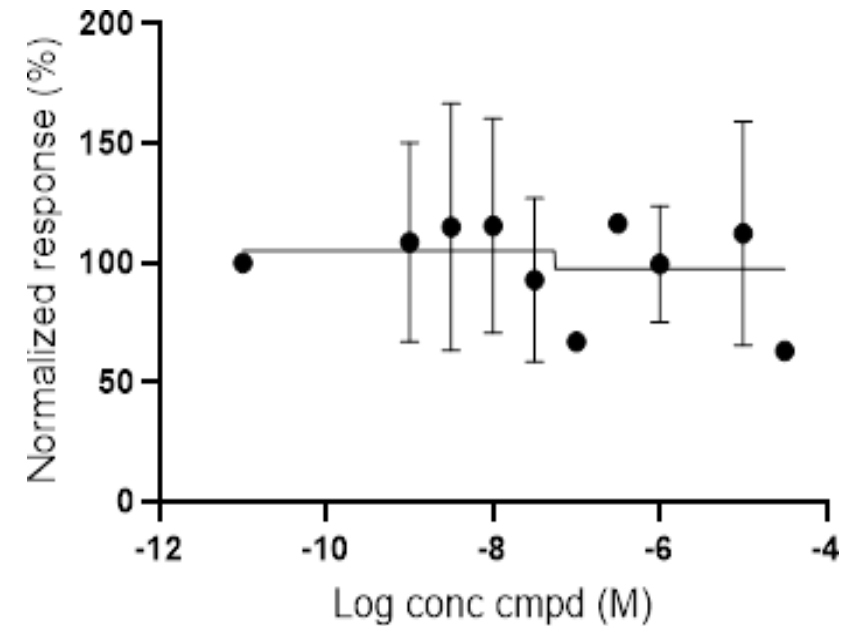...inical evidence is
...ntia and cognitive

...dditionally, we show
...aggregation and the
...ggregates with Aβ42;
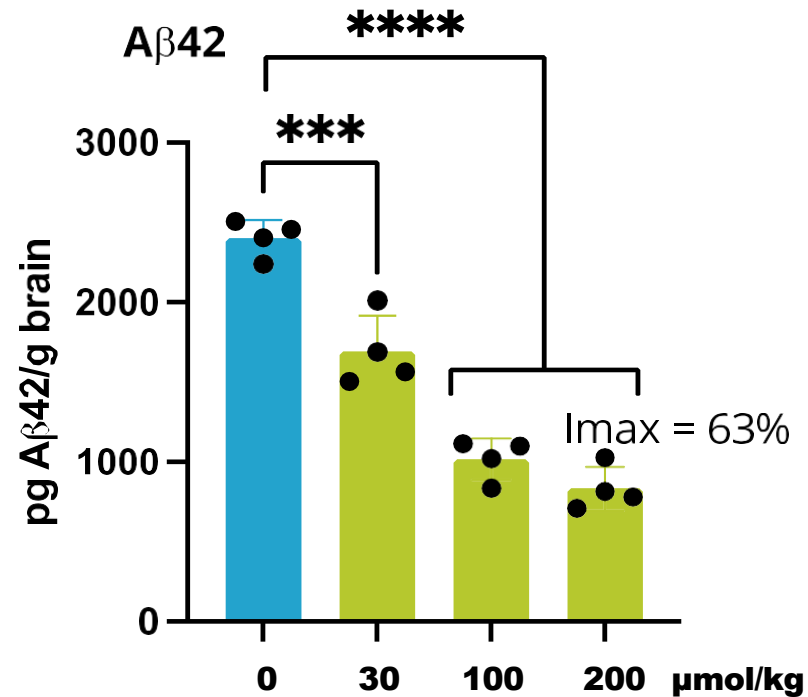
34

Alzstatin – potent reduction of toxic Aβ42

Alzstatin reduces toxic Aβ42 and Aβ40, while increasing protective Aβ38 and Aβ37 peptides
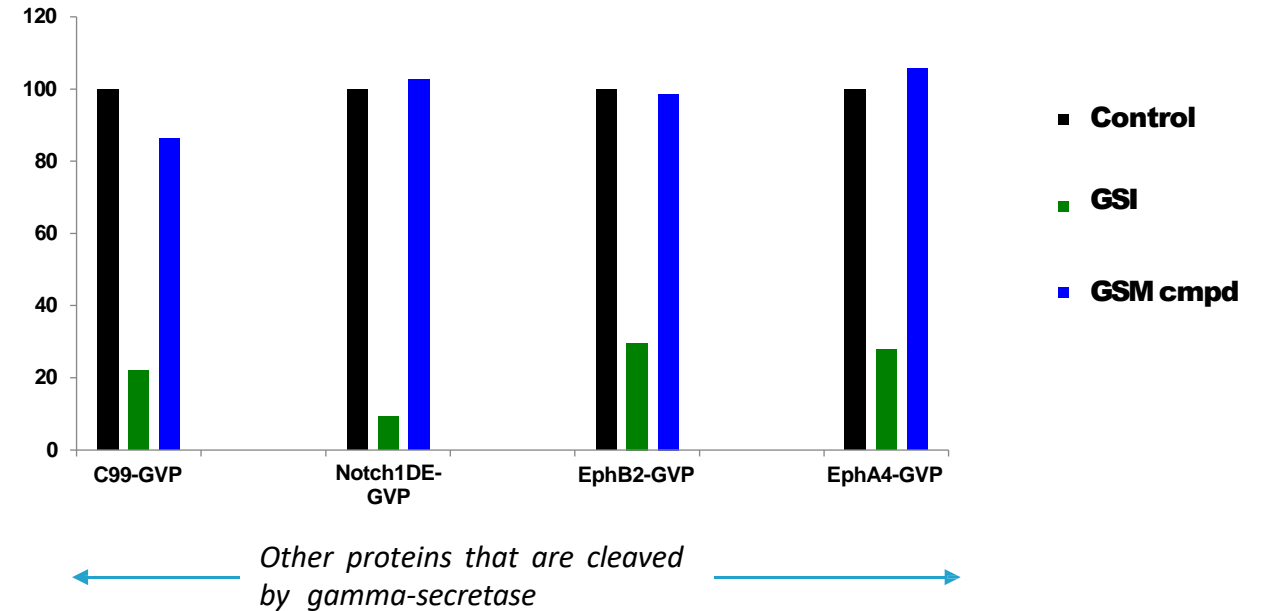
No effect on total Aβ Consistent with a GSM

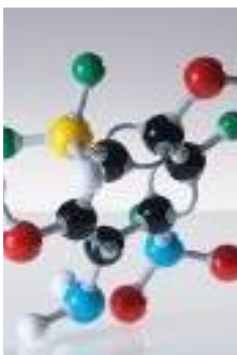# Alzstatin – efficacious in vivo based on a safer mechanism-of-action

Alzstatin potently reduces the amount of toxic brain Aβ42 in mice

Alzstatin compounds do not affect the formation of other gamma-secretase substrates, e.g. Notch

How Alzstatin is expected to differ from the Antibodies*
- Key advantages

Small molecule therapy

- Small molecules generally pass much more readily across the BBB to its target site - the brain
- Provides a more cost-effective treatment for chronic use than biologics

Oral formulation => Home treatment

- Don't need to go to the hospital once or twice a month for an infusion of the drug

Early treatment

- Taken before the brain is heavily damaged and the patient is diagnosed with cognitive decline and Alzheimer's disease, which is the case for the antibody

Fewer side effects

- Not expected to have the side effects of brain oedema and brain microbleedings (ARIA)
  - => Is not expected to demand regular brain scans, => minimizing hospital visits and costs

*) E.g. Aduhelm (aducanumab), Leqembi (lecanumab), Donanemab

Attractive profile with early clinical proof-of-mechanism

- Clinical PoM **and** central target engagement already in Phase I

  - **SAD/MAD studies conducted in healthy volunteers**

    - Evaluation of safety and tolerability after single and repeated administration

    - Possibility to explore biomarker effects **showing central target engagement** already in Phase I

      - Aβ42/40 – show **reduction of toxic Aβ-peptides**

      - Aβ37/38 – show **increase of shorter protective Aβ-peptides**, establishing gamma-secretase involvement and MoA

      - Measurements done both in CSF and plasma – **biomarker kits available**

Multiple target populations - preventive and maintenance therapy

Preventive therapy based on genetic risk factors* and biomarkers

- Early stand-alone treatment before onset of symptoms and any major neurodegeneration occurs

- Prevents build-up of amyloid – an early pathological feature of AD

- Suitable for preventive therapy - as a "statin" for Alzheimer's disease

- Familiar forms of the disease (incl. Downs syndrome) suitable for initial proof of concept clinical studies

*) E.g. ApoE4

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# Multiple target populations - preventive and maintenance therapy

Preventive therapy based on genetic risk factors* and biomarkers

- Early stand-alone treatment before onset of symptoms and any major neurodegeneration occurs
- Prevents build-up of amyloid – an early pathological feature of AD
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Maintenance therapy in patients with established Alzheimer's

- Potential for combination/maintenance treatment after initial plaque clearance provided by monoclonal antibody treatment (as initially proposed by Lilly) e.g., with:
  - Lecanemab (Eisai/Biogen/Bioartic)
  - Donanemab (Lilly)
  - Remternetug (Lilly)

*) E.g. ApoE4
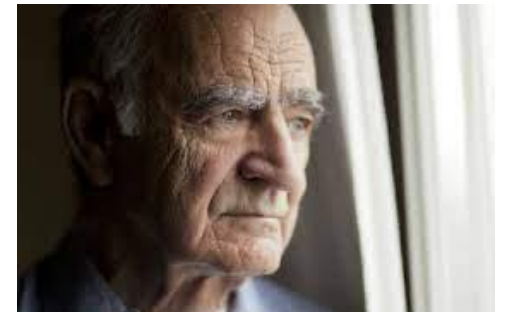
Competitive landscape

Main known competitors:

- UCSD-776890 (Steven Wagner)/NIH – Phase 1

- Roche RG6289 – Phase 1

Published data on Pfizer's PF-06648671 show that GSM's can display both potent efficacy and good safety in man. ➜

ARTICLE

Pharmacokinetic and Pharmacodynamic Effects of a γ-Secretase Modulator, PF-06648671, on CSF Amyloid-β Peptides in Randomized Phase I Studies

Jae Eun Ahn[1,*], Charles Carrieri[1], Fernando Dela Cruz[1], Terence Fullerton[1], Eva Hajos-Korcsok[1,3], Ping He[1,4], Constantino Kantaridis[2], Claire Leurent[1,5], Richann Liu[1,6], Jessica Mancuso[1], Laure Mendes da Costa[2] and Ruolun Qiu[1]

γ-Secretase modulators (GSMs) represent a promising therapy for Alzheimer's disease by reducing pathogenic amyloid-β (Aβ) peptide production. Three phase I studies (NCT02316756, NCT02407353, and NCT02440100) investigated the safety/tolerability, pharmacokinetics (PKs), and pharmacodynamics (PDs) of the oral GSM, PF-06648671. A PK/PD indirect-response model was developed (using biomarker data) to simultaneously characterize differential effects of PF-06648671 on multiple Aβ species in cerebrospinal fluid (CSF). Healthy subjects (n = 120) received single doses or multiple-ascending doses of PF-06648671/placebo for 14 days. No serious adverse events occurred; severe adverse events were deemed not drug related. PF-06648671 decreased Aβ42 and Aβ40 concentrations in CSF, with greater effects on Aβ42, and increased Aβ37 and Aβ38 levels, particularly Aβ37. No significant change in total Aβ was observed. The PK/PD model well described the tendency of observed CSF Aβ data and the steady-state effects of PF-06648671, supporting its use for predicting central Aβ effects and optimal dose selection for GSMs in future trials.

Development stage of Alzstatin in line with competitors

Summary
Advantages with Alzstatin

- ✓ Reduces amyloidogenic Aβ42 production

- ✓ Increase the shorter peptides Aβ37 and Aβ38 - suggested to have protective properties

- ✓ Do not affect the total amount of Aβ – thus any physiological function likely not affected

- ✓ Mode of action is the reverse of most familiar Alzheimer mutations

- ✓ Alzstatin compounds such as ACD680 potently reduce Aβ42 production both in vitro and in vivo

- ✓ PoM data achievable already in phase 1 clinical trials

- ✓ Potential for both preventive and maintenance treatment

Bart De Strooper on Alzforum regarding Lecanemab Phase 3 results:
"These results strongly suggest that we revisit previous drug targets such as γ-secretase and BACE, as small compounds modulating these activities might be, in the long run, the only cheap and feasible prevention for AD."

AlzeCure

Acknowledgement

- **Team at Alzecure Pharma**
  - Gunnar Nordvall
  - Boel Nilsson
  - Maria Backlund
  - Azita Rasti
  - Märta Dahlström
  - Magnus Halldin
  - Veronica Lidell
  - Sanja Juric
  - Cristina Parrado
  - Märta Segerdahl

- **Karolinska Institutet**
  - Prof. Bengt Winblad
  - Assoc. Prof. Lars Tjernberg

- **Göteborgs Universitet**
  - Prof. Henrik Zetterberg
  - Lotta Agholme, PhD
  - Stefanie Fruhwürth, PhD

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