February 19, 2024

Alzstatin

- a small molecule disease modifying therapy against Alzheimer's disease

Johan Sandin, CSO

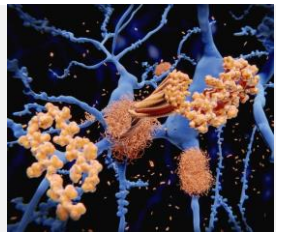
AlzeCure

Alzstatin® - Gamma-Secretase Modulator for Preventive Treatment of Alzheimer's

PROJECT OVERVIEW

Emanates from Big Pharma

- AlzeCure staff was **part of the conception** of the project at AstraZeneca
- Approximately **SEK 150m** already **invested** on project development
- Only Biotech with a gamma-secretase modulator (GSM)



Strong linkage to disease

- Gamma-secretase is a **key enzyme** producing **toxic Aβ42**
- **Genetic linkage to disease** - majority of all familiar mutations are linked to the gamma-secretase complex causing early onset of disease
- Alzstatin compounds **reduce** production of **Aβ42**

Positive preclinical data

- Two drug candidates, ACD679 and ACD680, in pre-clinical development phase
- Compounds **potently reduce Aβ42 production** - up to 60% in vivo
- GSM's also **produce shorter peptides** with suggested added beneficial effects

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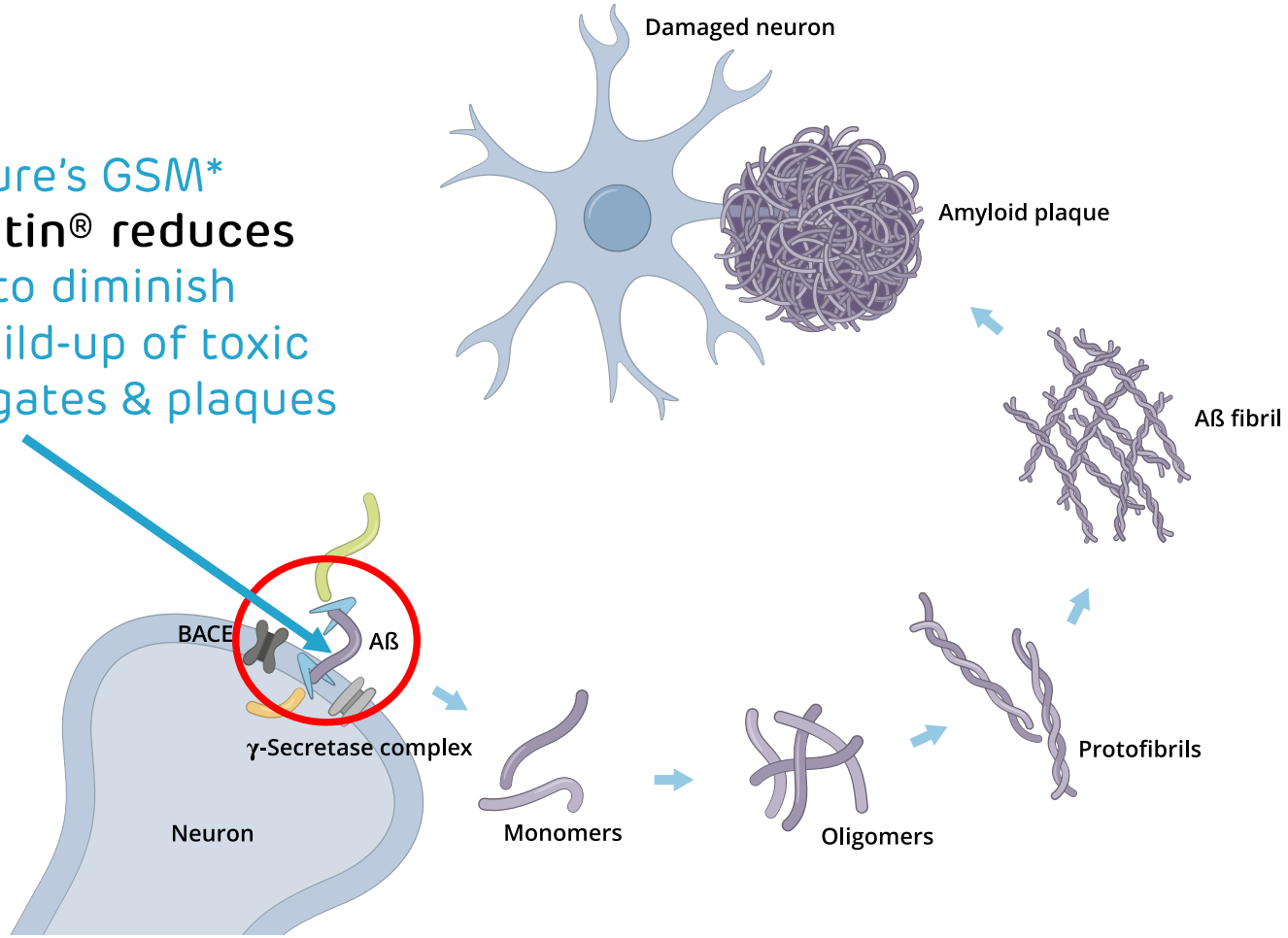
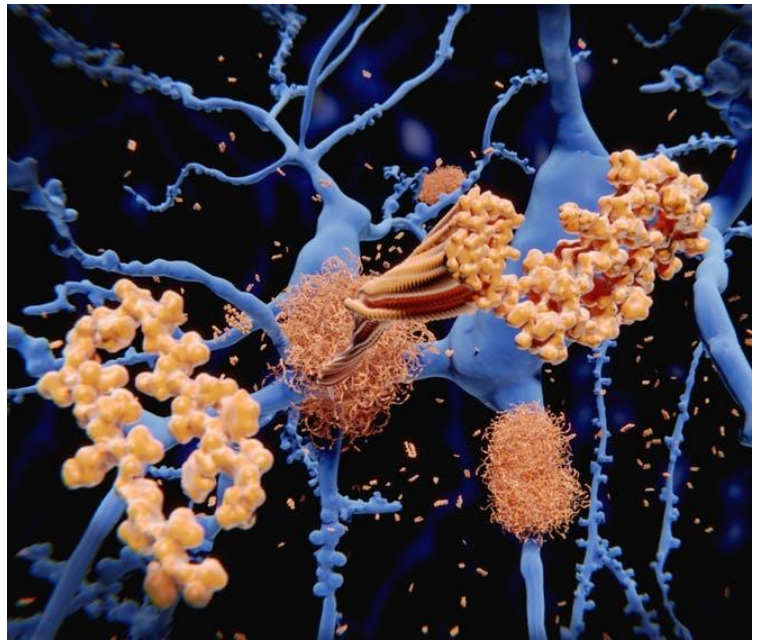
The Amyloid Cascade - Validated pathway that generates toxic Aβ fragments, resulting in damage to neurons and brain structures

AlzeCure's GSM*
Alzstatin® reduces
Aβ42 to diminish
the build-up of toxic
aggregates & plaques





*) GSM = Gamma Secretase Modulator

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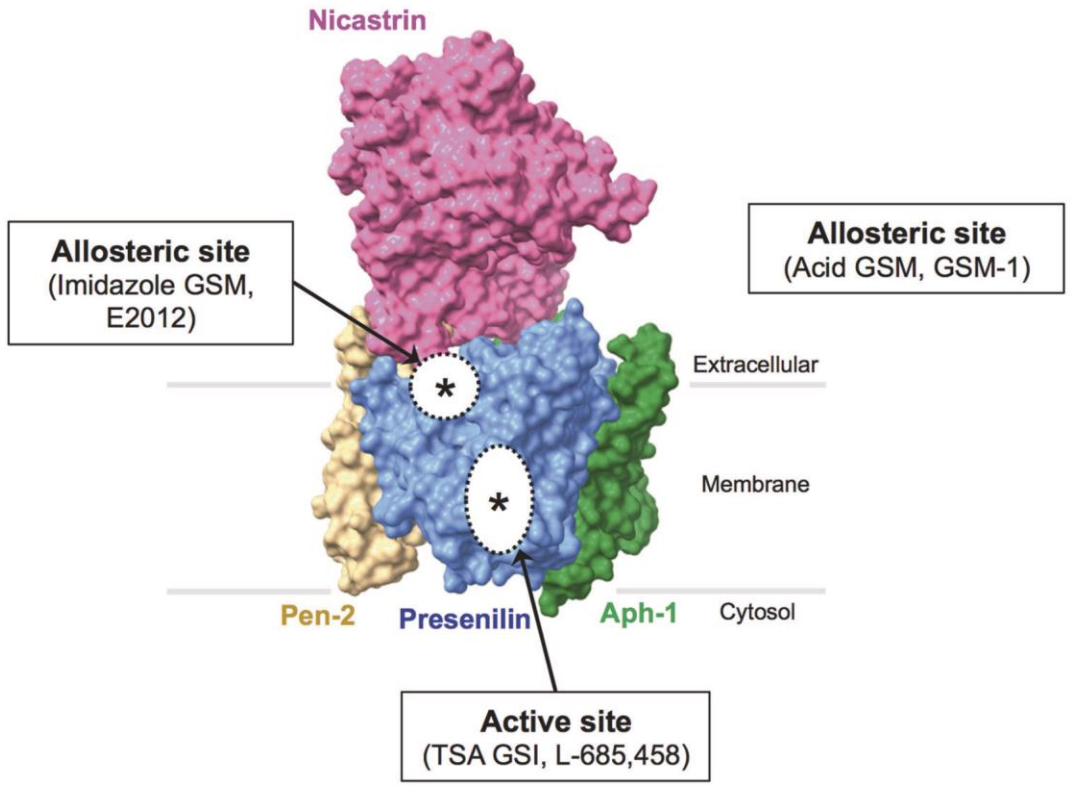
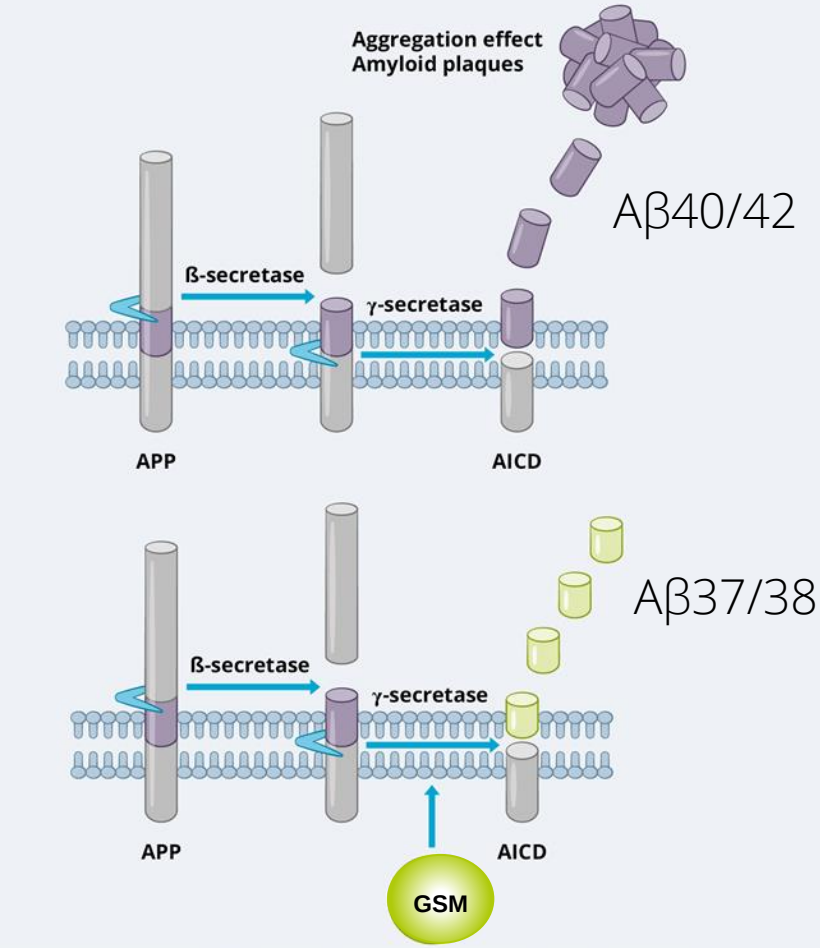
Mechanism of gamma-secretase modulators

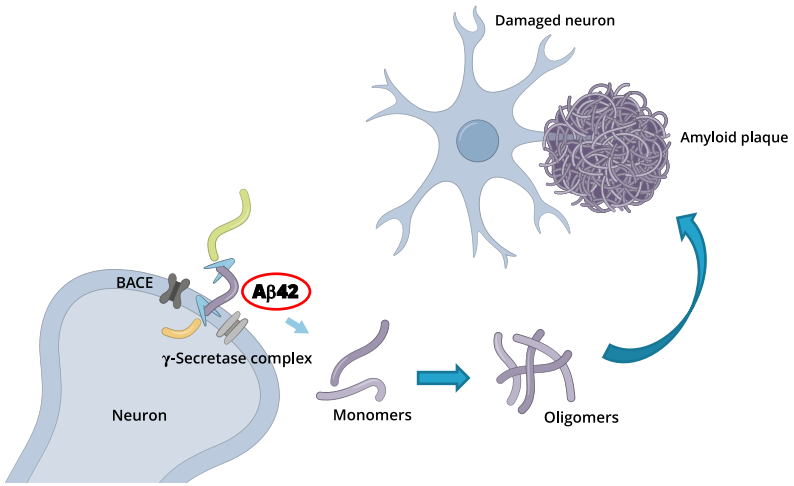




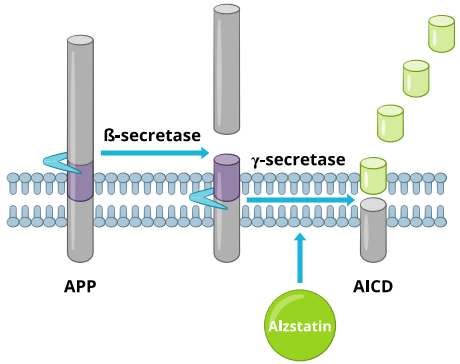
Alzstatin modulates the gamma secretase enzyme which results in the formation of shorter fragments that prevents the aggregation effect

Alzstatin, an Alzheimer's Disease Modifier – Preventing or Delaying Disease Progression

Aβ42 peptide is the main **culprit in AD progression**



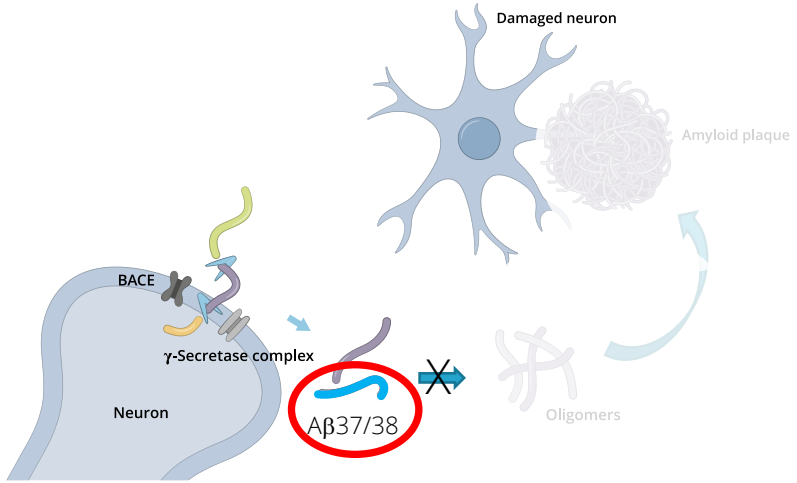
GSMs modulate the enzyme**, reducing Aβ42 & Aβ40** and shifting its cleaving pattern towards shorter forms and thereby **limits toxic oligomerization**



*Alzstatin **targets the gamma-secretase***

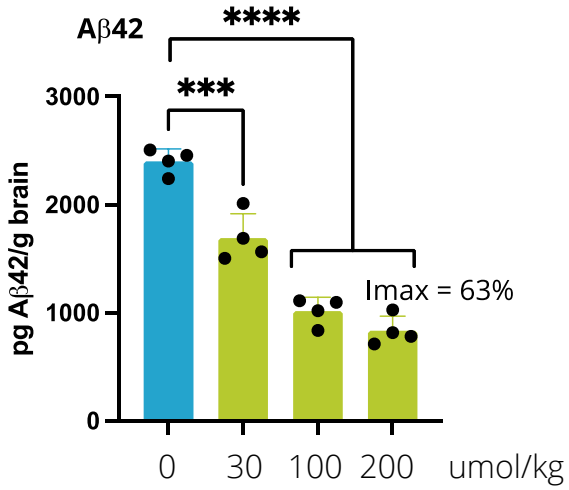
	Prone to self-aggregate	Inhibits formation of amyloid plaques	Toxic to cells
Aβ42	✓ ✓		✓ ✓
Aβ40	✓		✓
Aβ38		✓	
Aβ37		✓	

Alzstatin **produces more** non-toxic **Aβ37/38** which do not form amyloid aggregates, including oligomers

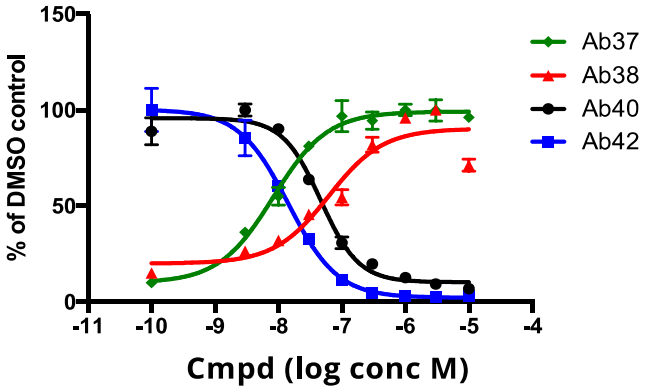


Aβ42 peptide is aggregation prone and toxic, while the **shorter forms Aβ37/38 exhibit protective properties**

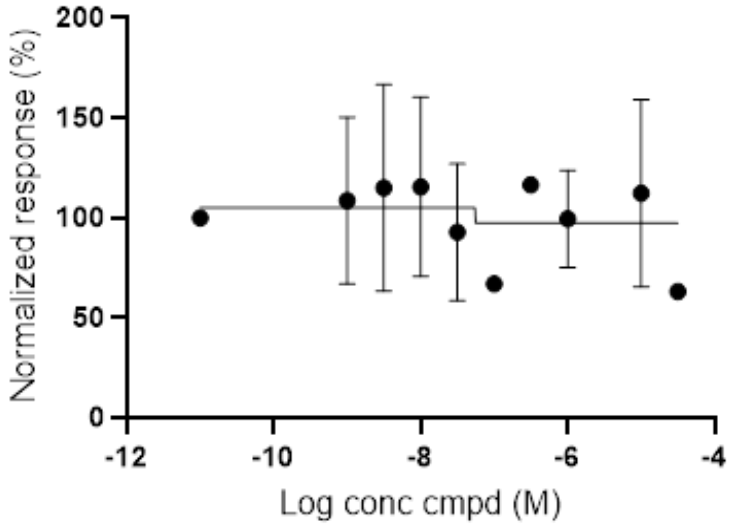
Alzstatin – Potent & Selective Reduction of Aβ42



Alzstatin compounds potently and dose-dependently **reduces the amount of toxic brain Aβ42** in mice after a single dose



GSMs reduce the amount of toxic Aβ42 & Aβ40, while **increasing the amount of the protective Aβ37 & Aβ38** species



Alzstatin compounds do not have any effect on total Aβ levels

➢ **GSMs - Potent Effect on toxic Aβ42 Production without affecting total enzyme activity**

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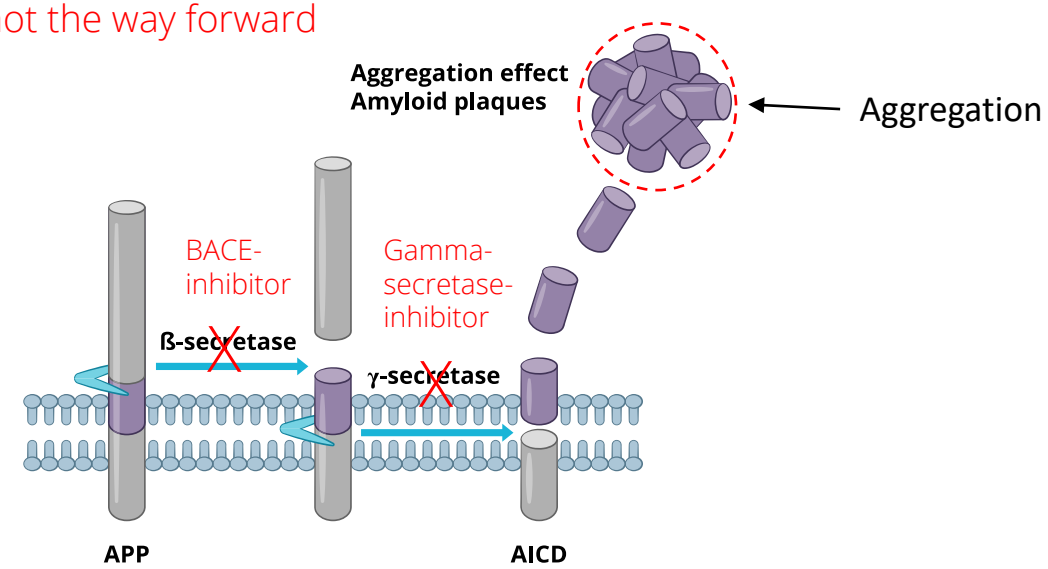
Differentiation from BACE* and Gamma secretase inhibitors

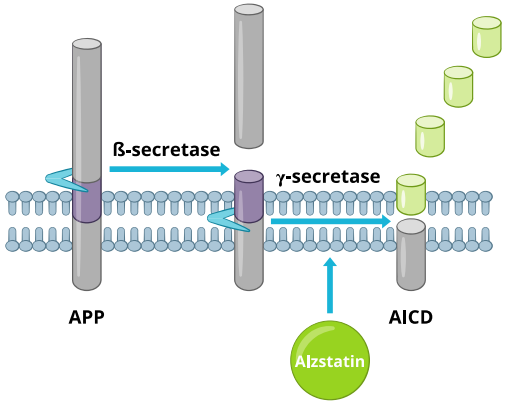
Both BACE- and gamma-secretase inhibitors caused significant side-effects due to inhibition of other key substrates of the enzyme → **inhibition** not the way forward

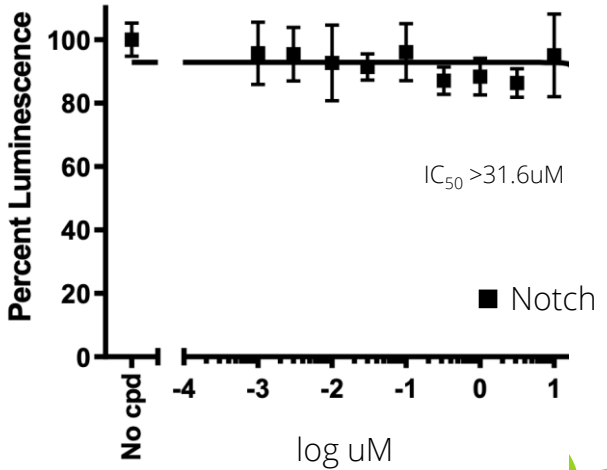


Aβ42 - main culprit in Alzheimer progression

GSM is a safer MoA than an inhibitor, e.g. BACE- or gamma-secretase inhibitor

Alzstatin **targets gamma secretase** as a **modulator** – does ***not*** block enzyme activity

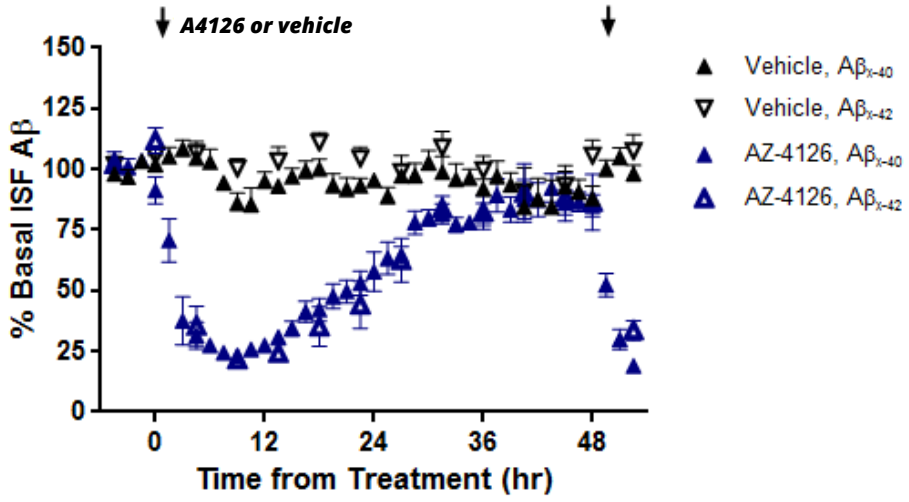




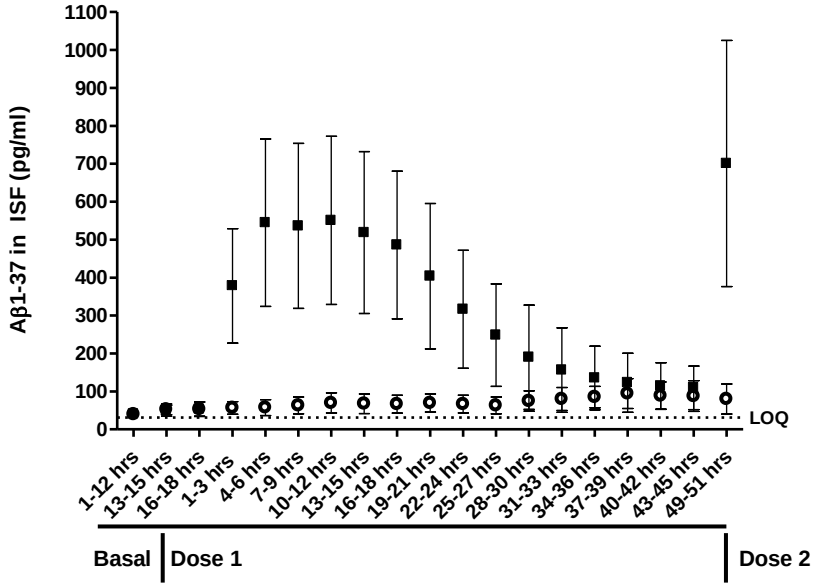
Alzstatin compounds **does not block the cleavage of other gamma-secretase substrates**, such as Notch

***BACE = beta-secretase**

Alzstatin compounds effectively modulate Aβ production in the brain in vivo



Tg2576 mice (6 months) treated with 100 μmol/kg A4126 (p.o.) show significant lowering of Aβ42 and Aβ40 in interstitial fluid



100 μmol/kg A4126 show significant increase in Aβ37 in interstitial fluid

Systemic administration of a GSM results in a large decrease in Aβ42/40 and an increase in Aβ37 in the interstitial fluid in an established mouse AD model

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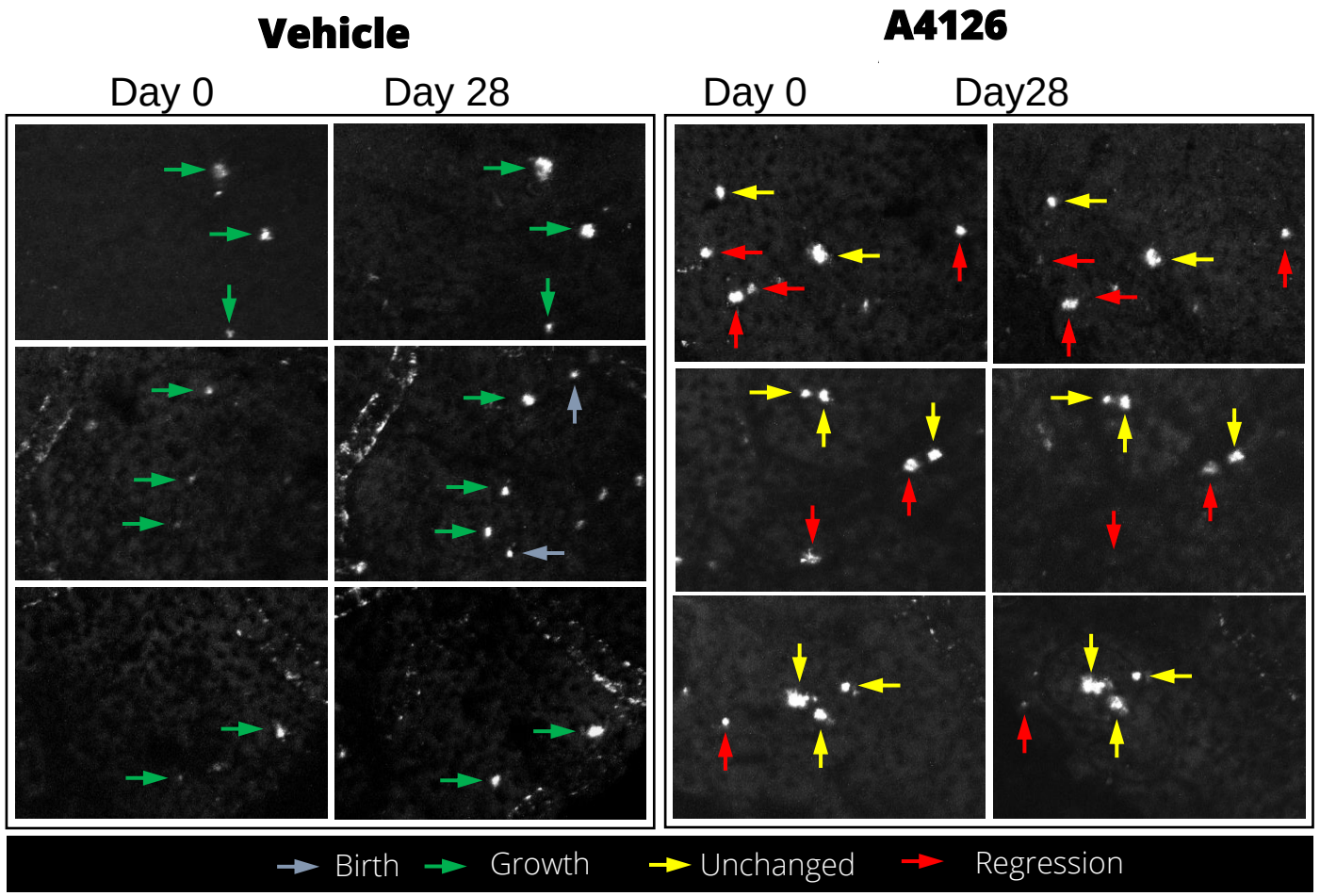
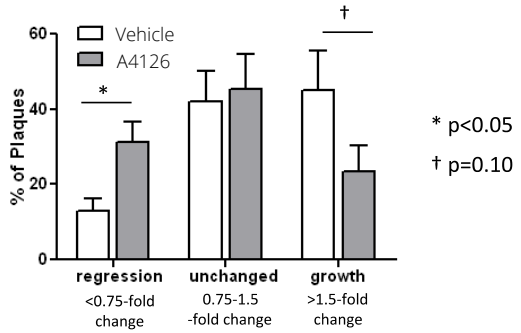
AlzeCure's GSM affects amyloid aggregation in APP/PS1 mice



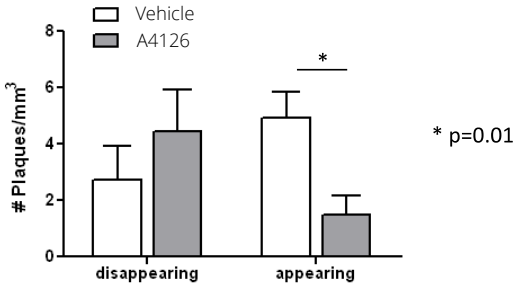
Distribution of Plaque Growth and Regression



* p<0.05

† p=0.10

Plaque appearance or disappearance



* p=0.01

28-day GSM treatment:

- **Attenuates amyloid plaque growth**
- **Decreases new plaque appearance**
- **Induces modest plaque regression**

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Beneficial effect of shorter Aβ peptides

RESEARCH ARTICLE OPEN ACCESS

Association of CSF $A\beta_{38}$ Levels With Risk of Alzheimer Disease–Related Decline

Nicholas Cullen, BS, Shorena Janelidze, PhD, Sebastian Palmqvist, MD, PhD, Erik Stomrud, MD, PhD, Niklas Mattsson-Carlgren, MD, PhD, and Oskar Hansson, MD, PhD, for the Alzheimer's Disease Neuroimaging Initiative

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Mr. Cullen
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Neurology® 2022;98:e958-e967. doi:10.1212/WNL.0000000000013228

Patients/populations that have:

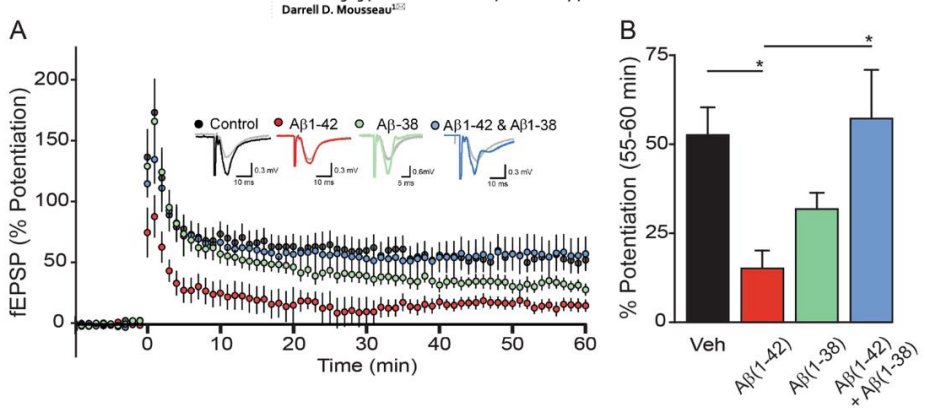
- Higher Aβ38 has a slower decline in MMSE
- High Aβ38 has a slower conversion in to AD

scientific reports

OPEN

The Aβ(1–38) peptide is a negative regulator of the Aβ(1–42) peptide implicated in Alzheimer disease progression

Maa O. Quartey[1], Jennifer N. K. Nyarko[1], Jason M. Maley[2], Jocelyn R. Barnes[3], Maria A. C. Bolanos[4], Ryan M. Heistad[1], Kaeli J. Knudsen[1], Paul R. Pennington[1], Josef Buttigieg[4], Carlos E. De Carvalho[5], Scot C. Leary[6], Matthew P. Parsons[3] & Darrell D. Mousseau[1]



Aβ38 reverses the negative impact of Aβ42 on long-term potentiation in acute hippocampal slices and on membrane conductance in primary neurons

Shorter peptides attenuates Aβ42 toxicity in C. elegans and Drosophila

Chemical Science

ROYAL SOCIETY OF CHEMISTRY

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Cite this: *Chem. Sci.*, 2022, **13**, 2423

All publication charges for this article have been paid for by the Royal Society of Chemistry

Amyloid-β peptide 37, 38 and 40 individually and cooperatively inhibit amyloid-β 42 aggregation†

Gabriel A. Braun, ‡[a] Alexander J. Dear, [abcd] Kalyani Sanagavarapu,§[a] Henrik Zetterberg[efgh] and Sara Linse *[a]

Higher levels of Aβ37/38 appear beneficial

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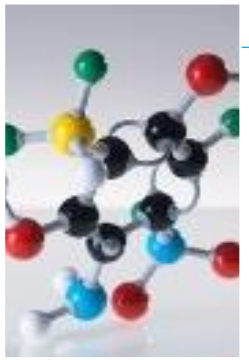
How Alzstatin is expected to differ from the Antibodies*
- Key advantages

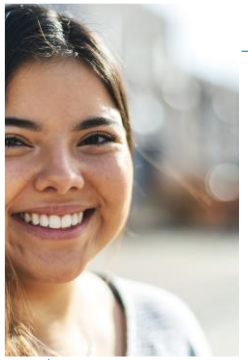


Small molecule therapy

- 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

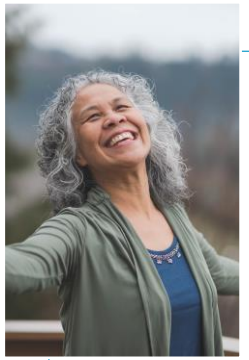
Oral formulation => Home treatment

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



Stand-alone or combination therapy

- Suitable both as stand-alone therapy as well as combination therapy together with anti-amyloid antibodies



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. Leqembi (lecanumab), Aduhelm (aducanumab), Donanemab

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Early Value Driving Proof-of-Mechanism in Phase I

- **Proof of Mechanism & Central Target Engagement**
  - Phase I - SAD/MAD studies to be performed
    - Evaluation of safety and tolerability after single and repeated administration
  - Possible to explore biomarker effects **showing central target engagement**
    - Aβ42/40 – show **reduction of toxic Aβ-species**
    - Aβ37/38 – show **increase of shorter protective Aβ-species**, establishing gamma-secretase involvement and MoA
    - Biomarker strategy employed previously by Pfizer (PMID: 31314925)
    - Measurements done both in CSF & plasma utilizing readily **available kits**

- **BBB-penetrant Small Molecule for Oral Use**
  - **Not expected to cause brain oedema** (ARIA-E) and brain microbleeds (ARIA-H) associated with mAb therapies*

* E.g., antibodies (mAb) like Leqembi ™ (lecanumab) & donanemab

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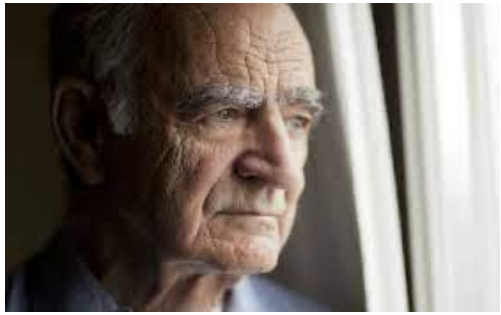
Multiple target populations - maintenance and preventive therapy

Maintenance therapy in patients with established Alzheimer's

- Treatment after initial plaque clearance by monoclonal antibody treatment (as initially proposed by Lilly) e.g., with: Lecanemab (Eisai/Biogen/Bioarctic), Donanemab (Lilly), Remternetug (Lilly)

Combination therapy together with monoclonal antibody treatment - early AD

- Combine plaque clearance by monoclonal antibody treatment and reduction of Aβ42 production by GSM



Preventive therapy based on genetic risk factors* & biomarkers (long-term possibility)

- Early stand-alone treatment before onset of symptoms and any major neurodegeneration occurs (prior to rapid increase in Tau pathology)
- Prevents build-up of amyloid – an early pathological feature of AD
- Familiar forms of the disease (incl. Downs syndrome) suitable for initial proof of concept clinical studies

*) E.g. ApoE4

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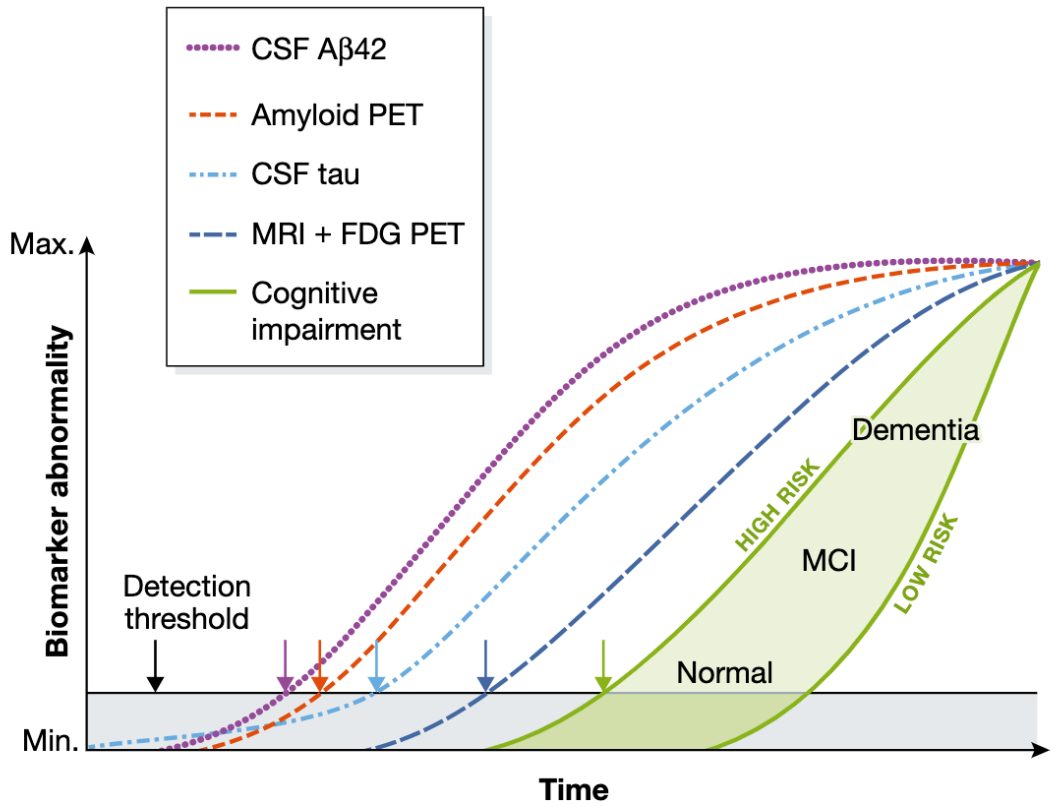
Well established biomarkers in the field



Possible blood/CSF biomarkers
Aβ42/40/38/37 and different ratios thereof
Tau: T-tau, pTau181, pTau217, and pTau231

NFL - neurodegeneration
GFAP - neuroinflammation

Collaboration with Prof. Zetterberg will enable us to select best biomarkers

Blood biomarker development will allow for early patient selection & detection, but at present confirmation by PET/CSF biomarkers is needed

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Summary

Advantages with Alzstatin

- ✓ Decreases Aβ42 production – reduces all forms of amyloid aggregates (oligomers, fibrils etc.)
- ✓ Increases the shorter peptides Aβ37 and Aβ38 - suggested to have protective properties
- ✓ Do not block enzyme activity and spares important physiological signaling – key for safety
- ✓ Genetically supported mechanism - mode of action is the reverse of most familiar Alzheimer mutations
- ✓ Small molecule compound – allows for cost-effective oral administration & good CNS exposure
- ✓ PoM data achievable already in phase 1 clinical trials
- ✓ Could also be used together with other disease-modifier therapies, e.g. antibodies
- ✓ Potential to prevent or slow disease progression

Bart De Strooper on Alzforum regarding Lecanemab Phase 3 results:

"These results strongly suggest that we revisit previous drug targets such as y-secretase and BACE, as small compounds modulating these activities might be, in the long run, the only cheap and feasible prevention for AD."

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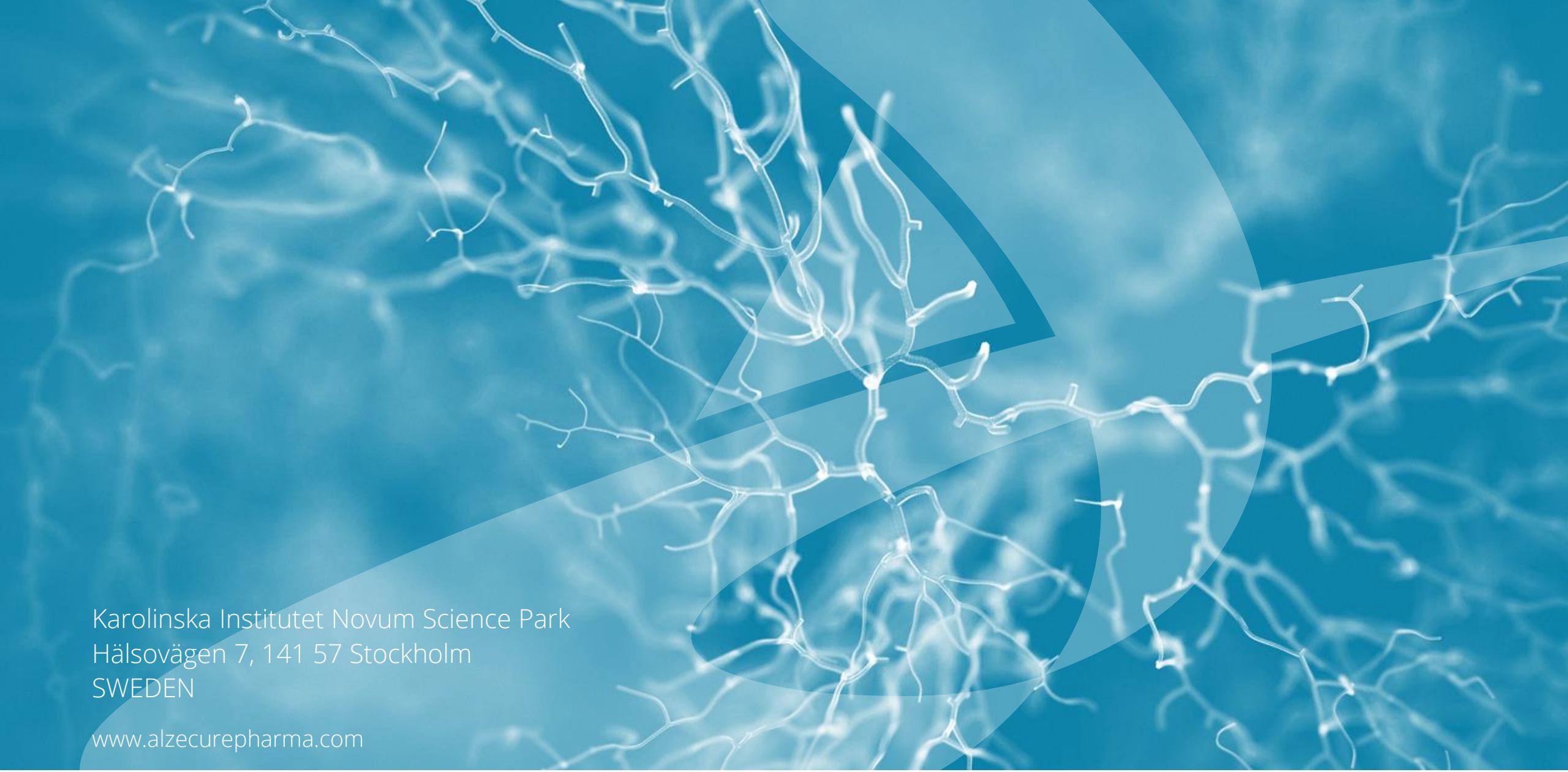

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Thank You
for attending

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