Disease-Modifying Therapy and Diagnostics for Alzheimer’s Disease

Oct 2016
Value proposition: Unique true targeting of disease-driving Aβ ”oligomers” (and more...)
Past, present and future

Research project

2007-2008

Discovery phase and start of preclinical development

GU Ventures

2009-2015

Preclinical phase, vaccine ALZ-101

2016-2017

Clinical phase, vaccine ALZ-101

Partner and/or capital needed

2018 -

AktieTorget

Göteborgs Universitet

Alzinova
Alzheimer’s disease: A progressive neurodegenerative disorder

Mild Cognitive Impairment
- Duration: 7 years
- Disease begins in Medial Temporal Lobe
- Symptoms: Short-term memory loss

Mild Alzheimer’s
- Duration: 2 years
- Disease spreads to Lateral Temporal & Parietal Lobes
- Symptoms: Reading problems, Poor object recognition, Poor direction sense

Moderate Alzheimer’s
- Duration: 2 years
- Disease spreads to Frontal Lobe
- Symptoms: Poor judgment, Implusivity, Short attention

Severe Alzheimer’s
- Duration: 3 years
- Disease spreads to Occipital Lobe
- Symptoms: Visual problems
The burden of Alzheimer’s disease

1 in 3 seniors (65+) dies of (or with) dementia

Alzheimer’s is the only one of the top 10 killers that cannot be prevented, cured, or slowed

Change in number of deaths between 2000 and 2010 (US numbers)

- Breast Cancer: -2%
- Prostate Cancer: -8%
- Heart Disease: -16%
- Stroke: -23%
- HIV: -42%
- Alzheimer’s Disease: +68%

Dementia care (80% Alzheimer’s): $604 billion world wide
Aggregation of a peptide (Aβ$_{42}$) leads to synapse dysfunction and cell death.

An age-related process not completely understood (65+)

Current consensus: The oligomer species is the "smoking gun"
Challenge: Not all forms of Aβ are toxic, and the target is behind the BBB!

Limited target engagement will reduce efficacy

“The apparent clinical benefit observed in PRIME could also be explained by the binding of aducanumab to oligomeric forms of Aβ...”
Alzinova’s AβCC technology provides stable toxins ("oligomers") for drug development.

**Problem:** Low amounts of unstable toxins

- Poorly defined & heterogeneous
- Low reproducibility
- Poor stability / fibrillogenic
- Often non-physiological conditions or additives

**Solution:** High amounts of stable toxins

- Well defined & homogeneous
- High reproducibility
- Unprecedented stability / non-fibrillogenic (*never* form fibrils)
- Physiological conditions
Alzinova’s AβCC technology as a tool to understand structure-activity relationships

The end state of AβCC aggregation is the β-hairpin oligomer structure

The only available high-resolution structure of an oligomer

(solid-state NMR model in Lendel et al. Angew. Chem. 2014)
A snapshot of the competition

**First generation**
- Side effects (ARIA:s)
- No clinical benefit
- \( \text{A}\beta_{40} \)
- \( \text{A}\beta_{42} \)

**Second generation**
- Side effects (ARIA:s)
- Signs of clinical benefit
- Toxic forms (oligomers)
- Insoluble A\(\beta\) forms (fibrils)

**Truly specific targeting**
- Not yet evaluated
- Toxic forms (oligomers)
- Insoluble A\(\beta\) forms (fibrils)

ALZ-101
ALZ-201
### Alzinova’s products ALZ-101 and ALZ-201 neutralize synaptotoxic Aβ

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<thead>
<tr>
<th>ALZ-101</th>
<th>ALZ-201</th>
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<tbody>
<tr>
<td>Peptide-based active vaccine (with Alum)</td>
<td>Monoclonal Ab (IgG)</td>
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<tr>
<td>Protects synapses (preclin. <em>in vivo</em> PoC)</td>
<td>Neutralizes toxins <em>ex vivo</em></td>
</tr>
<tr>
<td>Therapeutic (i.m. admin.)</td>
<td>Diagnostic and/or therapeutic (i.v. admin.)</td>
</tr>
<tr>
<td>GMP drug substance CoG ~€6 per dose</td>
<td>Cost of goods not determined</td>
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0.1-0.2% reaches brain tissue

Therapeutic antibodies engage the toxins, not the plaques
ALZ-101 protects synapses from Aβ-induced damage

Chronic preventive treatment of a transgenic mouse (Swe/Lon):
- Synapse density +25%
- Plaque load unaffected

WHY IS THIS INTERESTING?
- Synapse dysfunction is caused by oligomers and occurs early in the disease
- Synaptic density (not plaque load) correlates with disease progression
- Indicates specific targeting of oligomers
No safety concerns so far

- Mice and Rabbits tested
- Three vaccinations of ALZ-101
- No negative visual (microscopic) or weight changes on vital organs examined in either mice or rabbits
Challenges for future Alzheimer’s disease immunotherapies

Clinical trial data highlights three important requirements for future therapies:

- **High persistent Ab levels**
  - Required for brain penetration (BBB)
  - Safety concerns (vascogenic edema)
  - mAb are expensive therapies

- **Specificity for the target**
  - Required for target engagement behind the BBB
  - Reduces safety concerns

- **Early intervention**
  - Early (presymptomatic) diagnosis not possible
  - Preventive treatment desirable, but problematic for expensive mAb therapies

A truly oligomer specific vaccine will have a competitive advantage.
The case for "oligomeric" \( \text{A}\beta_{42} \) in Alzheimer’s disease is very strong

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<th>Genetics (early onset AD)</th>
<th>• Increases ( \text{A}\beta_{42} ) production or oligomerization</th>
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| Post mortem (IHC)         | • No correlation between disease severity and plaques (quantitatively, spatially, or temporally)  
                           | • Synapse density correlates with disease severity |
| \textit{In vivo}          | • Synapse dysfunction, cognitive impairment, tau phosphorylation, impairs efflux transporters |
| \textit{Ex vivo}          | • Soluble extracts from brains have a multitude of toxic effects  
                           | • Impairs LTP in mouse brain slices |
| \textit{In vitro}        | • Has a multitude of toxic effects exceeding those for other forms of the same peptide |
| Biophysics                | • Conformation distinct from fibril structure (\( \beta \)-hairpin vs cross-\( \beta \))  
                           | • Soluble aggregates |
Thank you

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