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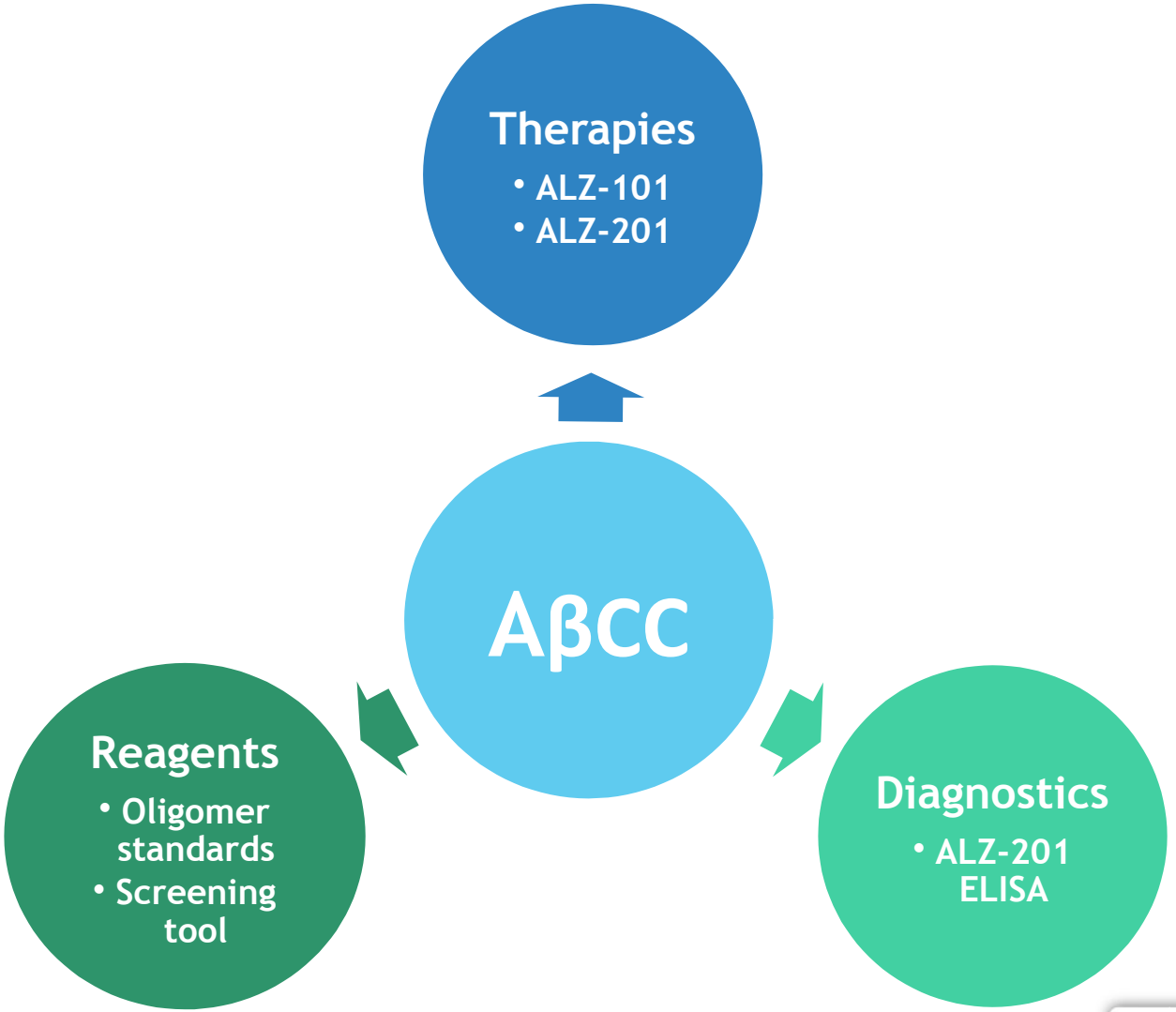
Disease-Modifying Therapy and Diagnostics for Alzheimer's Disease

Oct 2016

Value proposition: Unique *true* targeting of disease-driving Aß "oligomers" (and more…)



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Past, present and future

2007-2008

Research project

GÖTEBORGS UNIVERSITET

2009-2015

Discovery phase and start of preclinical development

GU Ventures
HOLDINGBOLAGET VID GÖTEBORGS UNIVERSITET

2016-2017

Preclinical phase, vaccine ALZ-101

AKTIETORGET

2018 -

Clinical phase, vaccine ALZ-101

Partner and/or capital needed

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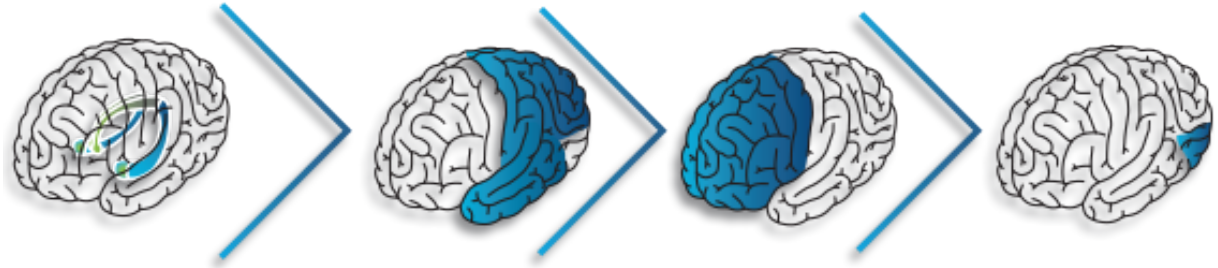
Alzheimer's disease: A progressive neurodegenerative disorder



Mild Cognitive Impairment	Mild Alzheimer's	Moderate Alzheimer's	Severe Alzheimer's
Duration: 7 years	Duration: 2 years	Duration: 2 years	Duration: 3 years
Disease begins in Medial Temporal Lobe	Disease spreads to Lateral Temporal & Parietal Lobes	Disease spreads to Frontal Lobe	Disease spreads to Occipital Lobe
Symptoms: Short-term memory loss	Symptoms include: Reading problems, Poor object recognition, Poor direction sense	Symptoms include: Poor judgment, Implusivity, Short attention	Symptoms include: Visual problems

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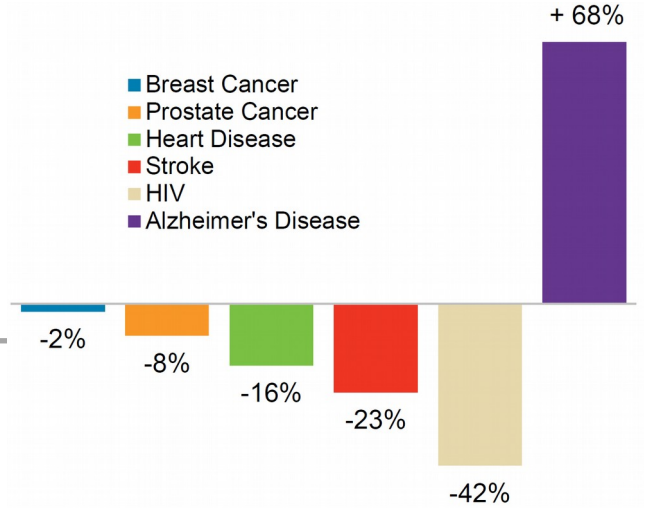
The burden of Alzheimer's disease

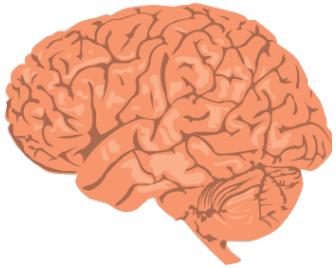
1 in 3 seniors (65+) dies of (or with) dementia

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



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

Dementia care (80% Alzheimer's): $604 billion world wide



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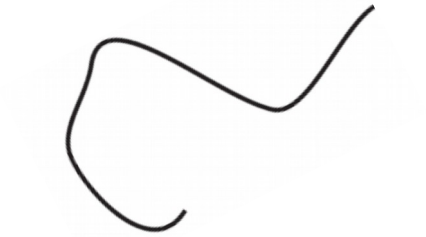
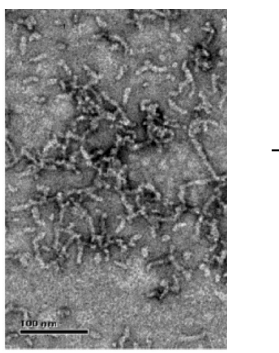
Aggregation of a peptide ($A\beta_{42}$) leads to synapse dysfunction and cell death

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



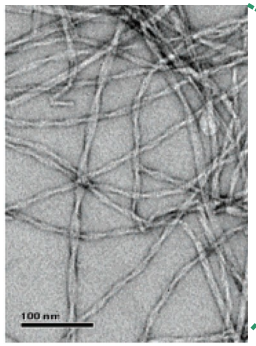
$A\beta_{42}$

Current consensus: The oligomer species is the ”smoking gun”

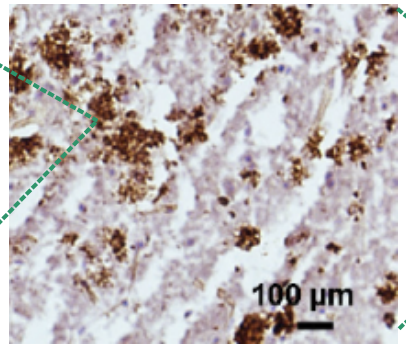


Oligomers

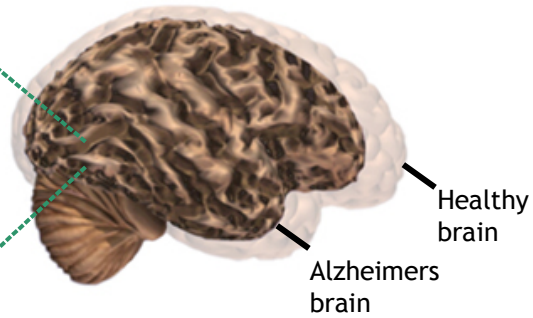
Toxic



Fibrils



Plaques



Brain shrinkage as nerve cells die

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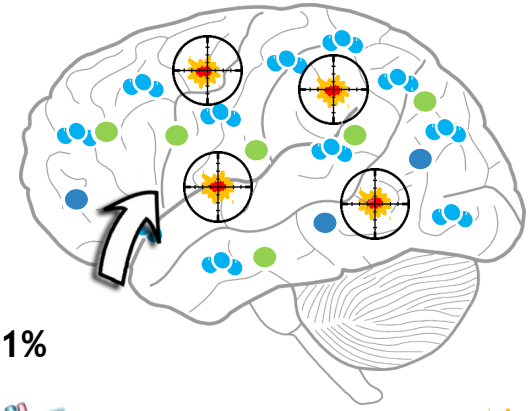
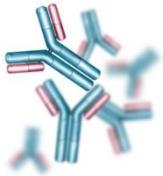
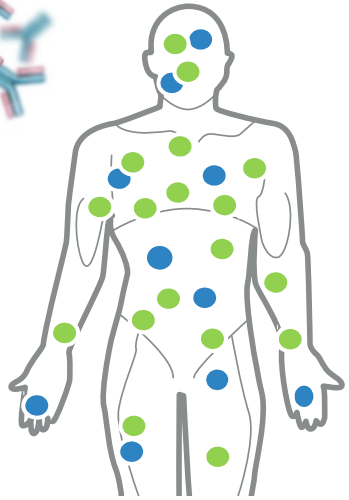
Challenge: Not all forms of Aß are toxic, and the target is behind the BBB!

Limited target engagement will reduce efficacy



0.1%





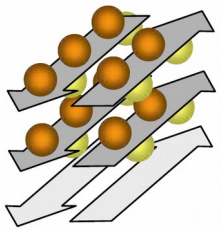
"The apparent clinical benefit observed in PRIME could also be explained by the binding of aducanumab to **oligomeric forms of Aß…**"

Toxic oligomers of Aβ

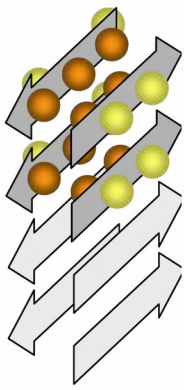
Stable insoluble aggregates Aβ fibrils

Aβ42 monomers

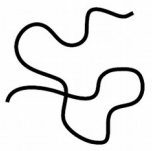
Aβ40 monomers



B-hairpin



cross-ß



unstructured

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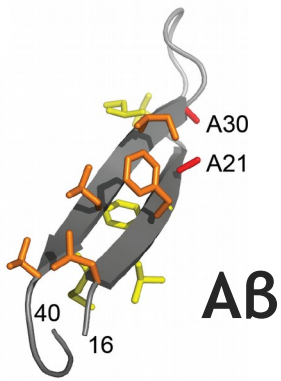
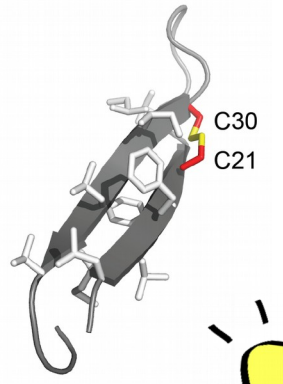
Alzinova's ABCC technology provides stable toxins ("oligomers") for drug development



AB

Conformational restriction



ABCC

Problem: Low amounts of unstable toxins

Solution: High amounts of stable toxins

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

- ✓ Well defined & homogeneous
- ✓ High reproducibility
- ✓ Unprecedented stability / non-fibrillogenic (never form fibrils)
- ✓ Physiological conditions

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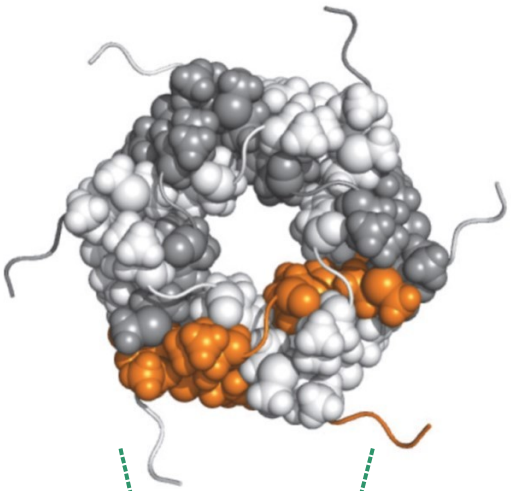
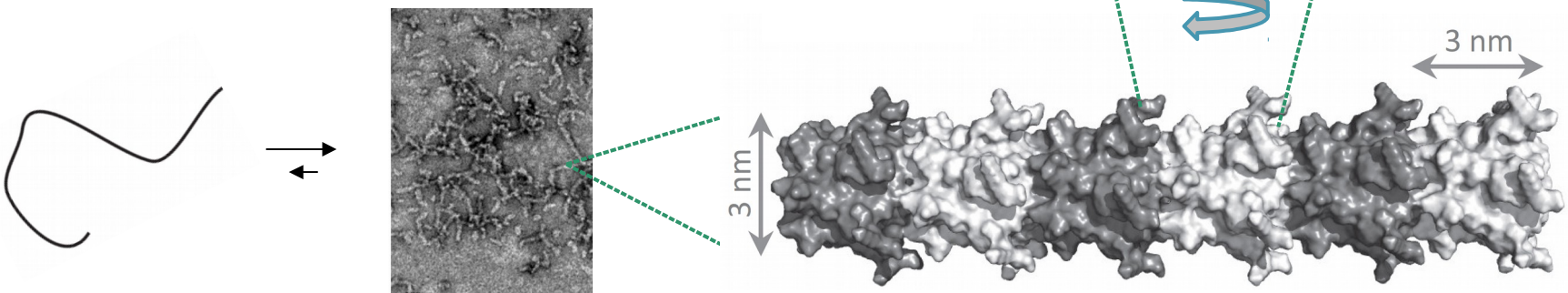
Alzinova's AβCC technology as a tool to understand structure-activity relationships

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)





$A\beta_{42}CC$ monomer

toxic oligomers

target

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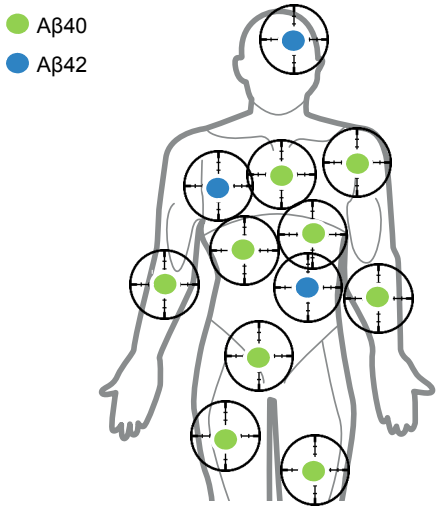
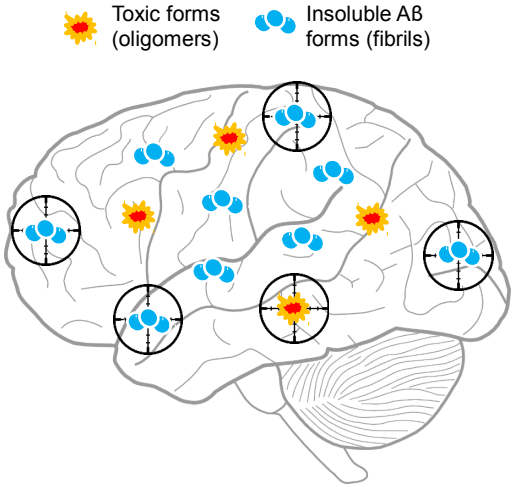
A snapshot of the competition

First generation



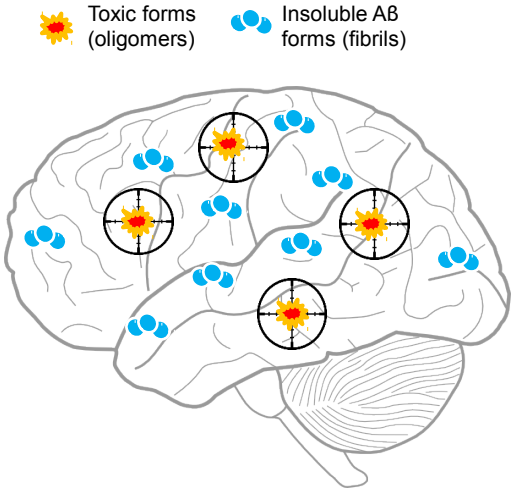
- Side effects (ARIA:s)
- No clinical benefit

Second generation



- Side effects (ARIA:s)
- Signs of clinical benefit

Truly specific targeting



- Not yet evaluated

ALZ-101

ALZ-201

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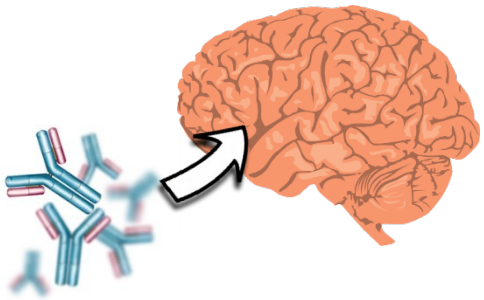
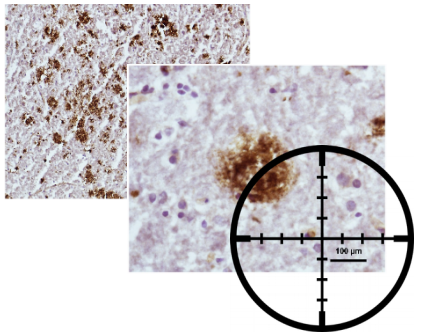
Alzinova's products ALZ-101 and ALZ-201 neutralize synaptotoxic Aß

High-precision therapeutic antibodies target oligomers specifically

ALZ-101	ALZ-201
Peptide-based active vaccine (with Alum)	Monoclonal Ab (IgG)
Protects synapses (preclin. *in vivo* PoC)	Neutralizes toxins *ex vivo*
Therapeutic (i.m. admin.)	Diagnostic and/or therapeutic (i.v. admin.)
GMP drug substance CoG ~€6 per dose	Cost of goods not determined



0.1-0.2% reaches brain tissue



Therapeutic antibodies engage the toxins, not the plaques

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ALZ-101 protects synapses

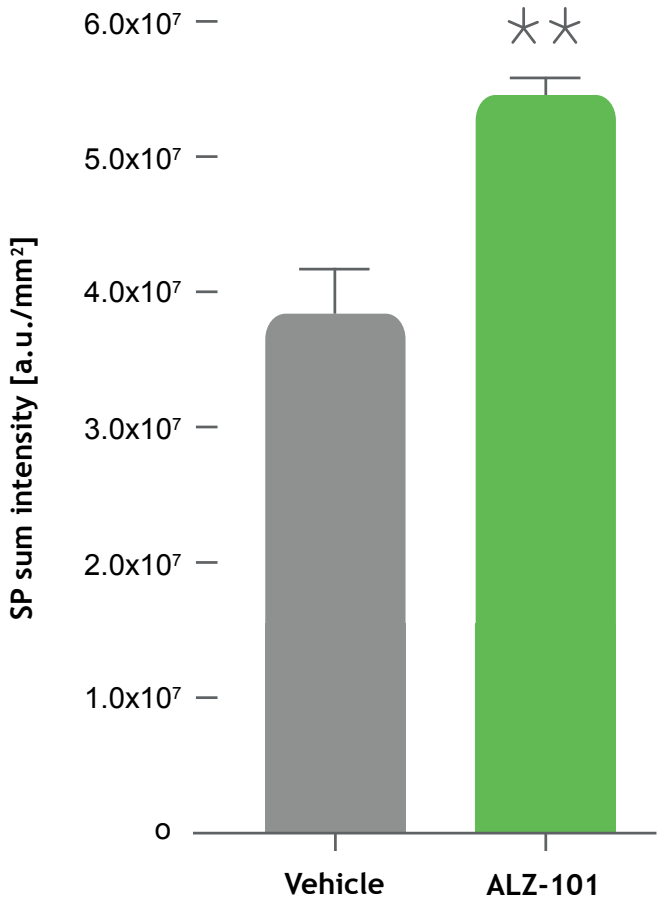
ALZ-101 protects synapses from Aß-induced damage

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



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No safety concerns so far

- Mice and Rabbits tested
- Three vaccinations of ALZ-101
- No negative visual (microscophic) 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 desireable, but problematic for expensive mAb therapies

A truly oligomer specific vaccine will have a competitive advantage

The case for "oligomeric" $A\beta_{42}$ in Alzheimer's disease is very strong

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

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Thank you

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