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Process of Amyloid Aggregation: What is Toxic?

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Overview

- There are at least two general classes of amyloid oligomers that can be distinguished by conformation-dependent antibodies: prefibrillar oligomers and fibrillar oligomers.

- Both types of oligomers may be implicated in Alzheimer pathogenesis and serve as targets for therapeutic development.

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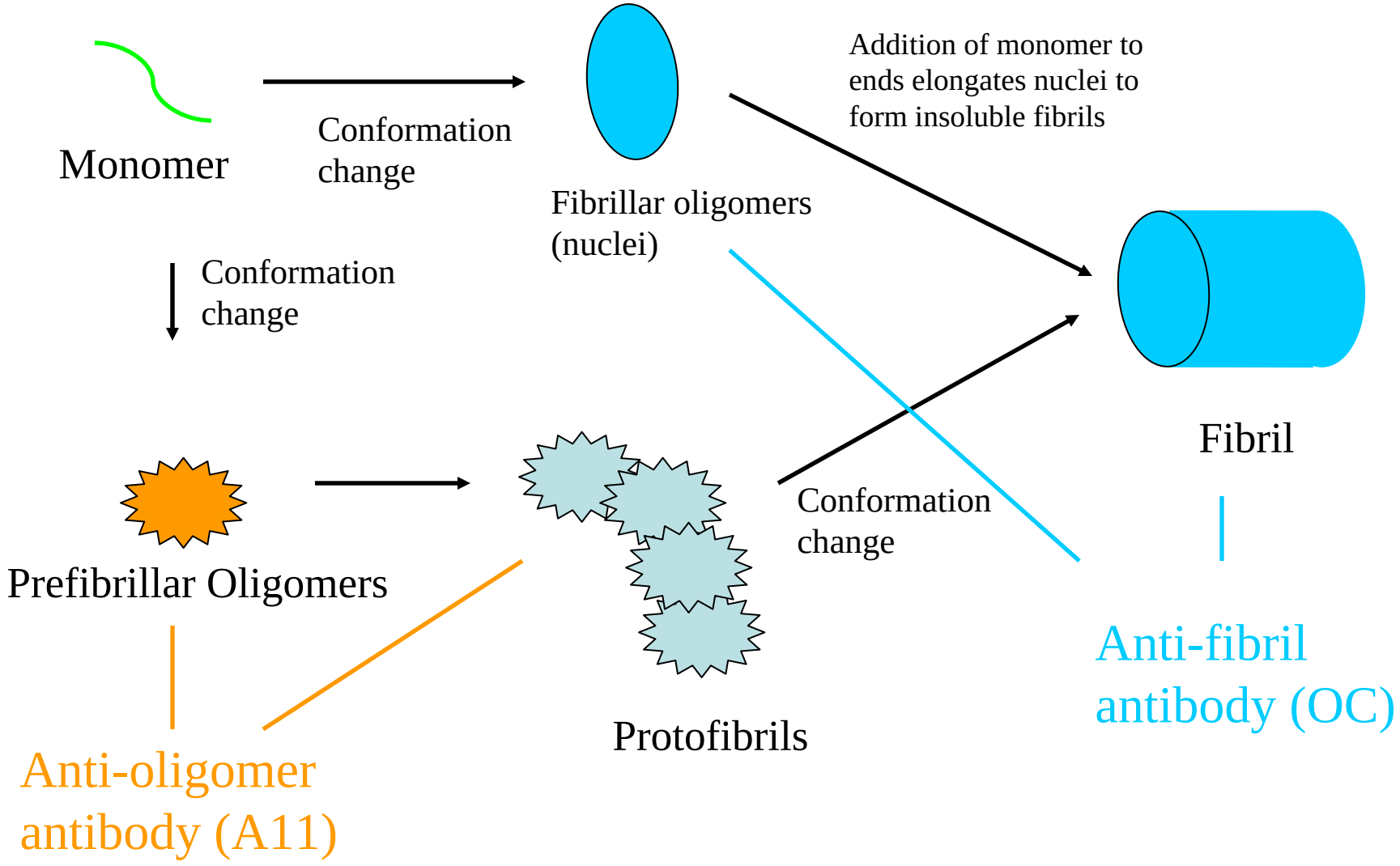
Alternative pathways and assembly states of amyloid



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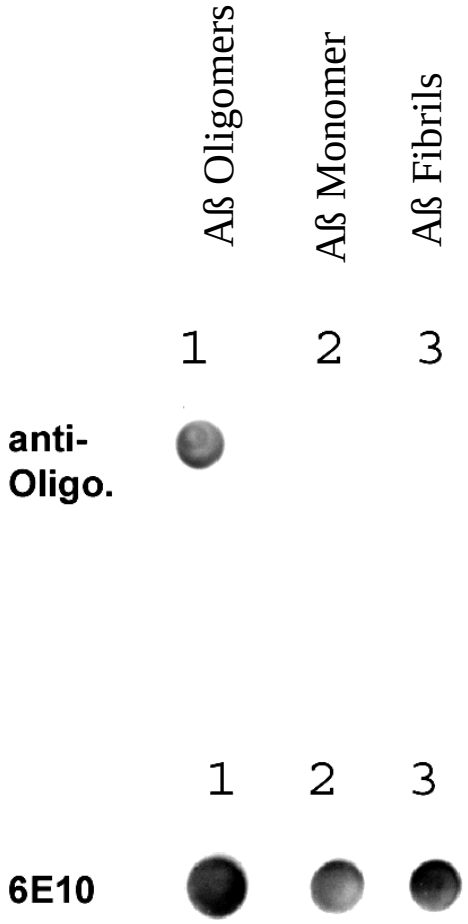
A11 anti-oligomer antibody recognizes a generic prefibrillar oligomer epitope

Dot blot



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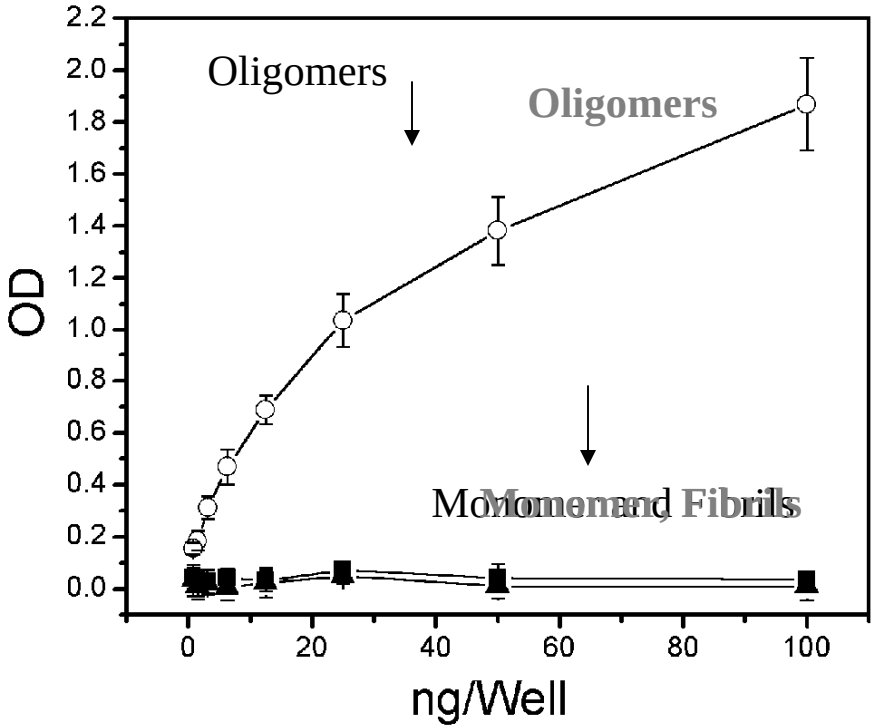

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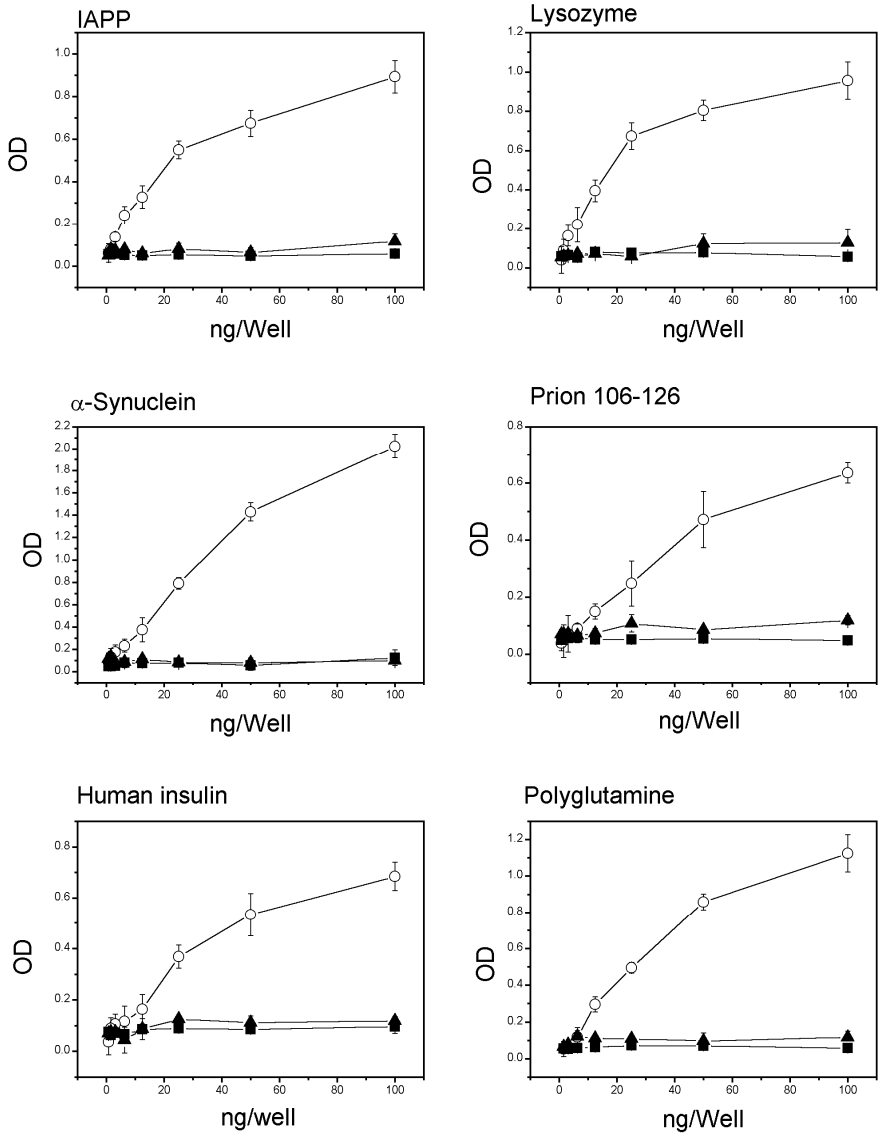

A11 Anti-Oligomer antibody recognizes soluble oligomers from other types of amyloids.

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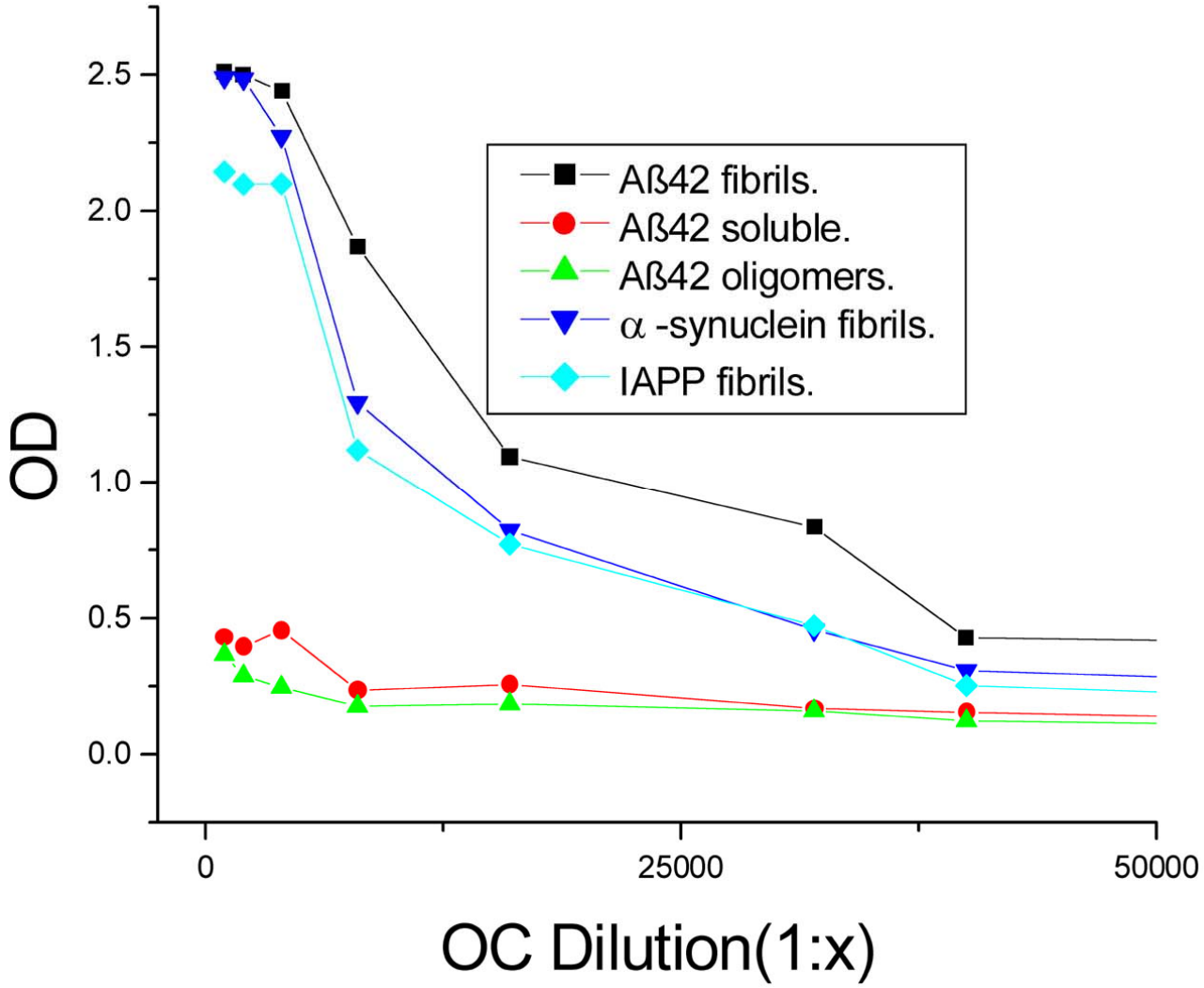
OC antibody recognizes a generic fibril-specific epitope.



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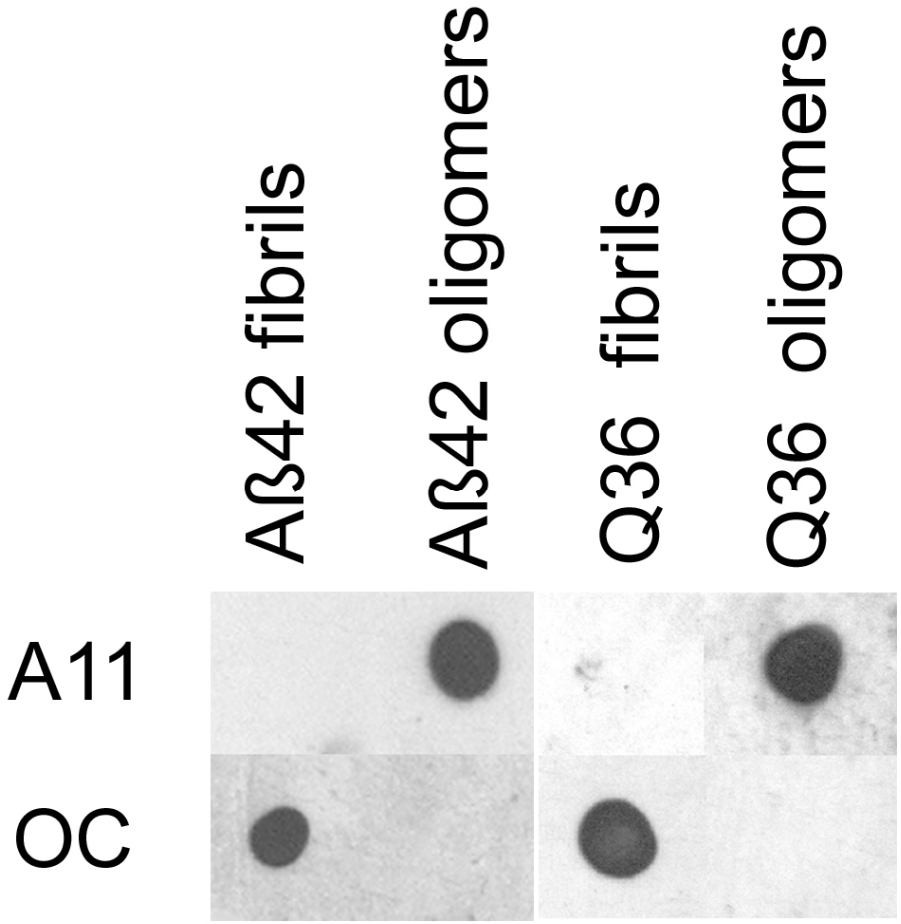
OC and A11 recognize distinct epitopes



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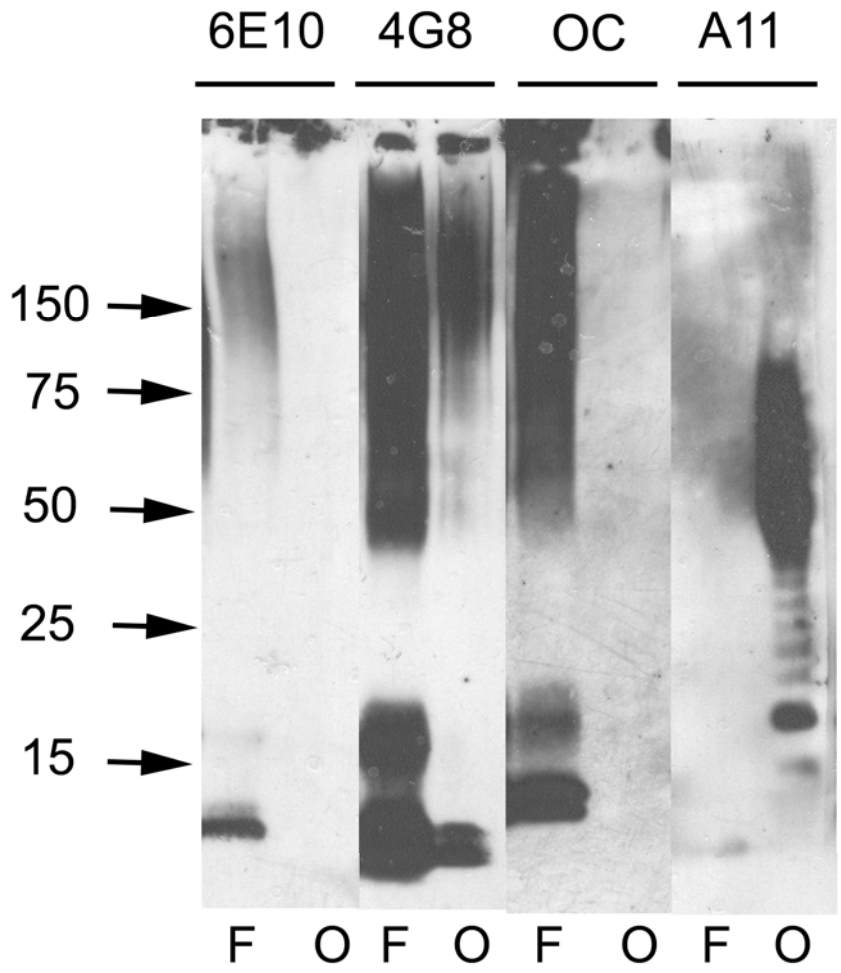
Size is not a reliable indicator of oligomer conformation.



F - Aß42 fibrils

O – Aß42 prefibrillar oligomers

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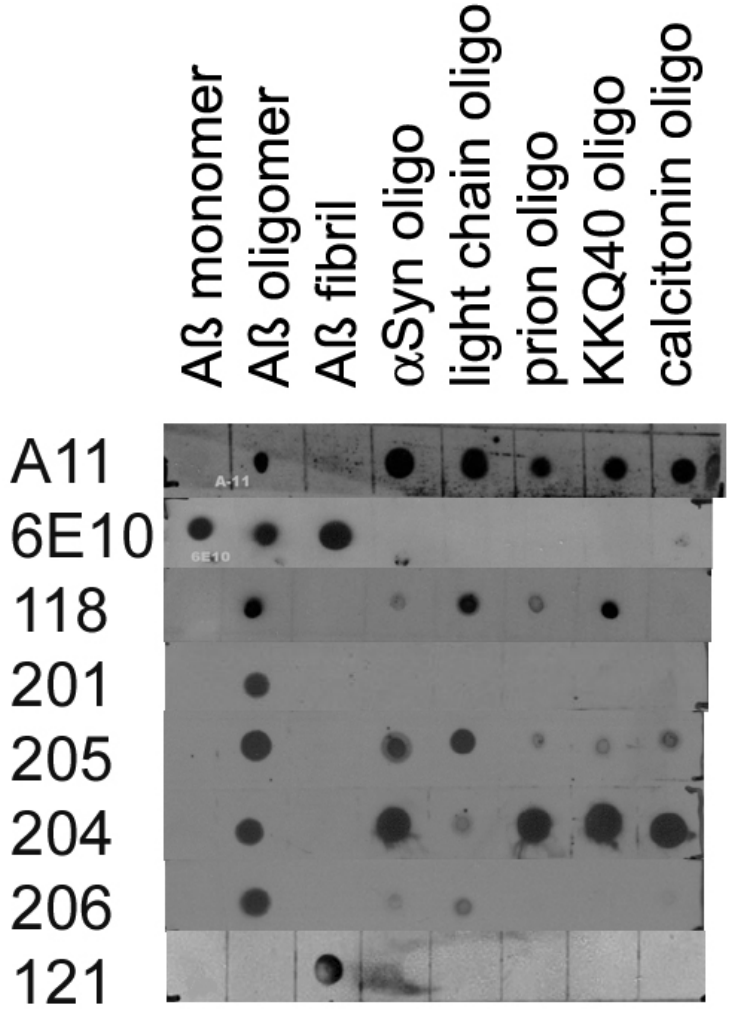
Conformation dependent monoclonal antibodies have distinct specificities.

118, 204, 206 and 206 recognize “generic” epitopes found on many types of oligomers.

201 is specific for Aß prefibrillar oligomers and 121 is specific for Aß fibrils.



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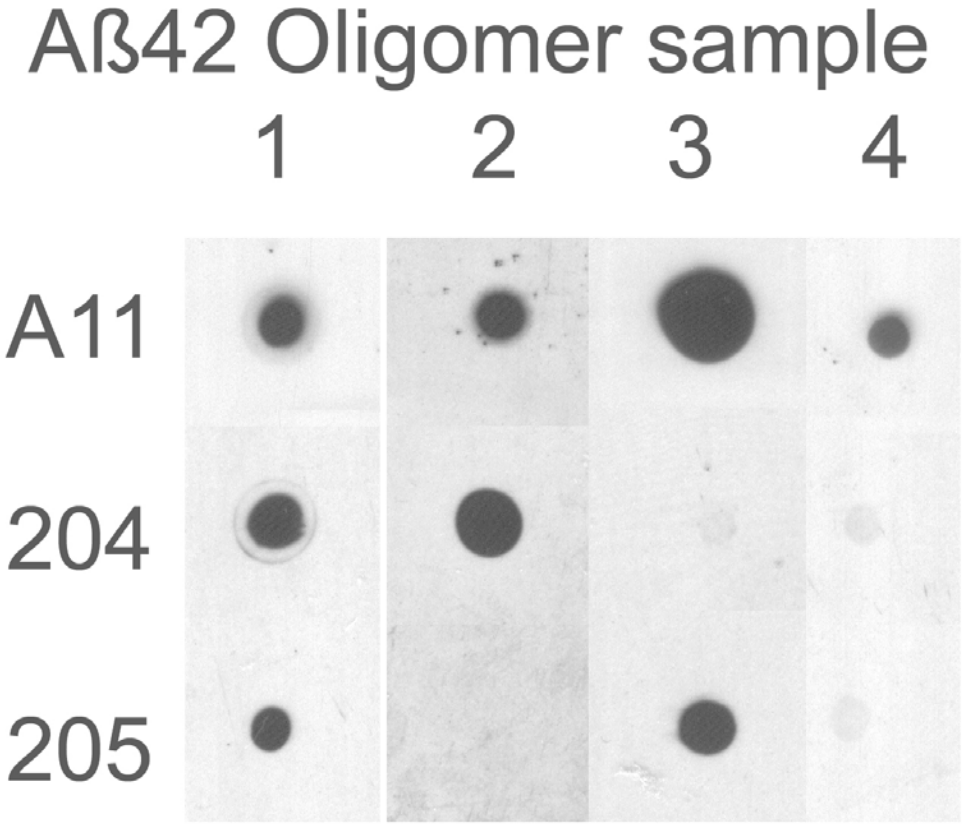
Conformation dependent monoclonals identify at least 3 distinct types of Aß 42 prefibrillar oligomers.



This immunological variation in Aß oligomer structure may be analogous to prion strain variation.

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Summary

- There are two structurally distinct classes of amyloid oligomers: Prefibrillar oligomers, and fibrillar oligomers.
- The two classes of oligomers differ in the generic arrangement of the peptide backbone and are independent of the specific amino acid sequence.
- Within theses classes of Aß prefibrillar oligomers and fibrils, there are distinct structural variants or “strains”.
- **Is this structural variation important for toxicity and pathogenesis?**

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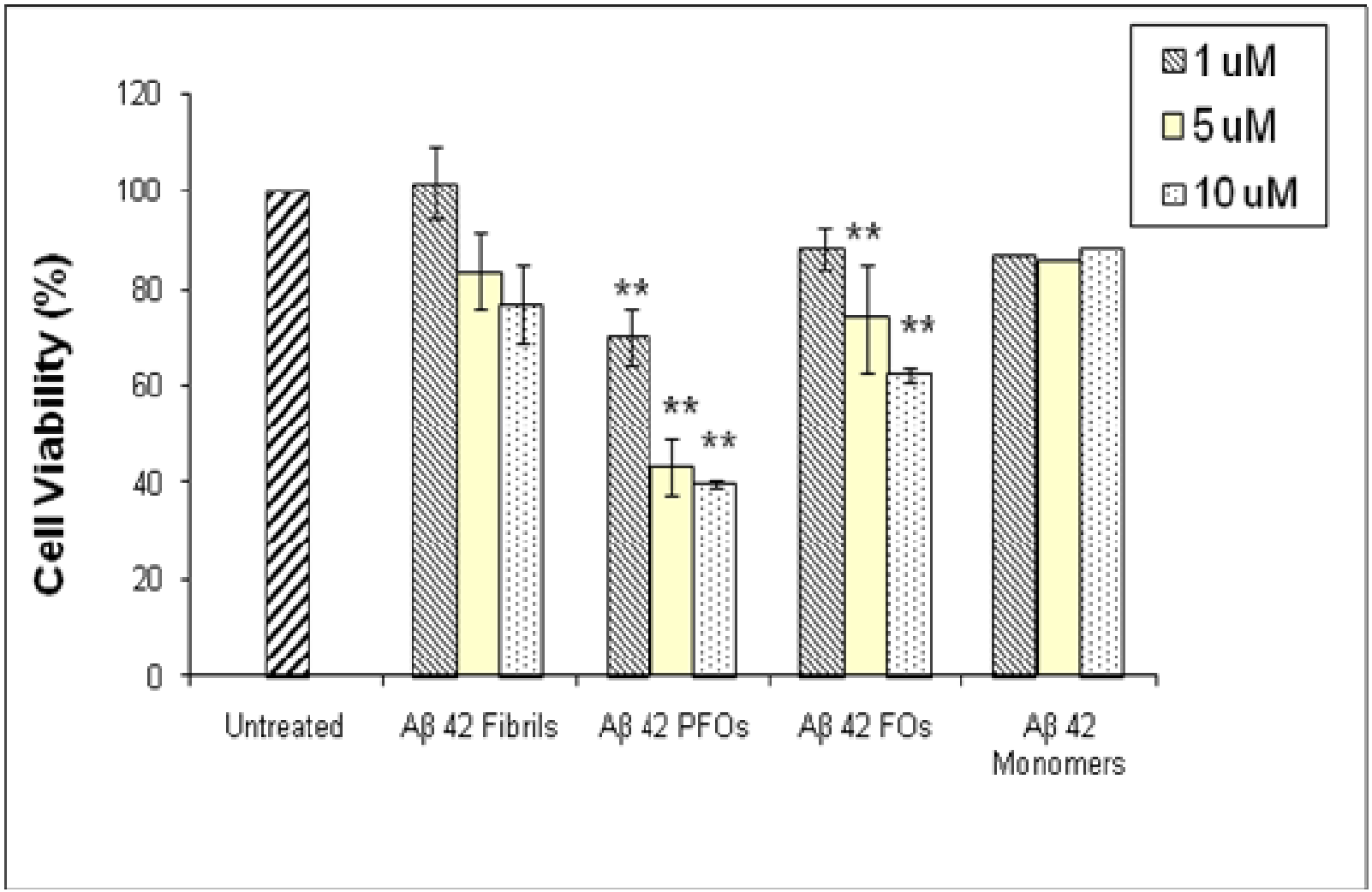
Both fibrillar and prefibrillar oligomers are toxic in vitro.



** P < .01

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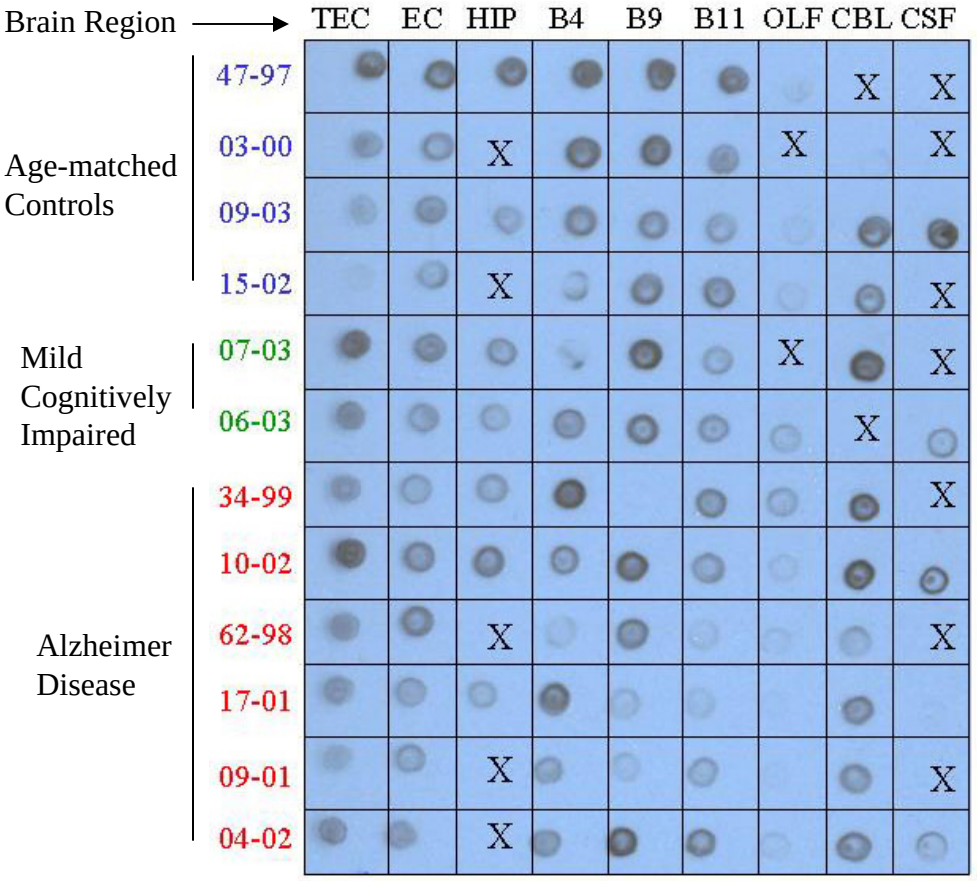
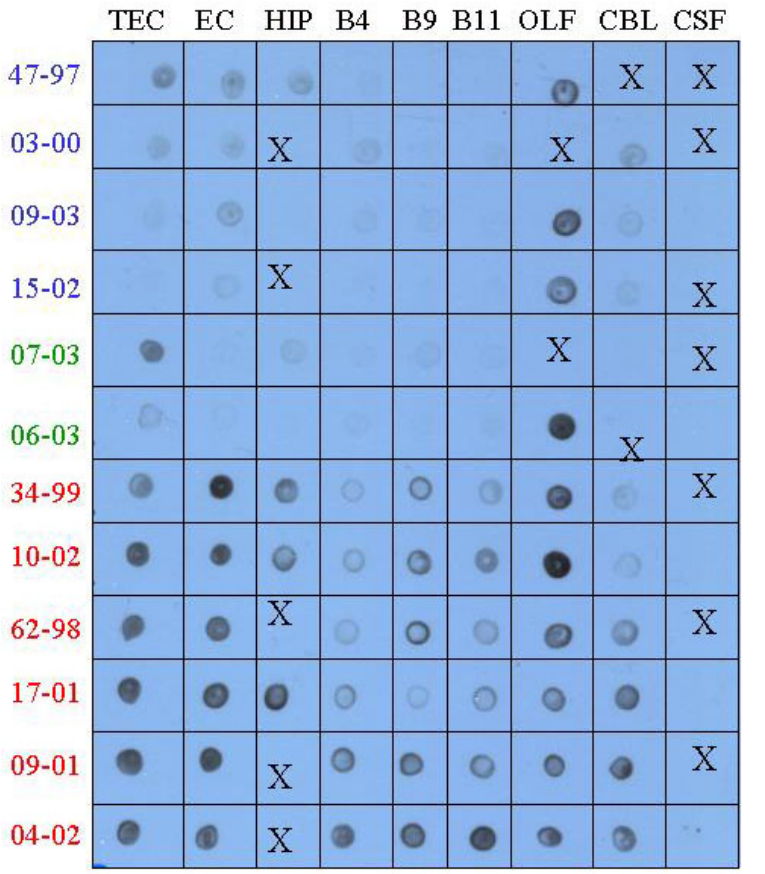
Fibrillar oligomers are elevated in AD brain

A11 (prefibrillar oligomers)



OC (fibrillar oligomers)



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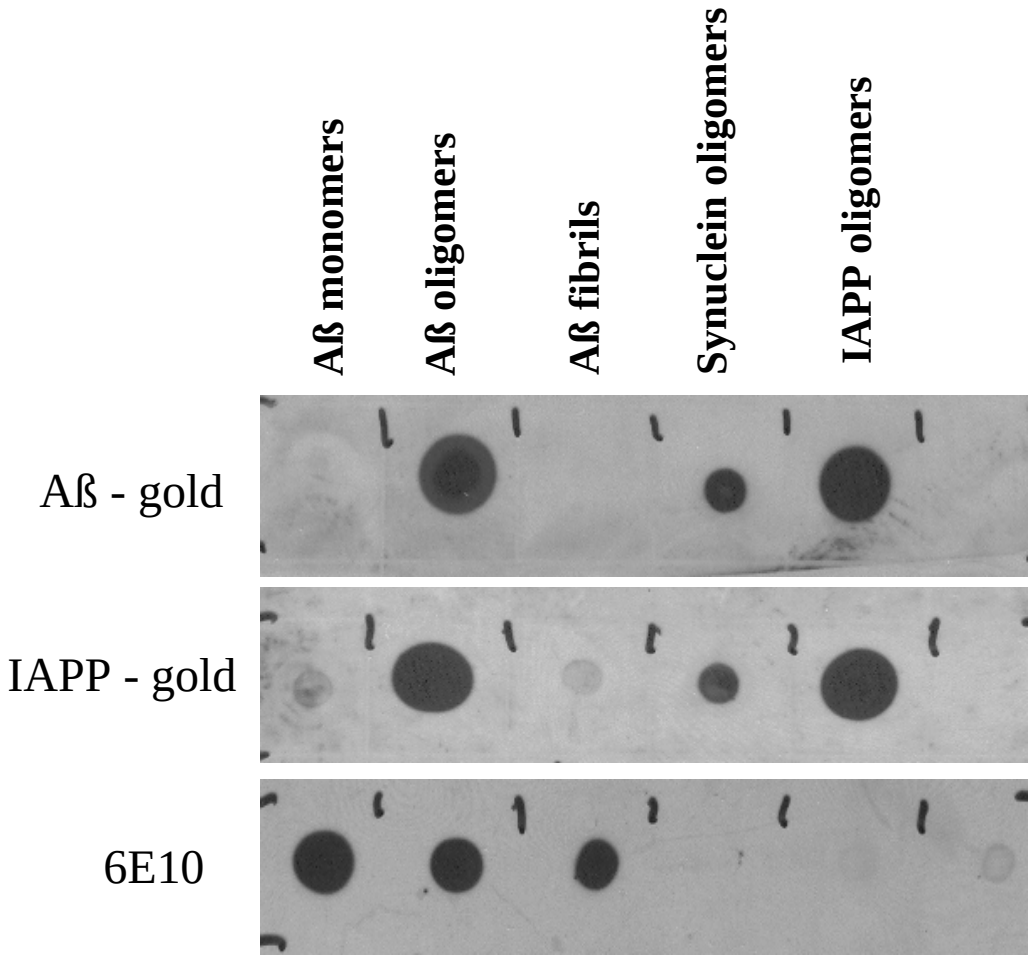
Other peptide sequences coupled to colloidal gold give the same prefibrillar oligomer specific immune response.



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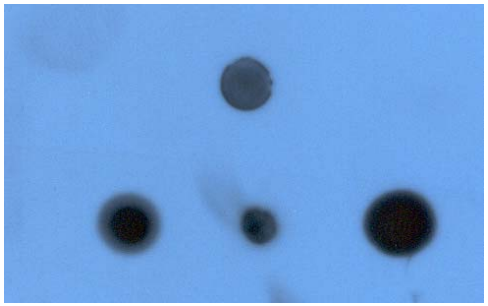
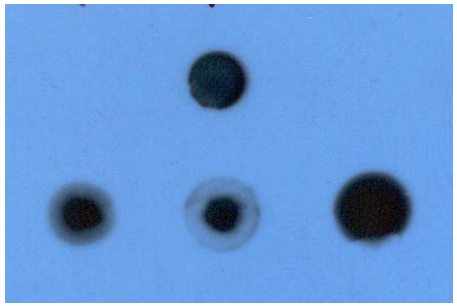
Immunization with a non-human random sequence antigen gives rise to the same oligomer-specific immune response.

Aß42 monomer	Aß42 Oligomers	Aß42 Fibrils
Calcitonin Oligo.	Light Chain Oligo.	KKQ40KK Oligo

Aß prefibrillar Antigen1:2000





Random sequence Antigen 1:1000

Pre-immune 1:1000

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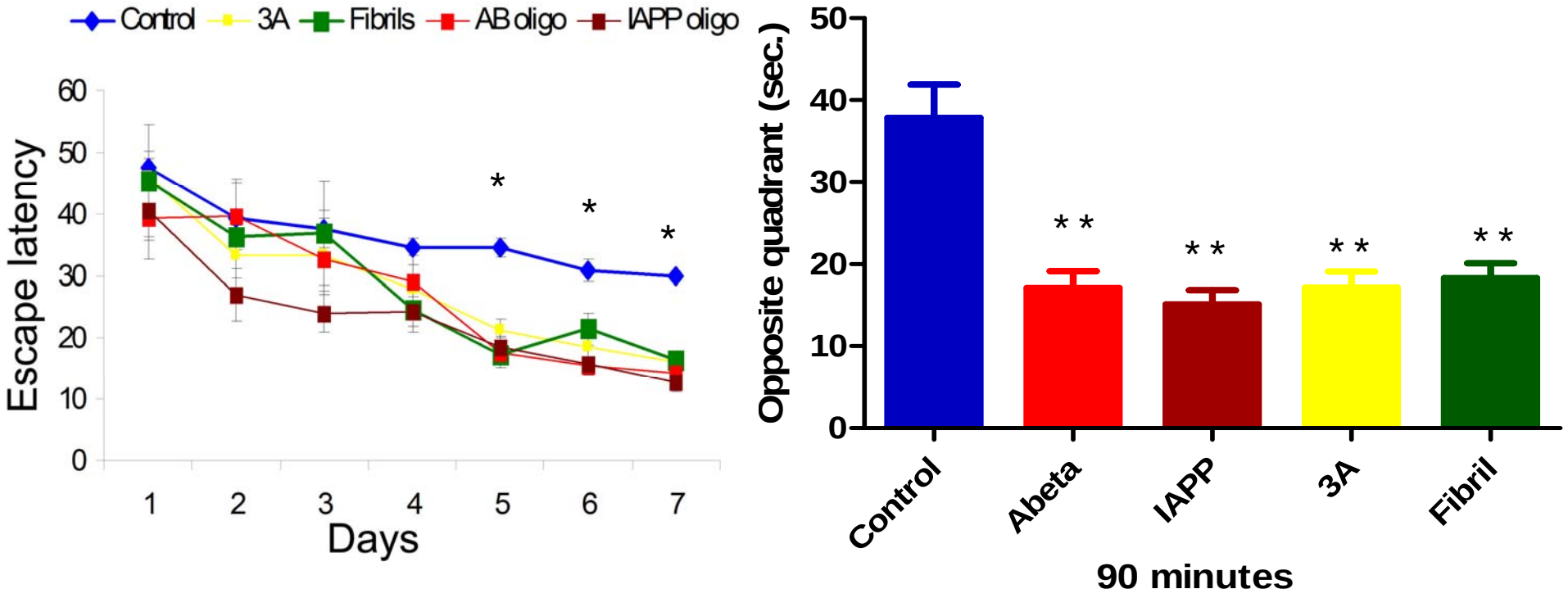
Immunization against fibrils or prefibrillar oligomers is equally effective in preventing cognitive decline in Tg2576



* P < 0.05; ** P < 0.001

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Conclusions

- There are two fundamental classes of amyloid oligomers: Prefibrillar and fibrillar oligomers.
- Within these two classes, structural variants exist that can be distinguished by monoclonal antibodies.
- Both prefibrillar and fibrillar oligomers are toxic in vitro.
- Fibrillar oligomers are elevated in Alzheimer's disease.
- Vaccination against prefibrillar oligomers and fibrils is equally effective in preventing cognitive dysfunction.
- A random peptide sequence prefibrillar oligomer antigen gives rise to the same protective immune response as Aß, suggesting that it may be an effective therapeutic without autoinflammatory immune consequences.

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