Protein Misfolding: Therapeutic Implications

Opportunities for Therapeutic and Diagnostic Development for Degenerative Diseases

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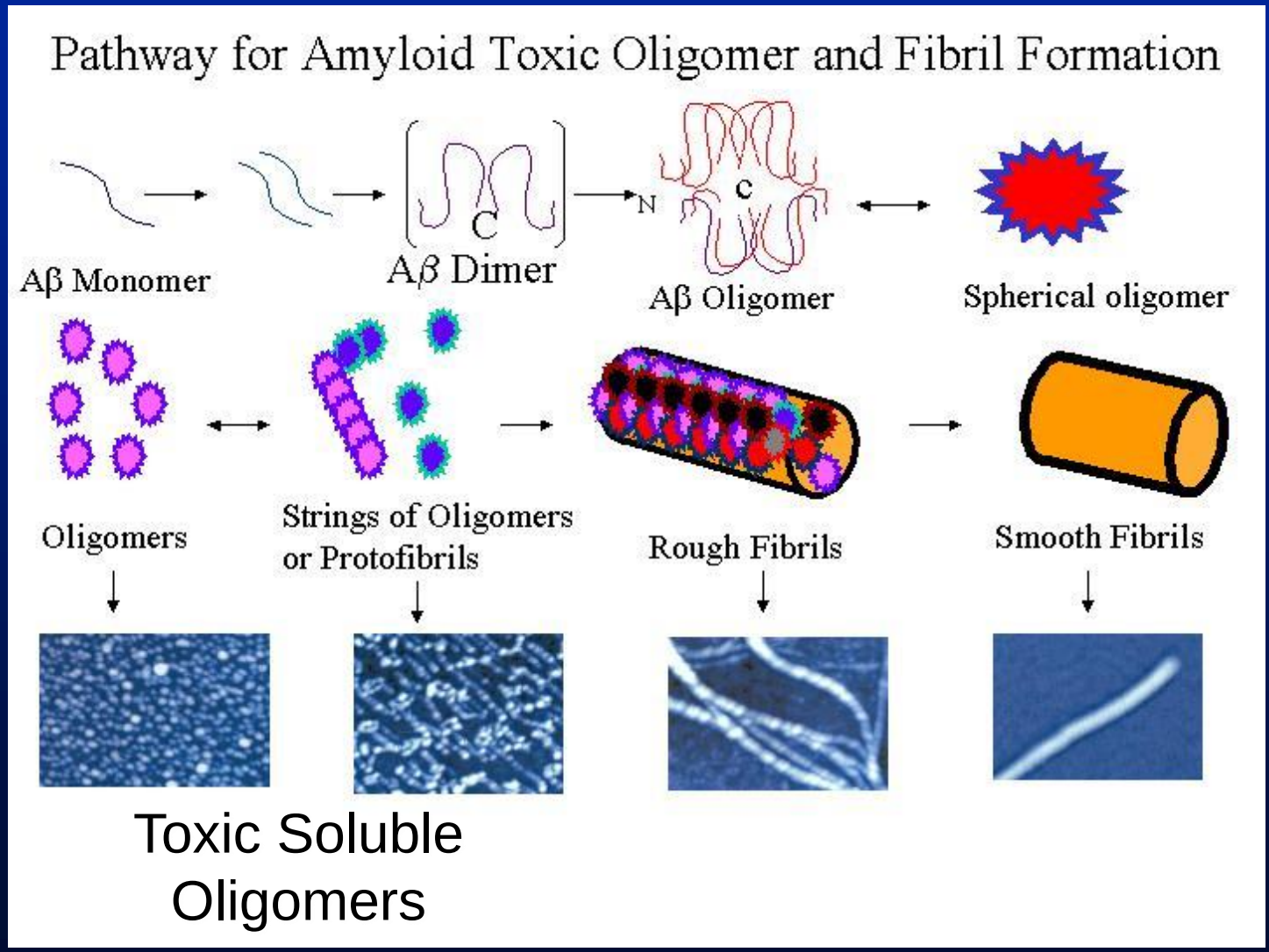
Overview

- Conformation-dependent antibodies specifically recognize toxic soluble amyloid oligomers and distinguish them from natively folded protein, denatured monomer and amyloid fibrils.
- This provides a means of specifically targeting soluble amyloid oligomers through immunization.
- Immunization may be an effective treatment for AD and other degenerative diseases.

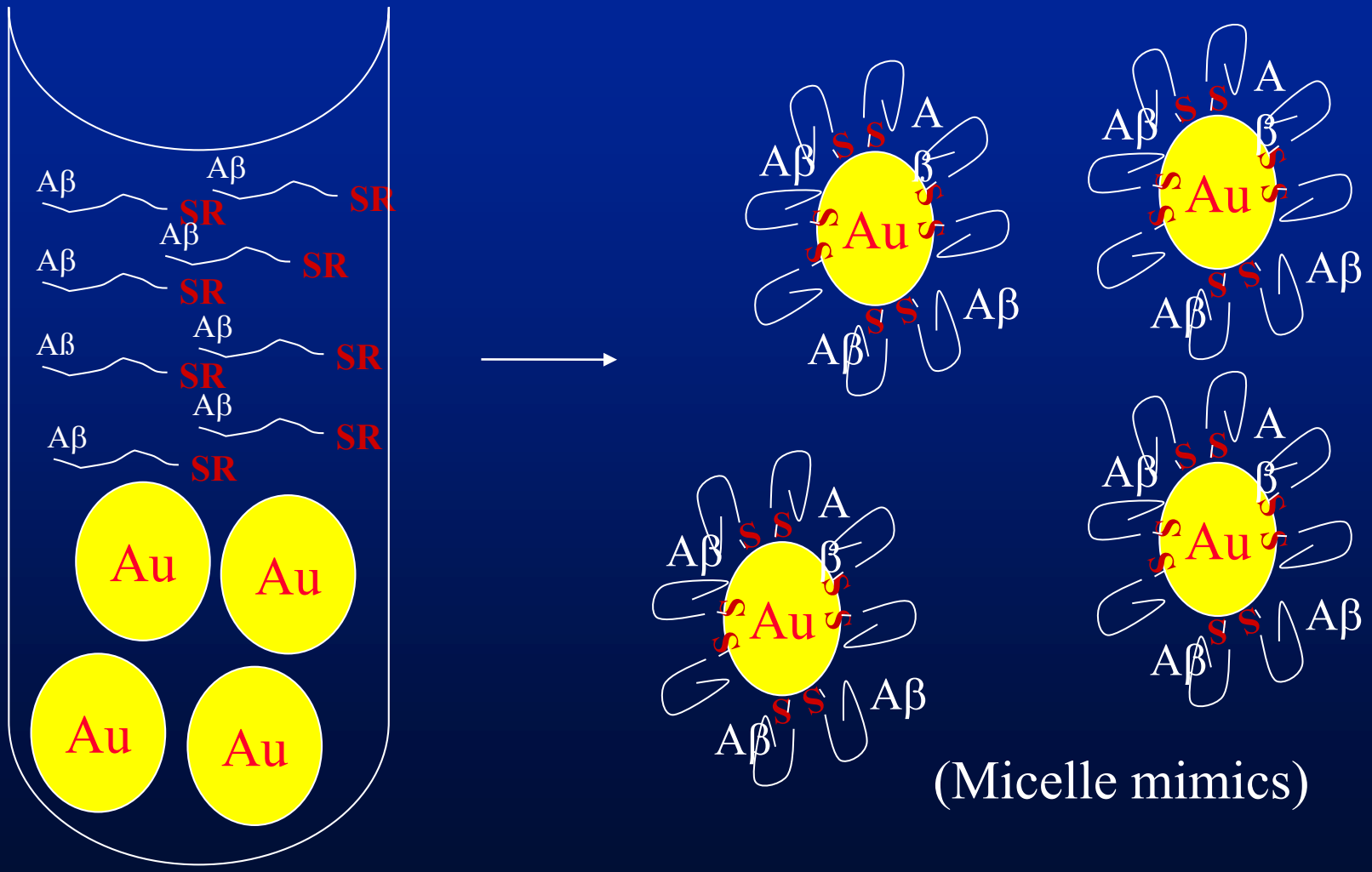
Soluble amyloid oligomers are suspected to be a causative agent in a broad range of degenerative diseases disease.

- **Alzheimer's disease**
- Type II diabetes
- Parkinson's disease
- Huntington's disease
- Prion (Mad Cow's) disease
- Serum amyloidosis
- Familial Amyloid Polyneuropathy
- Macula Degeneration.
- Amyltropic Lateral Sclerosis
- Inclusion Body Myositis
- Idiopathic Cardiomyopathy

Soluble Amyloid Oligomers are a Common Intermediate in Amyloid Fibril Formation.

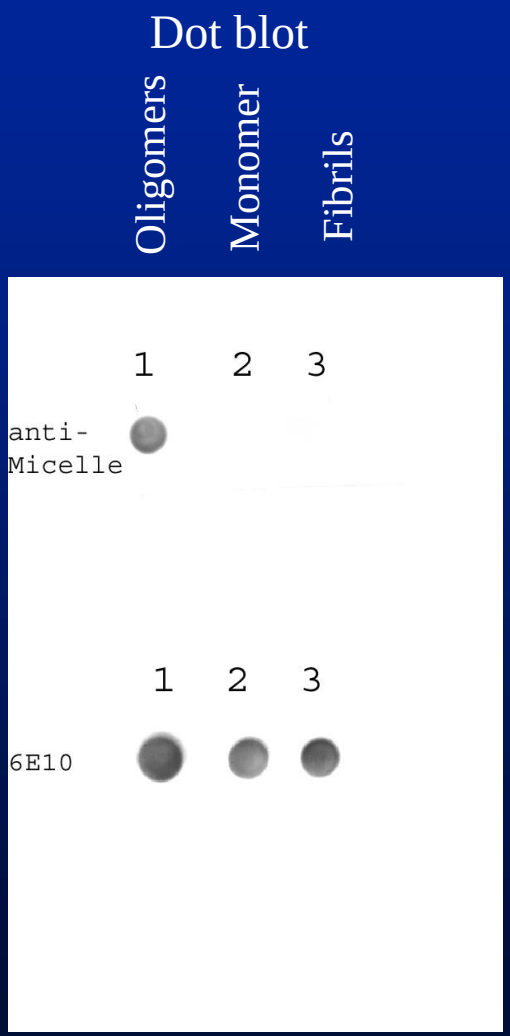


Antigen Preparation



Anti-Oligomer antibody specificity

Dot blot



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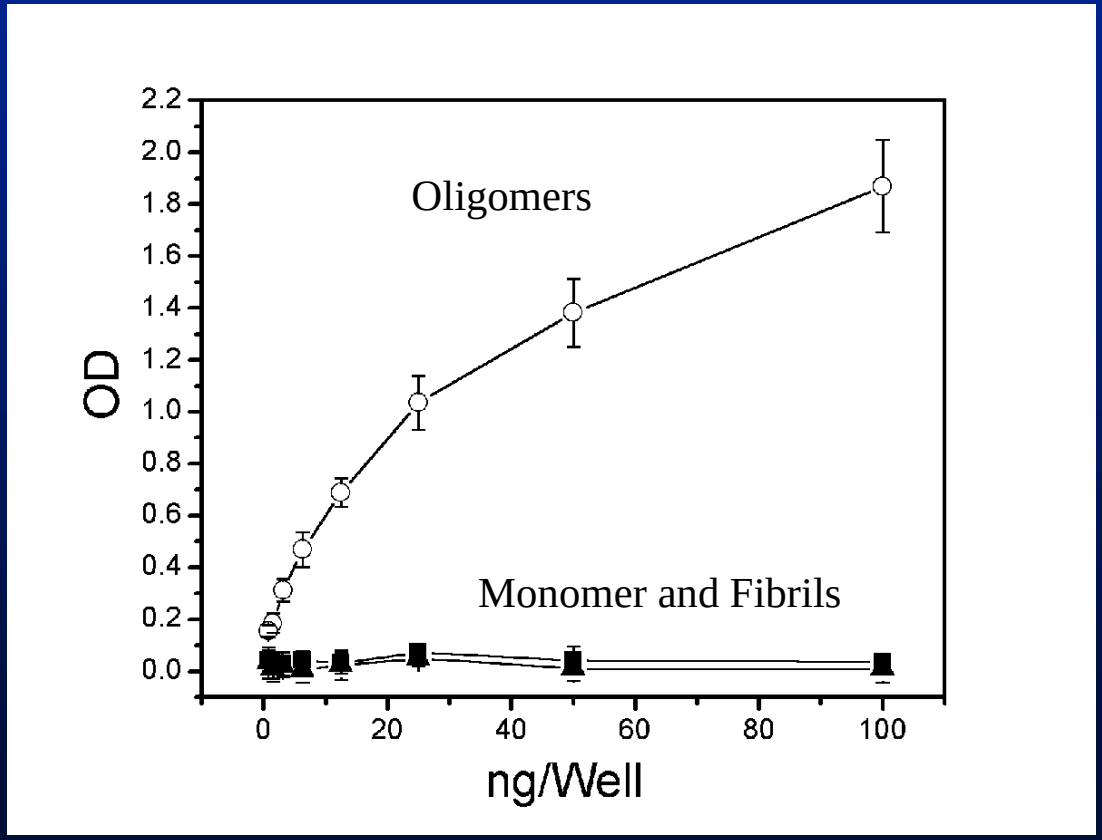
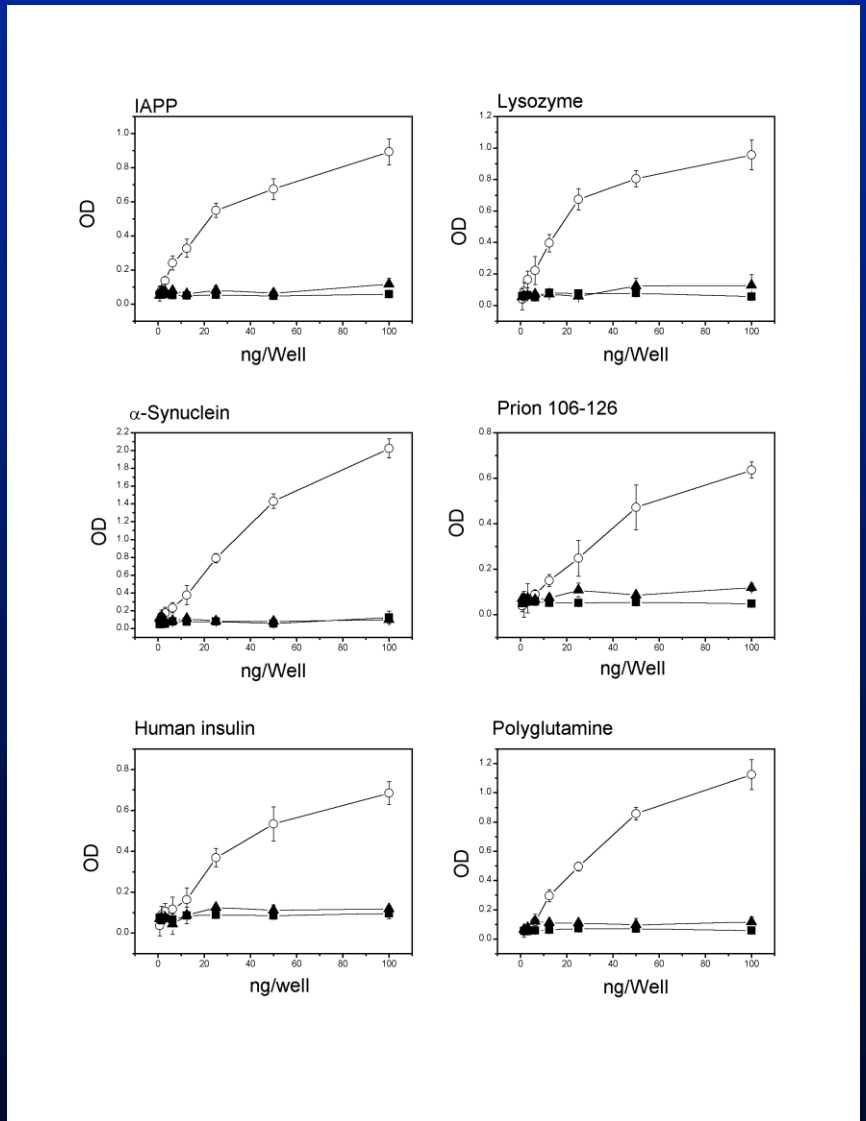


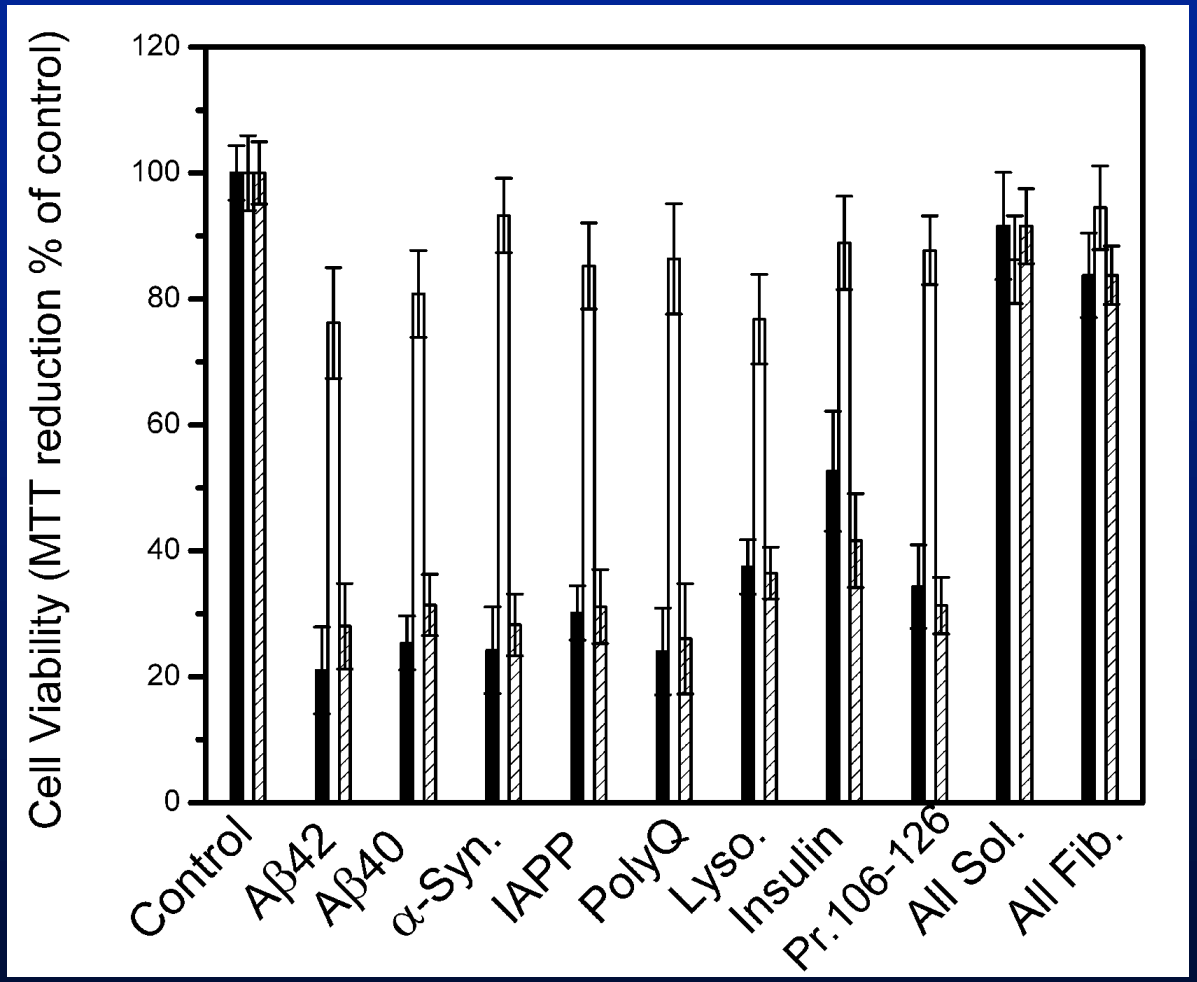
Characteristics of immune response to Aß-gold oligomer mimics.

- The immune response is specific. No immunoreactivity against "normal" sequence dependent Aß epitopes after 12 injections.
- The immune response is long lasting: Titer does not drop significantly within 6 months after vaccination.
- Adjuvant is not required for high titer immune response.

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



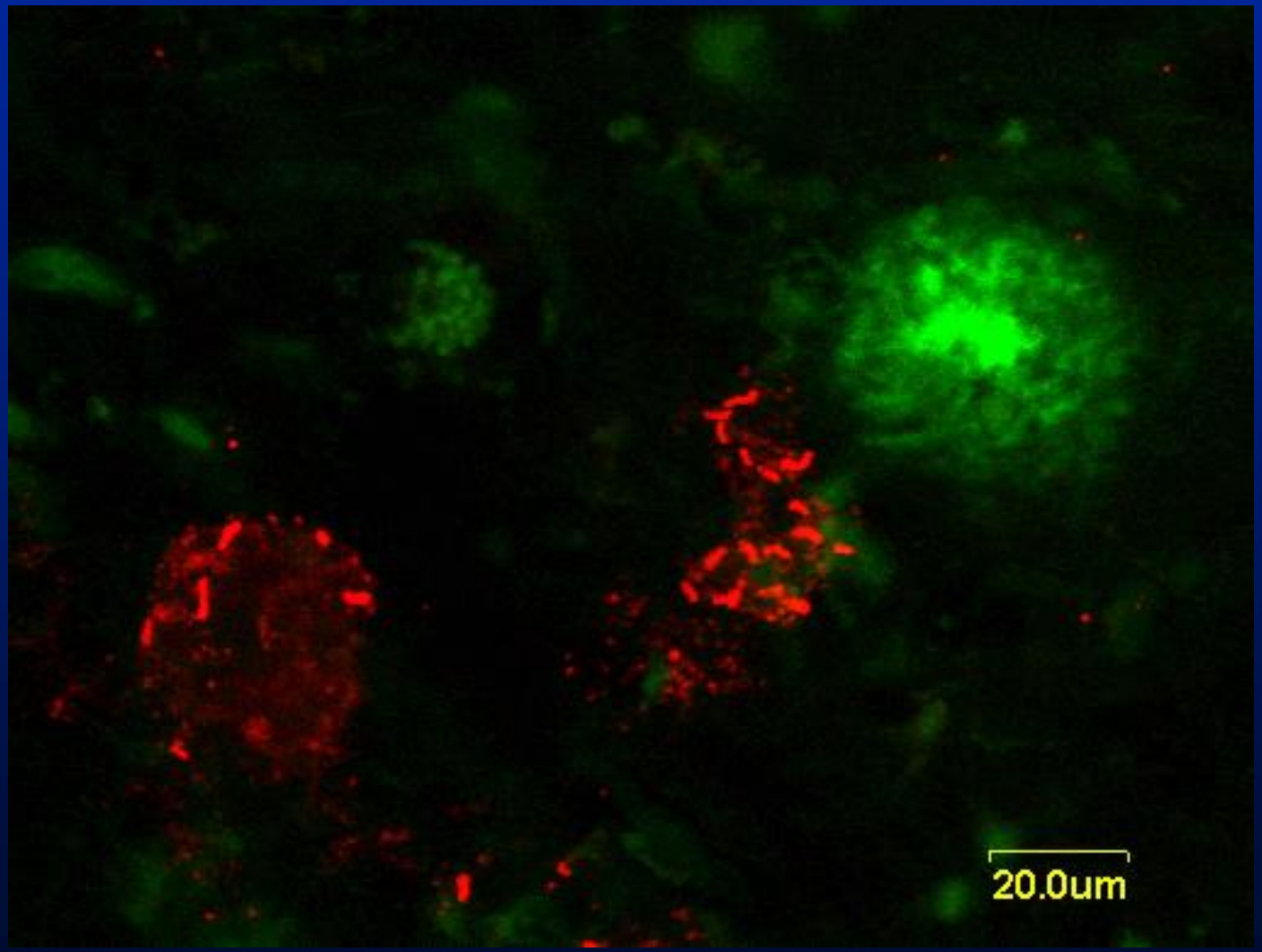
Anti-Oligomer neutralizes the toxicity of all types of amyloid oligomers.



Summary

- Immunization with a molecular mimic of Aß micelles produces a polyclonal antibody (Anti-Oligomer), that is specific for the soluble, high molecular weight micellar oligomeric intermediate that is common to all amyloids tested.
- Anti-Oligomer does not recognize APP, soluble monomeric Aβ or fibrillar peptides.
- Anti-Oligomer neutralizes the toxicity of all types of oligomers.
- The fact that soluble amyloid oligomers have a common structure suggests that they share a common mechanism of toxicity and pathogenesis.

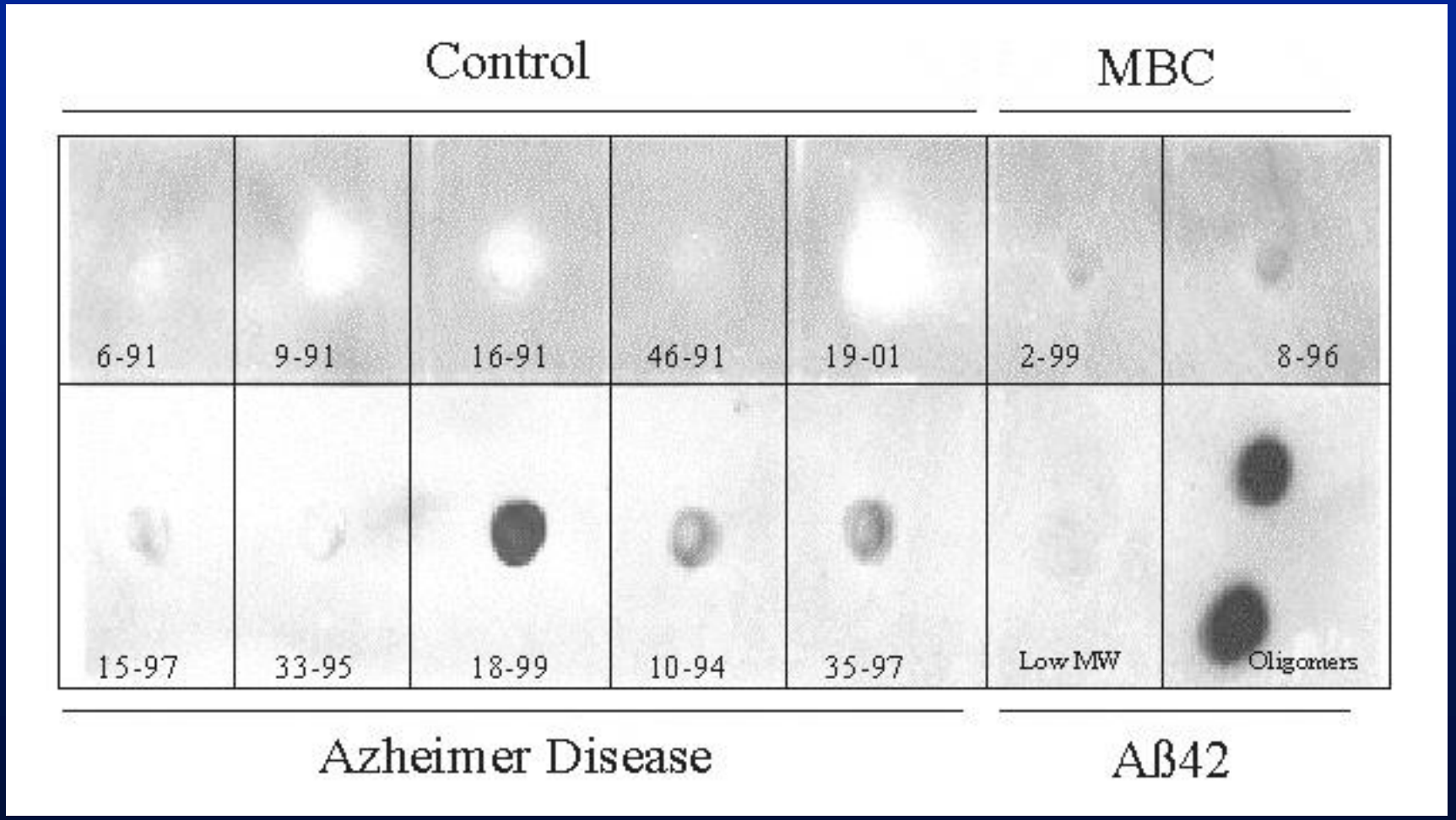
Anti-Oligomer immuno-reactivity in human AD brain.



Red: Anti-Oligomer

Green: Thio S staining of amyloid fibers

Oligomer levels in soluble extracts of human brain.



Summary

- Anti-Oligomer stains small, focal deposits in AD and Tg mouse brain that are distinct from Thio-S positive and diffuse plaques.
- Anti-Oligomer immunoreactivity is elevated in AD brain.
- Oligomeric Aß represents a small fraction of the total Aß.

Summary

• Vaccination with Aß-gold oligomer molecular mimics may be as effective as preventing amyloid accumulation as fibrillar Aß, but yet it may avoid the inflammatory complications associated with the first generation of Alzheimer's disease vaccine.

Potential Applications

- The Aß oligomer molecular mimic antigen may be useful for development of a specific vaccine that avoids autoimmune and inflammatory complications.
- Anti-Oligomer antibody may be useful as a diagnostic tool to determine the levels of the soluble oligomers in biological fluids.
- The anti-Oligomer antibody may be a valuable specific surrogate marker to evaluate the therapeutic effectiveness of agents that are designed to decrease or eliminate the neurotoxic amyloid.
- Anti-Oligomer antibody may be useful for high-throughput screening for drugs that inhibit oligomer formation.

Opportunities for Therapeutic and Diagnostic Development

		Diabetes Type II	Alzheimer's Disease	Mad Cow's Disease	Parkinson's Disease	Huntington's Disease	Serum amyloidosis
1.	Vaccine	X	X	X	X	X	X
2.	Drug Discovery	X	X	X	X	X	X
3.	Diagnostic	X	X	X	X	X	X

A single focus on the common toxic oligomers provides a large number of opportunities for product development.

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