

Prions are Prototypes: Other Neurodegenerative Diseases

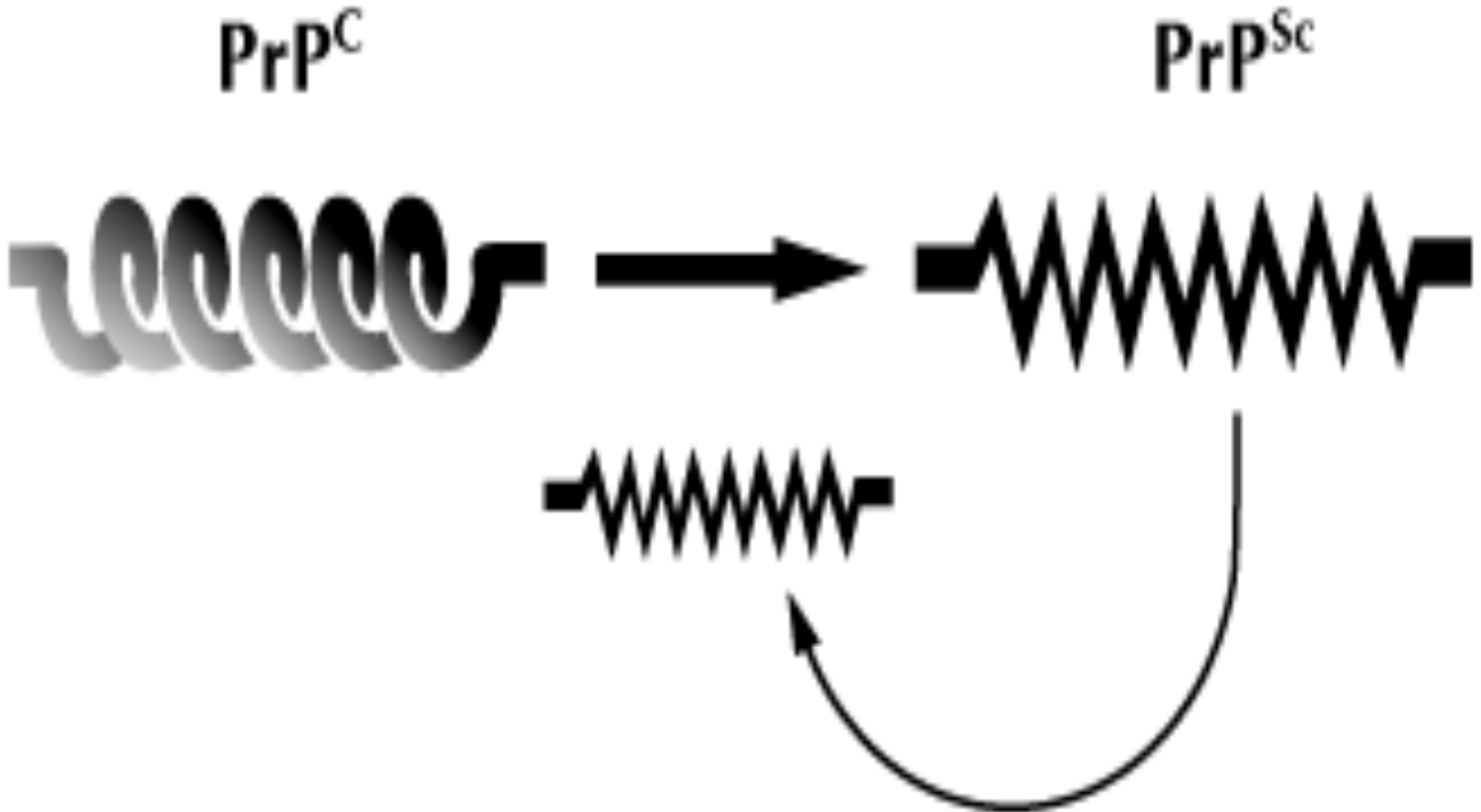
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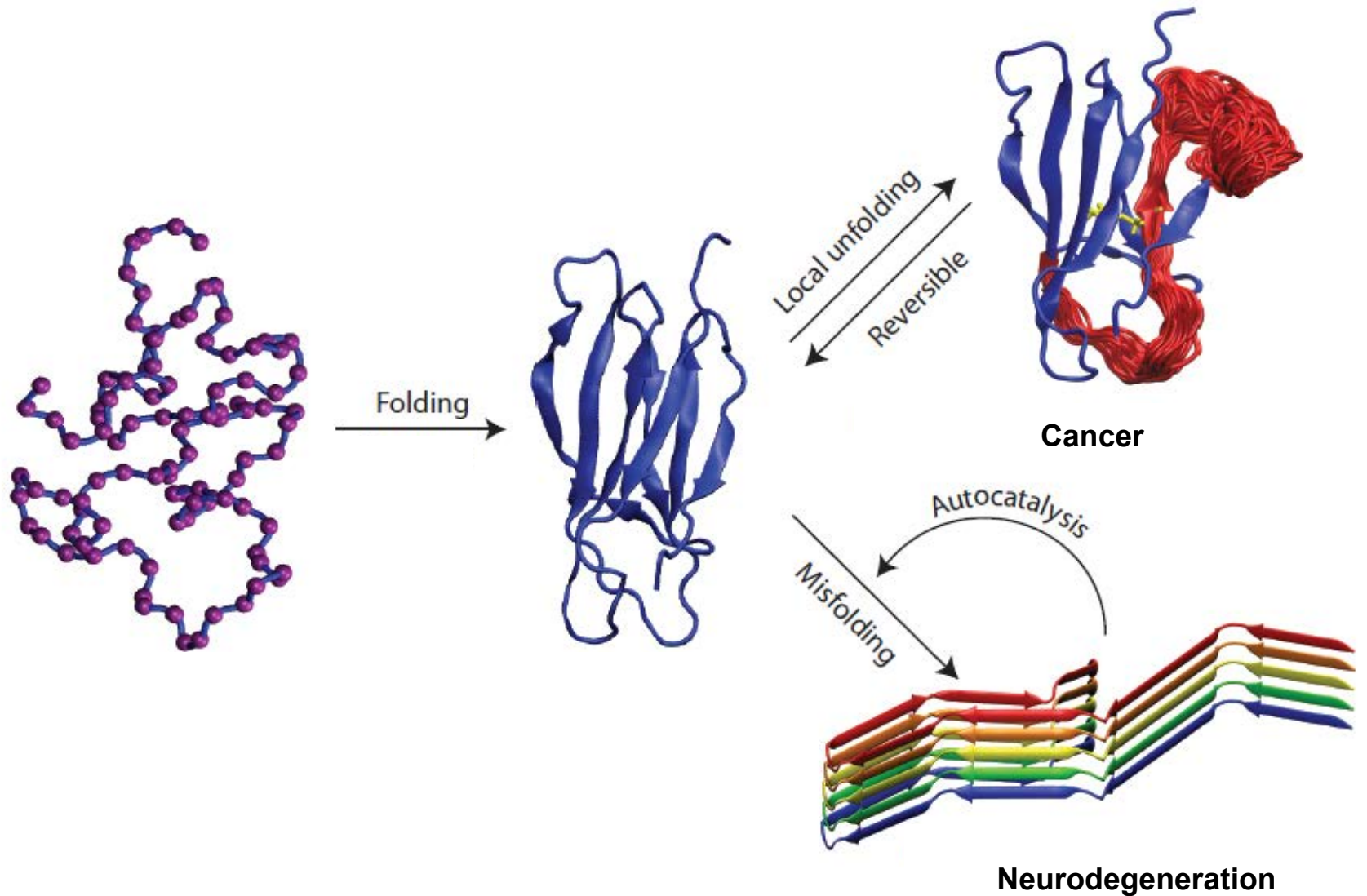
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**Founder and CSO
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Prion Hypothesis



Disruptive Idea 1: Protein Misfolding and Disease



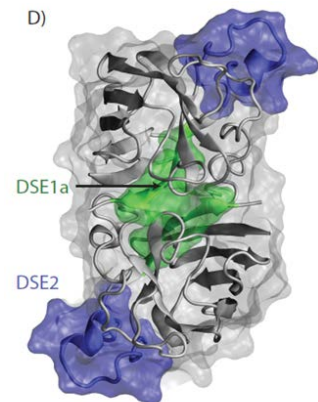
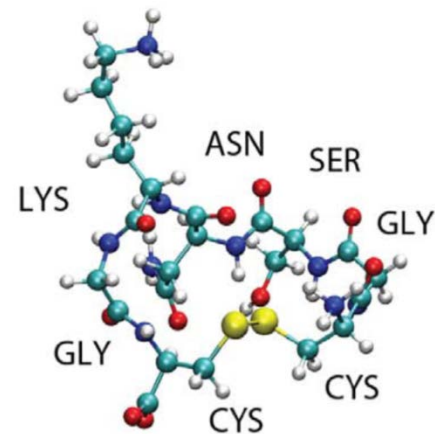
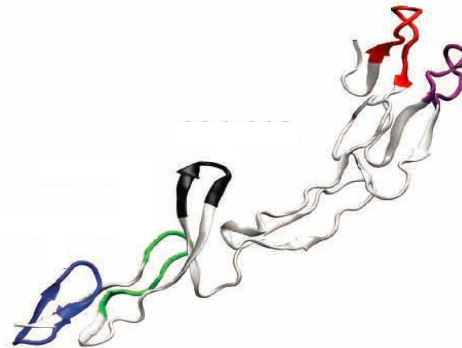
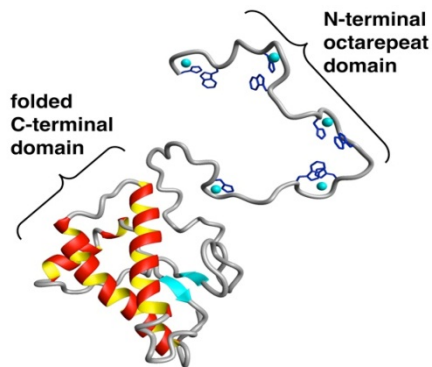
Disruptive Idea 2: Antibodies Can Selectively Target Misfolded Proteins while Sparing Native Isoforms

Efficacy: Specific targeting of a pathogenic species

- Neutralization of toxicity
- Blockade of propagation
- Acceleration of degradation
- Minimal “target distraction”

Safety: Selective sparing of normal proteins

- Preservation of normal function
- Minimization of autoimmunity
- Minimal regimens in therapeutic vaccines



Alzheimer's Disease

AD is the most common cause of dementia

500,000 Canadians have AD or other dementias – a number that is expected to double by 2038

Annual cost of care for Canadians with Alzheimer's disease is **\$15 billion** per year; **\$153 billion by 2038**

5.4 million Americans are living with Alzheimer's disease

Payments for care are estimated to be **\$200 billion** in the United States in 2012.

Around the world a new case of dementia occurs every four seconds; equivalent of **7.7 million new cases each year**¹

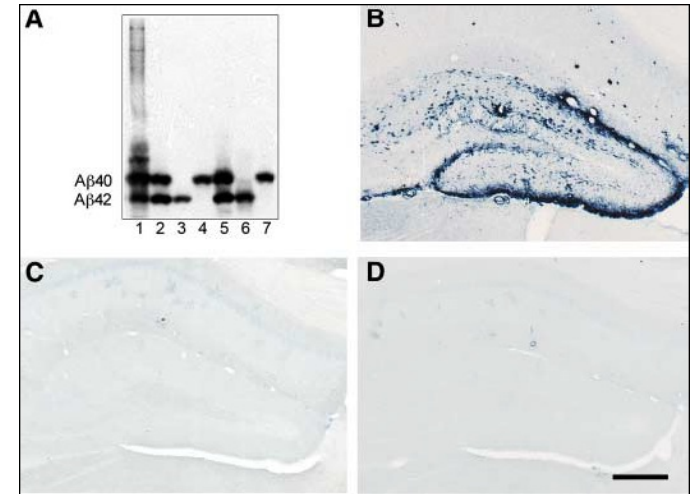
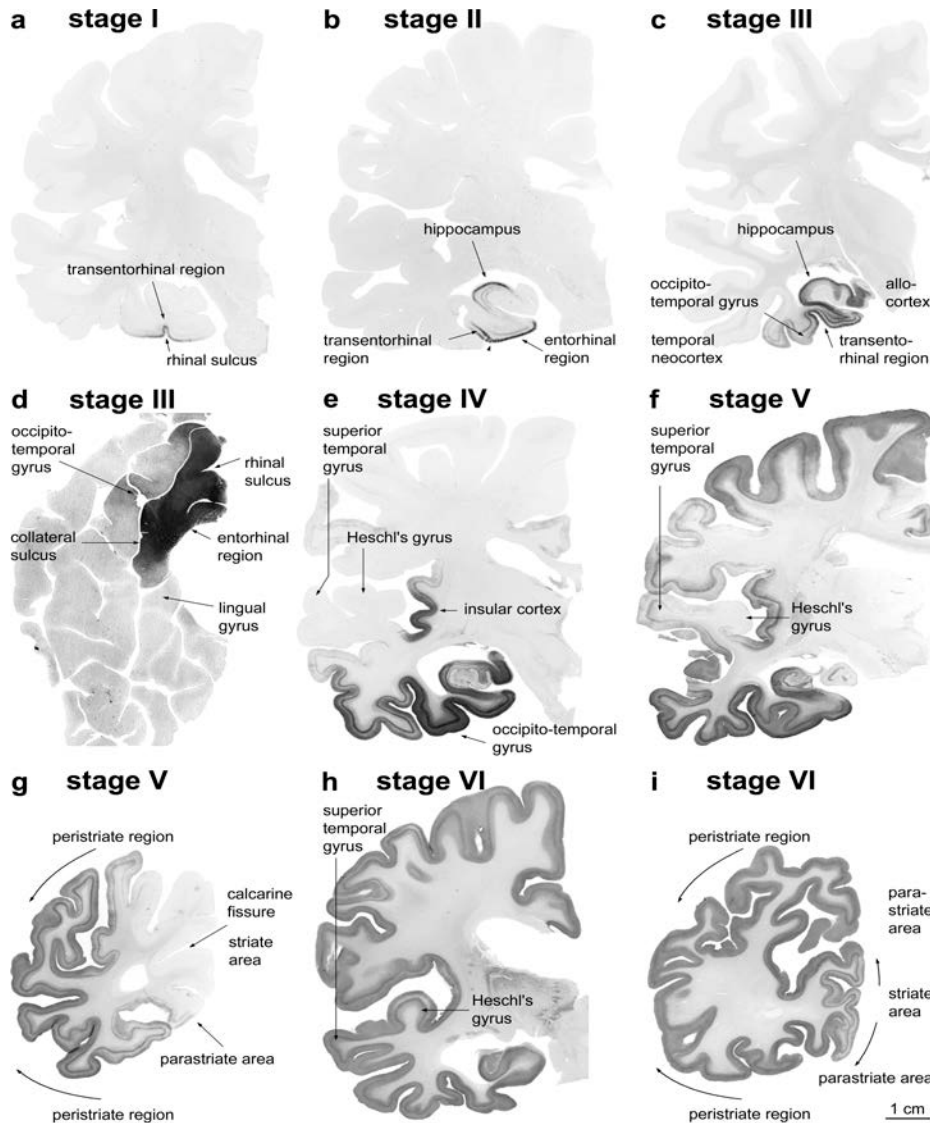
Delaying AD for just five years would save an estimated **\$50 billion** in annual healthcare costs in the US²



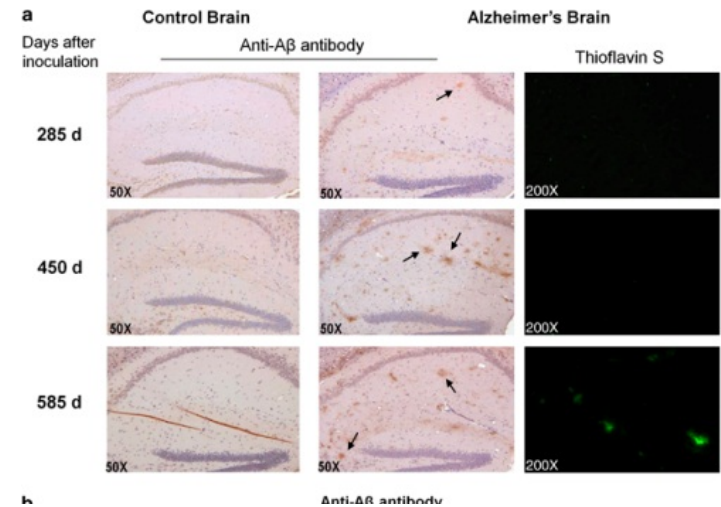
¹ World Health Organization (WHO) and Alzheimer's Disease International (ADI) in their report [Dementia: A Public Health Priority](#)

² Mount and Downton, *Nat Med*, 2006. 12(7): p. 780-4

Alzheimer's Disease: Regional Propagation of tau and A β Pathology

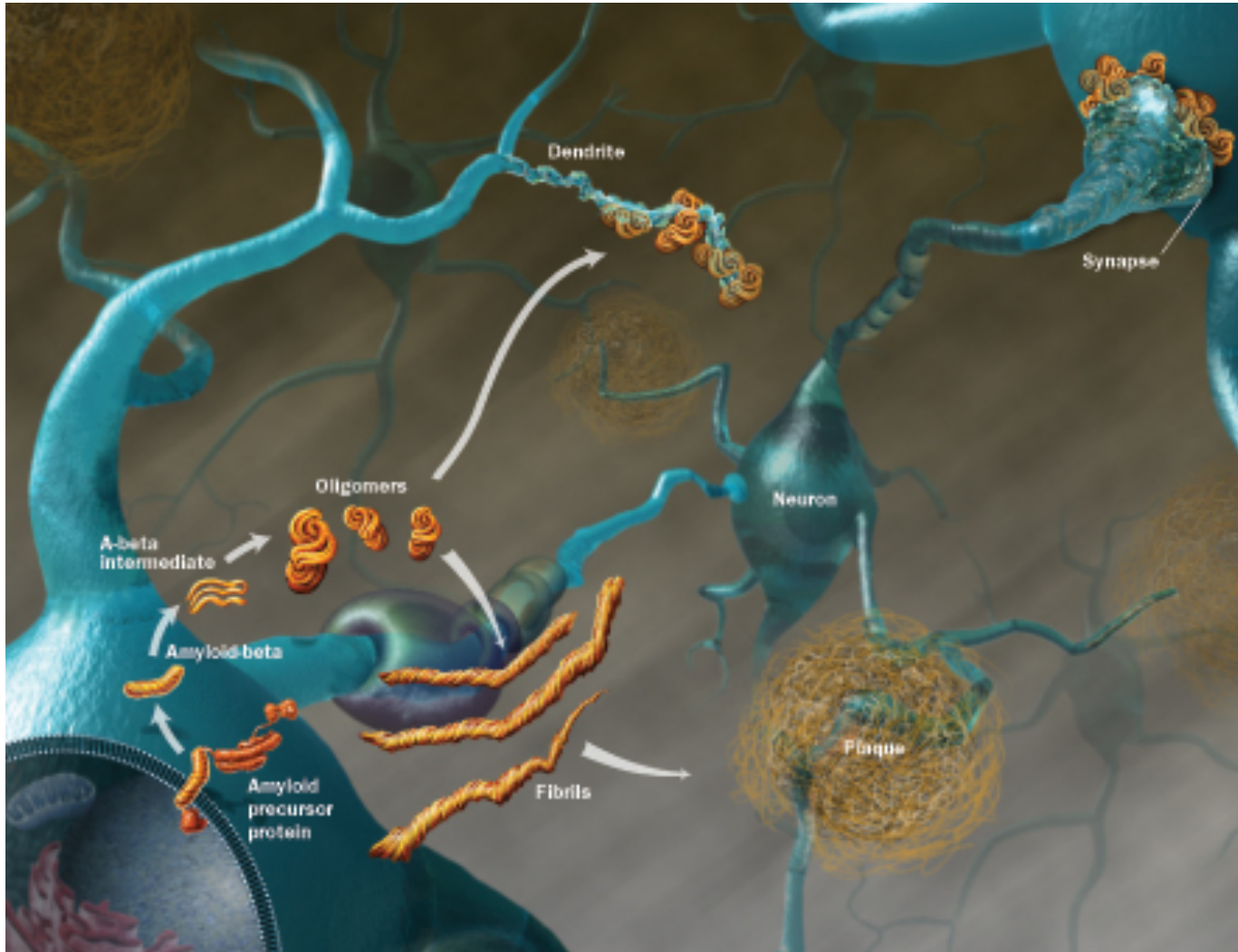


Meyer-Luehmann, et al, Science 2006



Morales et al, Mol Psych 2011

A β Oligomers in Alzheimer's Disease



Amyloid cascade hypothesis

Missense mutations in *APP*, *PS1*, or *PS2* genes

Increased A β 42 production and accumulation

A β 42 oligomerization and deposition
as diffuse plaques

Subtle effects of A β oligomers on synapses

Microglial and astrocytic activation
(complement factors, cytokines, etc.)

Progressive synaptic and neuritic injury

Altered neuronal ionic homeostasis;
oxidative injury

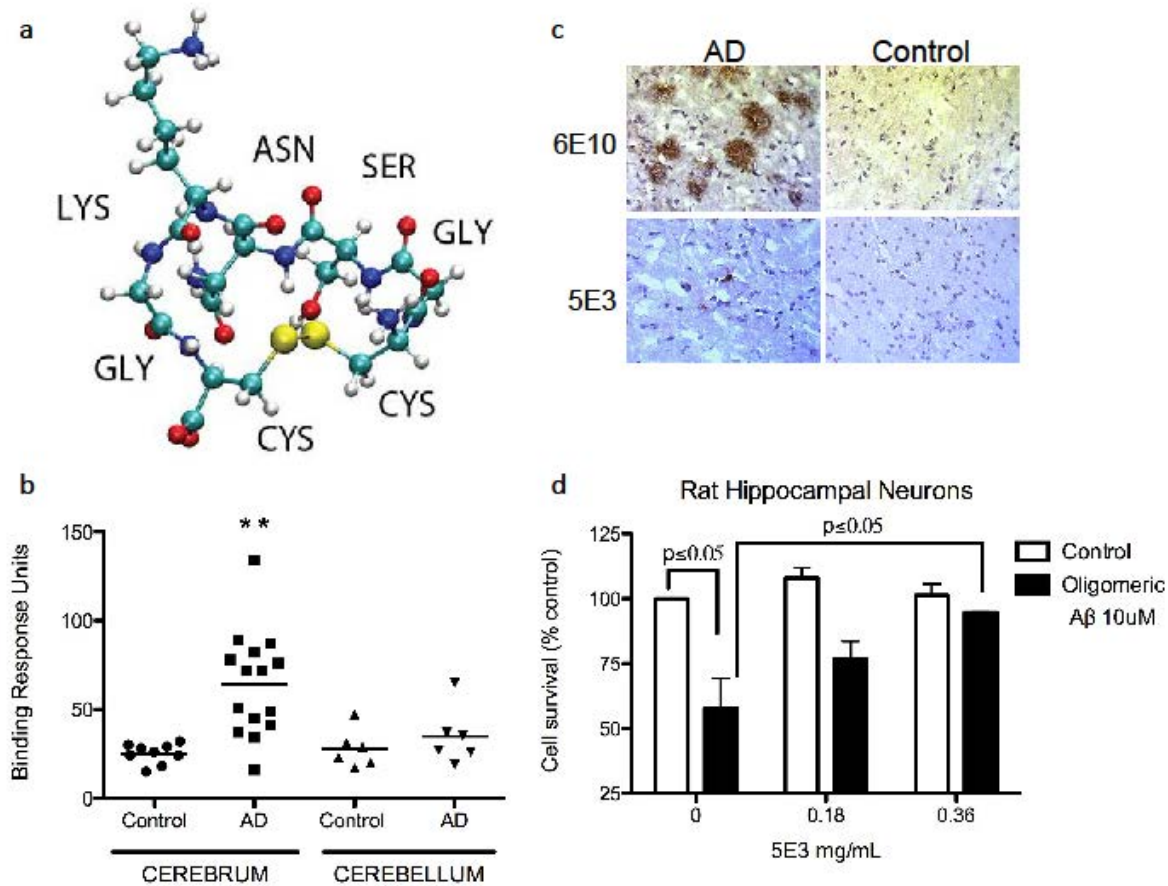
Altered kinase/phosphatase activities \blacktriangleright tangles

Widespread neuronal/neuritic dysfunction
and cell death with transmitter deficits

Dementia

Image courtesy of Nicolle Rager

An A β Oligomer-Specific Epitope: Cyclic-Constrained Ser-Asn-Lys (cSNK)



Amyotrophic Lateral Sclerosis

ALS (Lou Gehrig's Disease) is a fatal motor neuron disease

Most often appears between the **ages of 45 and 65**

>50% of patients often **die within 3 years** of onset

2,500 - 3,000 Canadians currently live with ALS

As many as **35,000 Americans** have ALS

Of every 100,000 people, between **6-7** will be **diagnosed** with ALS worldwide

The cost of caring for an ALS patient in the **U.S.** can reach **\$200,000/year** in the advanced stages of the disease¹

Environmental exposures have been proposed as the explanation for an **increased incidence** of ALS in **US Gulf War veterans**²



¹ Nebraska Coalition for Lifesaving Cures

² Haley 2003, Horner *et al.* 2003

Is ALS a Prion-Like Disorder?

Sporadic and autosomal dominant disease

Normal until disease onset, earlier with mutation

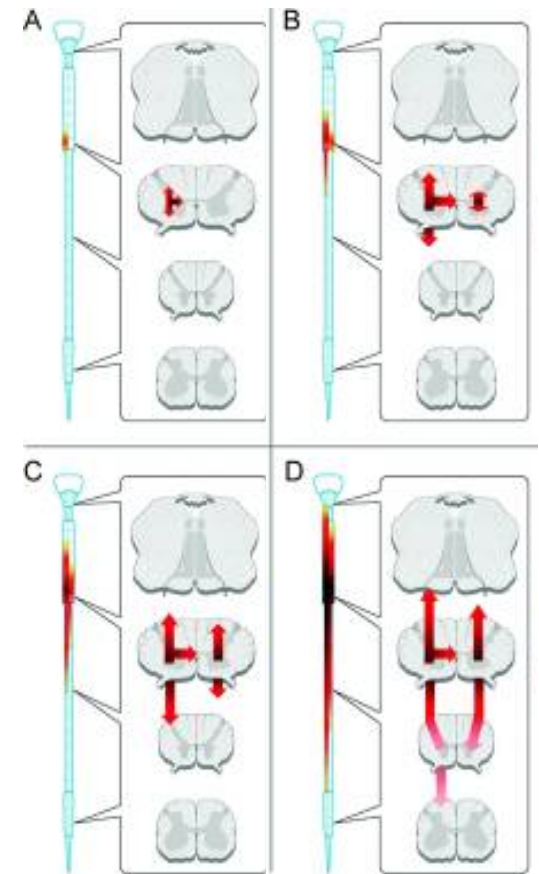
Mutations disrupt protein structure

Protein aggregates contain candidate protein

Protein aggregates toxic to neural cells

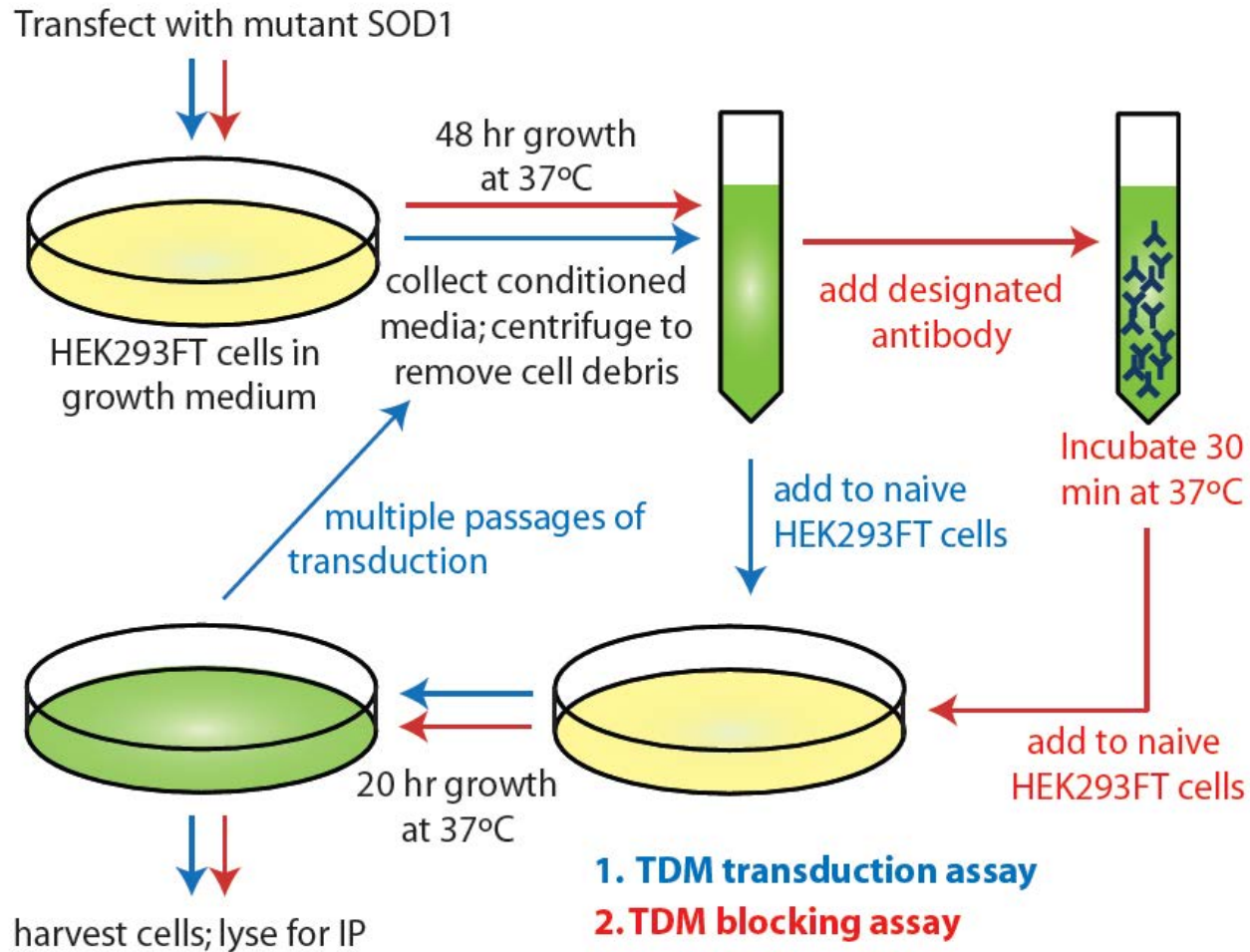
Sensitive to substrate concentration and structure

Propagation from onset site



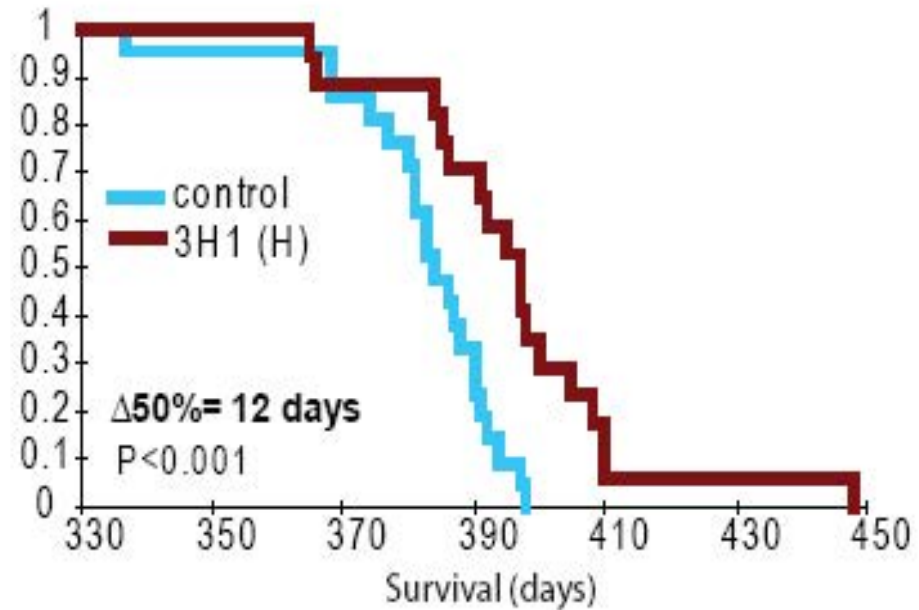
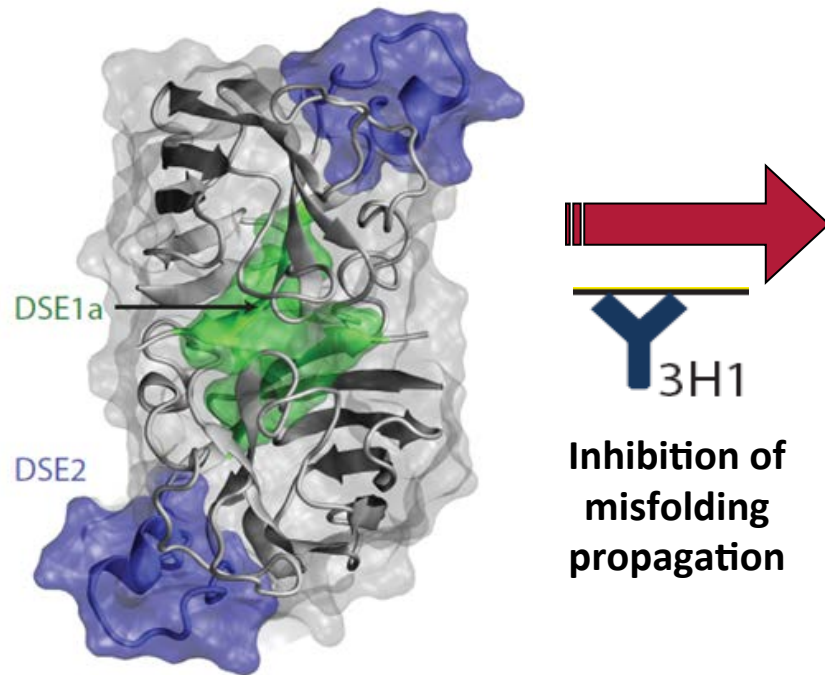
Ravits and La Spada (2009)
Neurology 73(10):805-11. Review.

Cell-to-Cell Propagation of SOD1 Misfolding



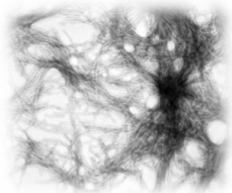
Grad LI, Yerbury JJ, Turner BJ, Guest WC, Pokrishevsky E, O'Neill MA, Yanai A, Silverman JM, Corcoran L, Luheshi L, Yousefi M, Coleman BM, Hill AF, Plotkin SS, Mackenzie IR, Cashman NR. Intercellular propagated misfolding of wild-type Cu-Zn superoxide dismutase occurs via exosome-dependent and independent mechanisms. *Proc Natl Acad Sci* 2014 .

Prion-like Propagation of SOD1 Misfolding is a Therapeutic Target in ALS

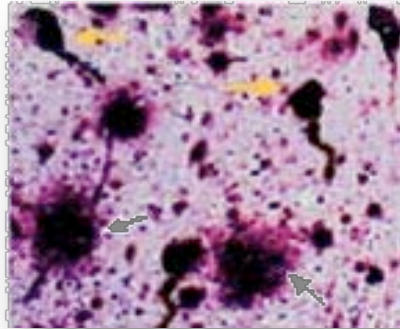


Propagated Protein Misfolding Diseases

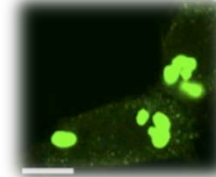
Huntington's disease
(aggregates)



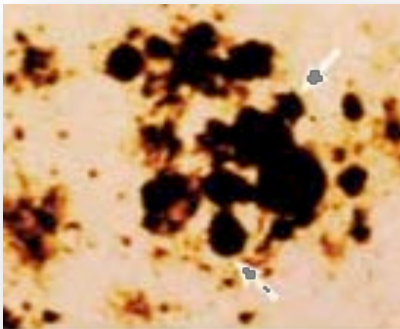
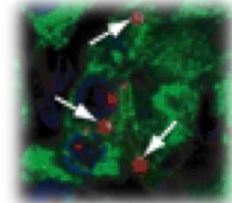
Alzheimer's diseases
(plaques and tangles)



Schizophrenia
(aggregates)



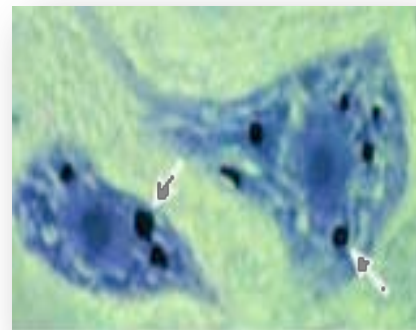
Type 2 diabetes
(aggregates)



Prion diseases
(PrP amyloid plaques)

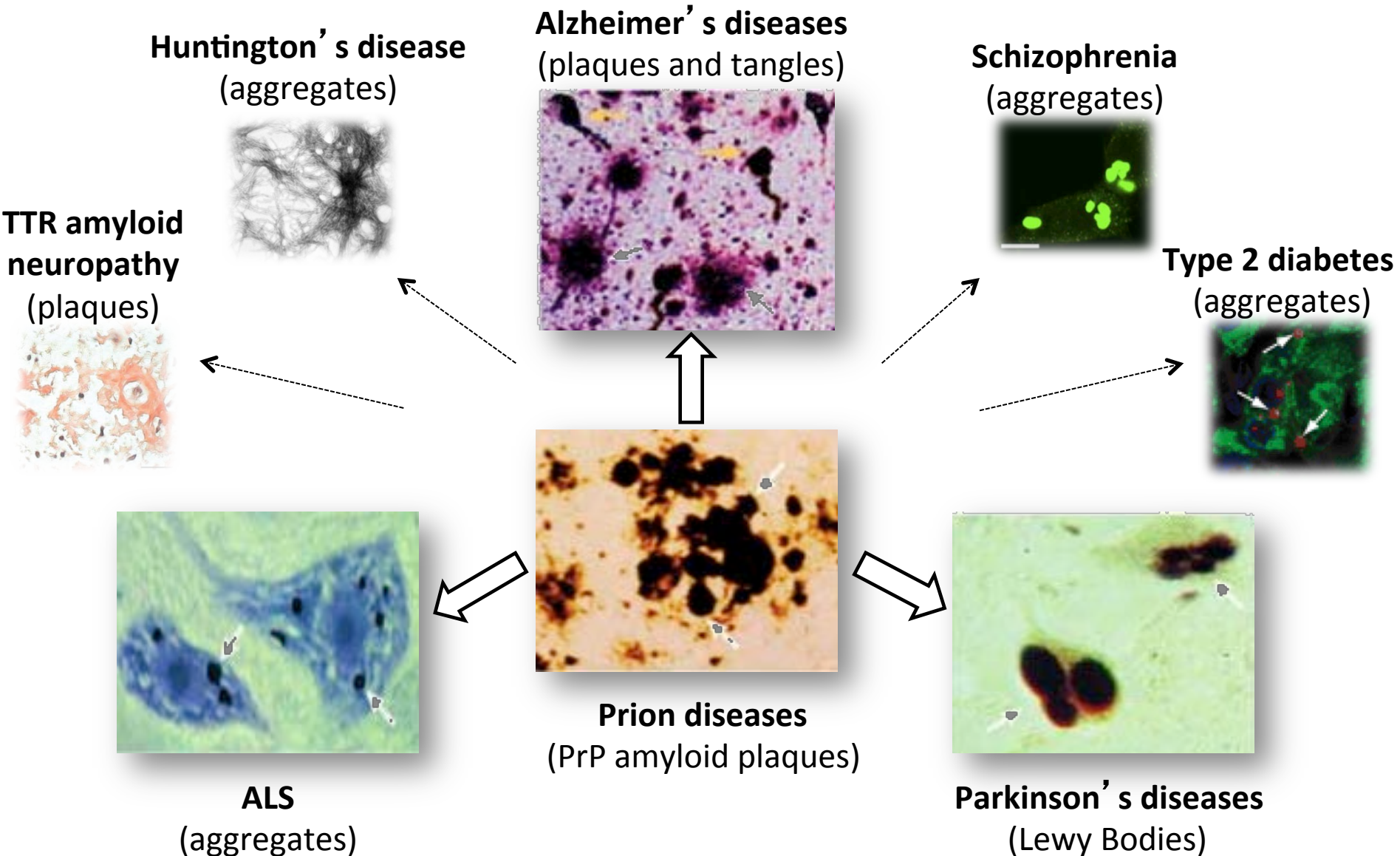
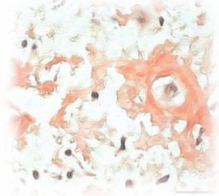


Parkinson's diseases
(Lewy Bodies)



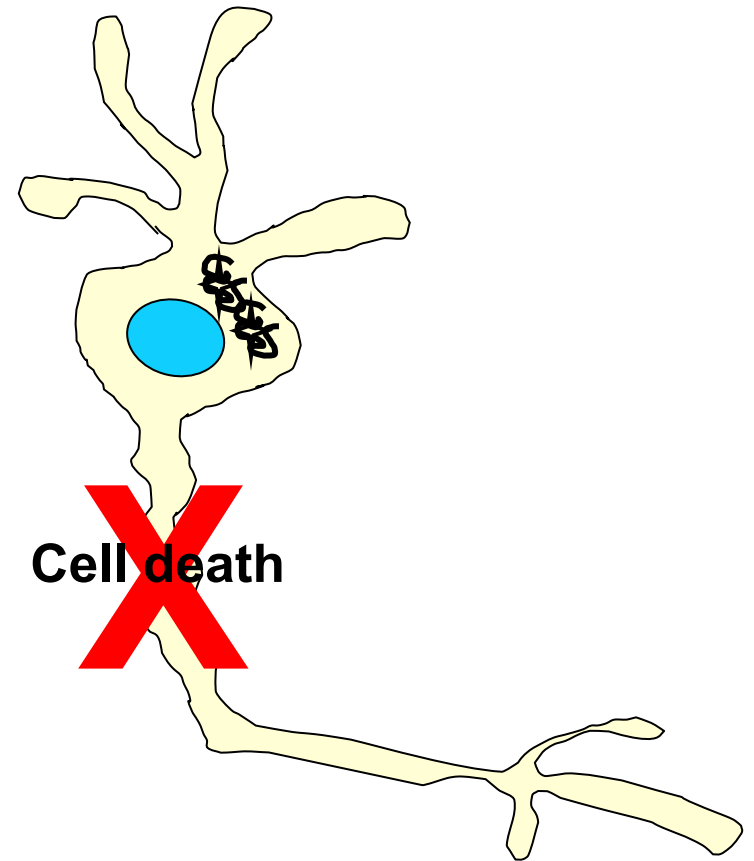
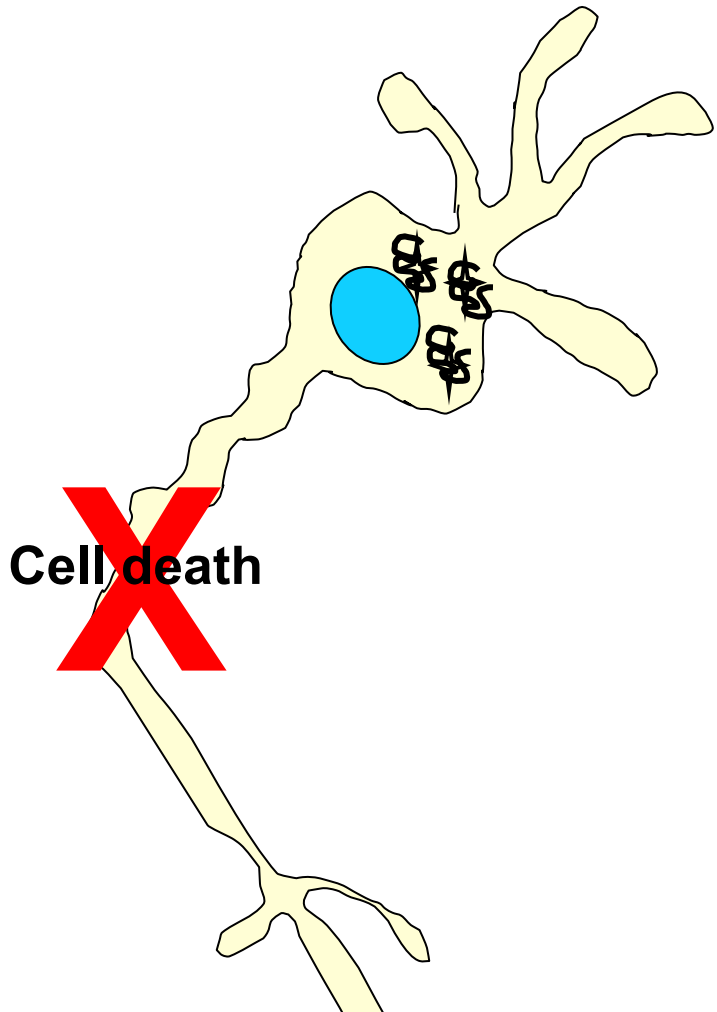
ALS
(aggregates)

TTR amyloid neuropathy
(plaques)



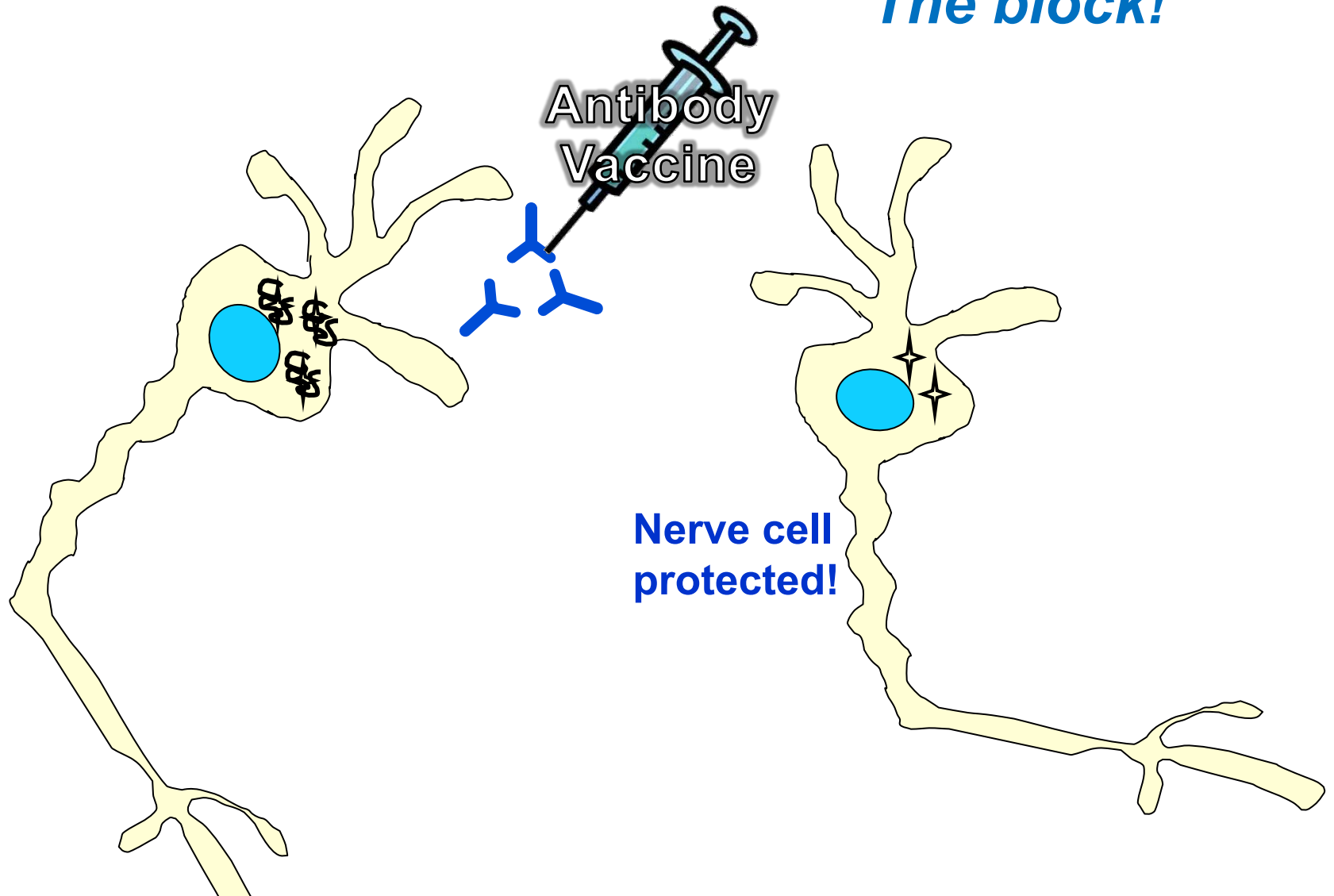
Propagated Protein Misfolding: Mechanism

The spread...



Propagated Protein Misfolding: Treatment

The block!



Antibody
Vaccine

Nerve cell
protected!

Acknowledgements

CIHR: III, IA, INMHA
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Napper group

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Cashman group
Plotkin group
Mackenzie group
Jia group
Marziali group
Wang group
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