Prions are Prototypes: Other Neurodegenerative Diseases

Neil R. Cashman MD
Professor and Canada Research Chair
Department of Medicine (Neurology)
University of British Columbia

Academic Director, ALS Centre
GF Strong Hospital

Founder and CSO
ProMIS Neurosciences
Prion Hypothesis
Disruptive Idea 1: Protein Misfolding and Disease

Folding → Cancer

Misfolding → Neurodegeneration

Local unfolding → Reversible

Autocatalysis

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 year¹

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
Alzheimer’s Disease: Regional Propagation of tau and Aβ Pathology


Morales et al, Mol Psych 2011
Aβ Oligomers in Alzheimer’s Disease

Amyloid cascade hypothesis

- Missense mutations in APP, PS1, or PS2 genes
- Increased Aβ42 production and accumulation
- Aβ42 oligomerization and deposition as diffuse plaques
- Subtle effects of Aβ 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 → tangles
  - Widespread neuronal/neuritic dysfunction and cell death with transmitter deficits
  - Dementia

Image courtesy of Nicolle Rager
An Aβ 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 disease

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

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

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

Inhibition of misfolding propagation

\[ \Delta 50\% = 12 \text{ days} \]

\[ P < 0.001 \]
Propagated Protein Misfolding Diseases

Huntington’s disease (aggregates)

Alzheimer’s diseases (plaques and tangles)

Schizophrenia (aggregates)

Prion diseases (PrP amyloid plaques)

ALS (aggregates)

Parkinson’s diseases (Lewy Bodies)

TTR amyloid neuropathy (plaques)

Type 2 diabetes (aggregates)
Propagated Protein Misfolding: Mechanism

The spread...
Propagated Protein Misfolding: Treatment

The block!

Antibody Vaccine

Nerve cell protected!
Acknowledgements

CIHR: III, IA, INMHA
ALS Canada
PrioNet Canada
Canada Research Chairs
CFI & BCKDF

University of Toronto
  Chakrabartty group
  Pai group
  Prosser group

U Sask – VIDO, PREVENT
  Napper group

Biogen-Idec Corp

UBC
  Cashman group
  Plotkin group
  Mackenzie group
  Jia group
  Marziali group
  Wang group
  Wellington group

University of Alberta
  Wishart group
  Kovalenko group

ProMIS Neurosciences