Fixing the Misfolded Proteins That Cause Dementia and Organ Failure

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Lita Annenberg Hazen Professor of Chemistry

Wednesday May 15, 2024 4:00 PM PT

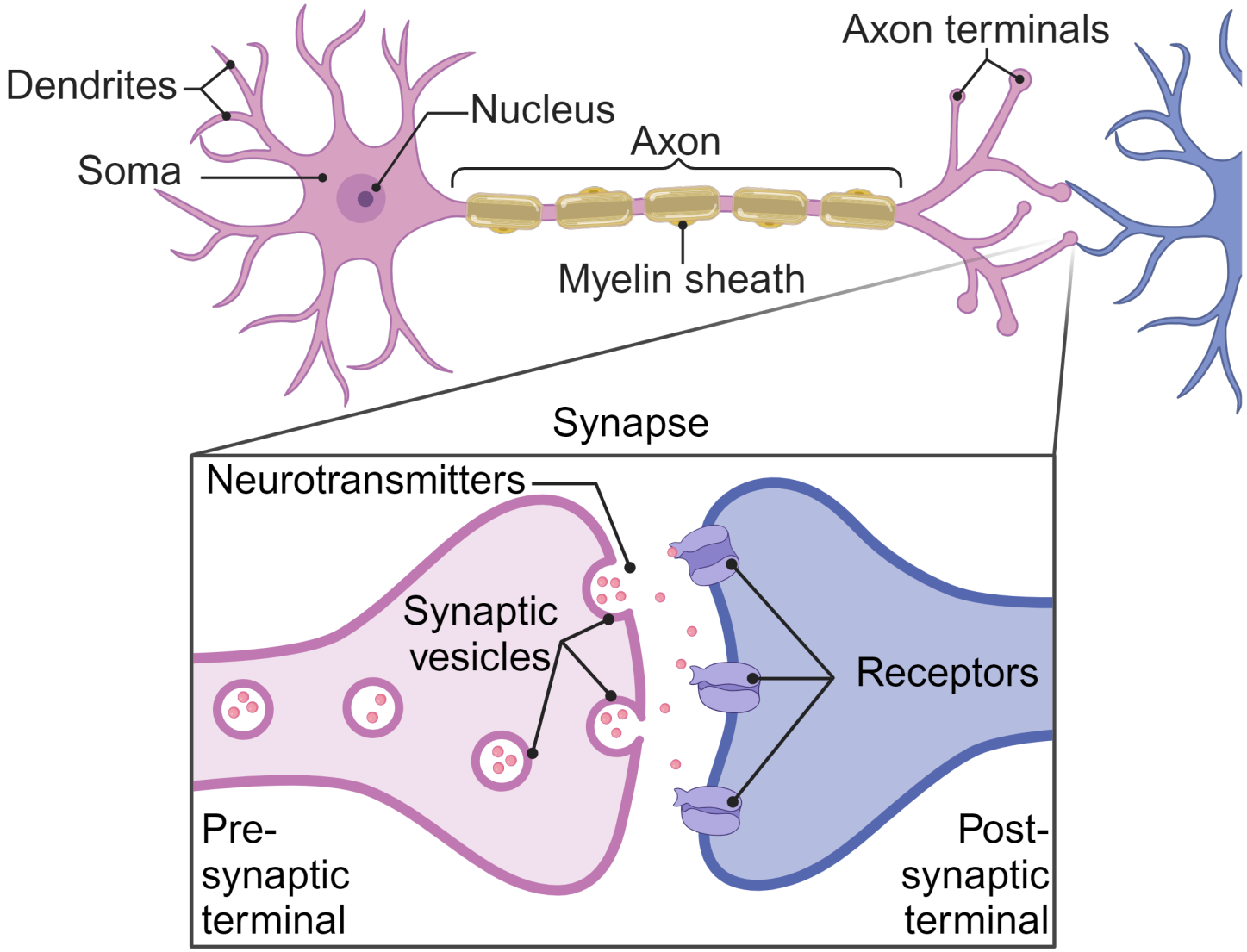
A Very Brief Personal History

- Growing up in a small Western New York town
- High School Chemistry Teacher–Mr. Tierney
- SUNY College at Fredonia–Professor Phil Kumler
- How did a chemist get interested in neurodegeneration–Rockefeller University ?
- Scripps is a community of fantastic scientists that shaped me
- Where have we been and where are we going with respect to dementia medicines?

Common Neurodegenerative Diseases

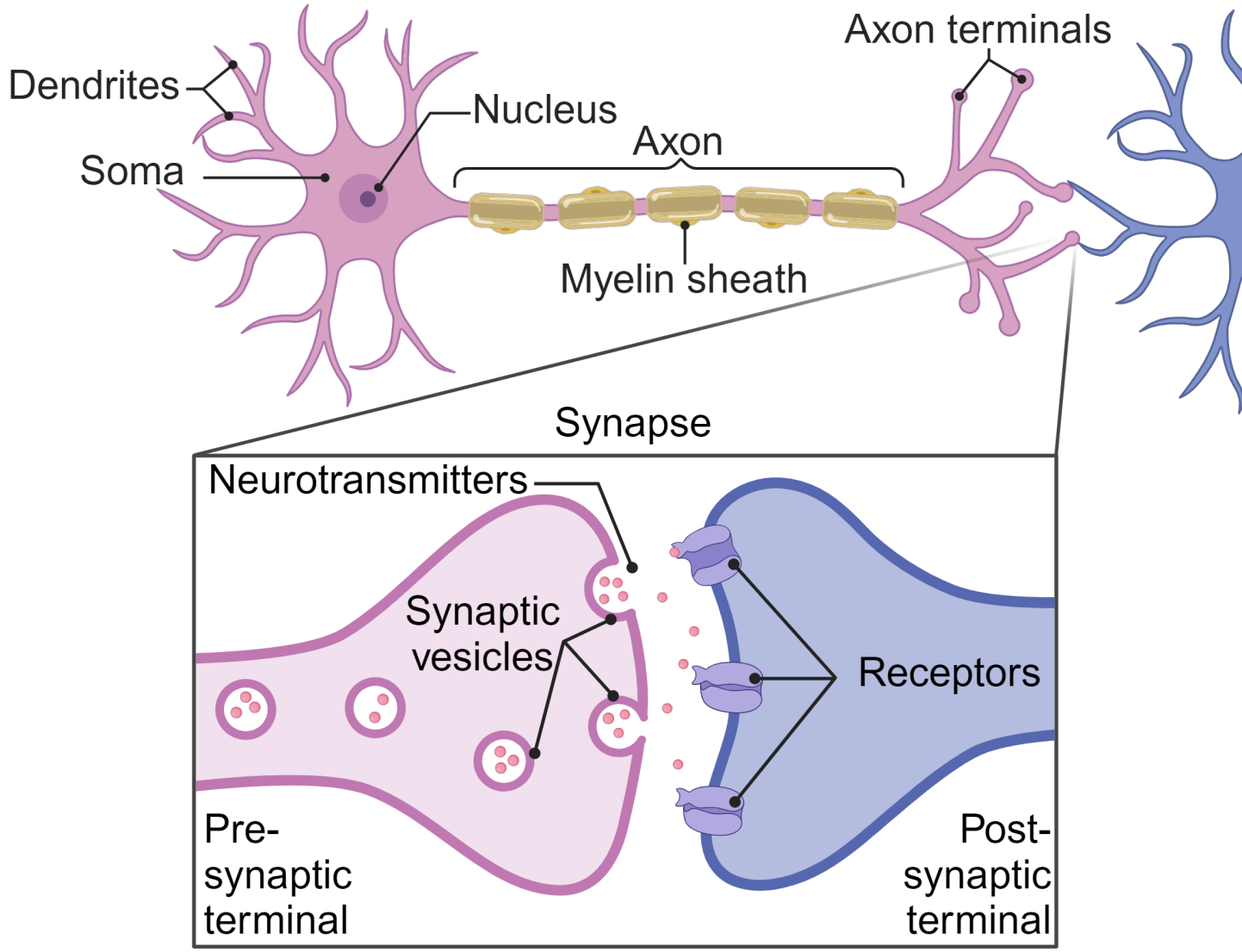
- Alzheimer's disease–Dementia-Economic cost $ 300 billion-Worsened caregiver health, 50 million Patients worldwide, 5th Leading cause of death
  - Impaired ability to remember & think, serious enough to impede daily life
- Parkinson's disease–Movement disorder & dementia-Economic cost $ 52 billion-Worsened caregiver health, 10 million Patients worldwide, 14th leading cause of death
- Transthyretin Amyloidosis–Polyneuropathy & dementia / cardiomyopathy-Economic Cost $ 10 billion-Worsened caregiver health, ≈ 5 million Patients worldwide

Introduction to Neurons



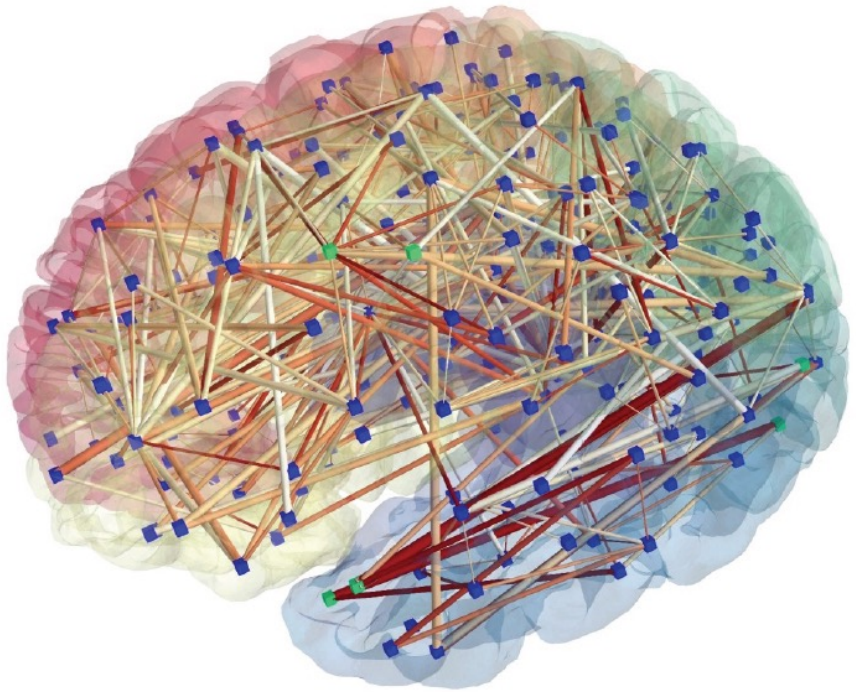
Neurodegenerative Diseases

Neurons do not easily regenerate and are thus susceptible to degeneration upon sustained insult, thus a subset of neurons can die in the aging brain

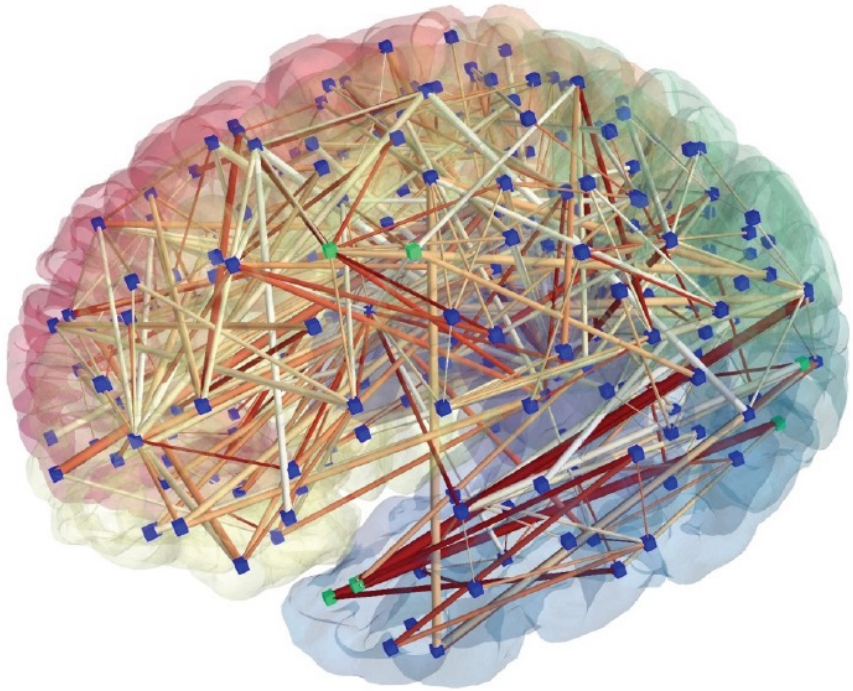


Brain Function Requires Neuronal Communication

Thus dying or dysfunctional neurons in the brain impairs connectivity and normal brain function / communication

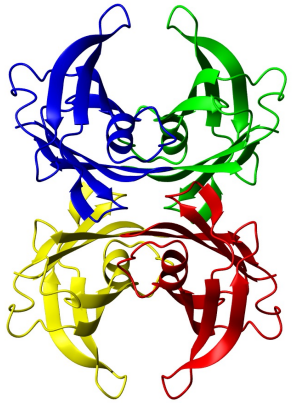


Brain Function Requires Neuronal Communication

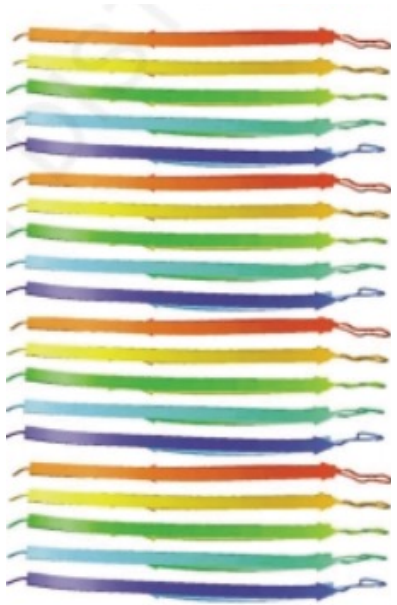


Several Organ Systems are Compromised!

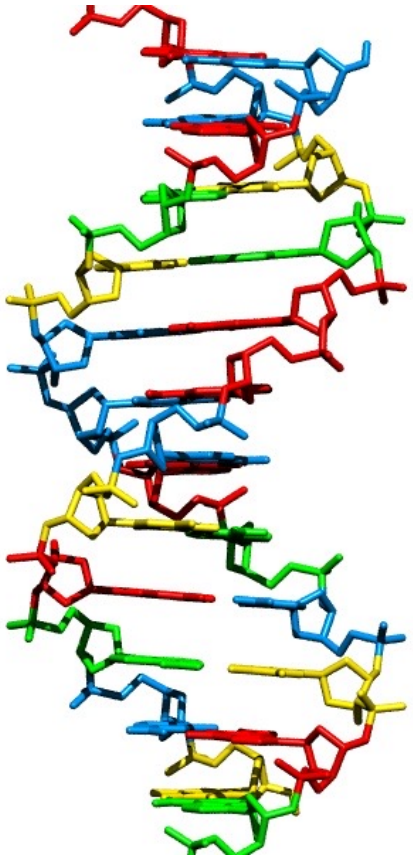
Mechanistic Take-home message: Neurodegenerative diseases are disorders of protein shape



Proteins having a normal shape are generally spherical (2-3 nm diameter)



Abnormal protein shapes associated with degenerative diseases are rectangular (1-2 nm x ≈ 3000 nm)



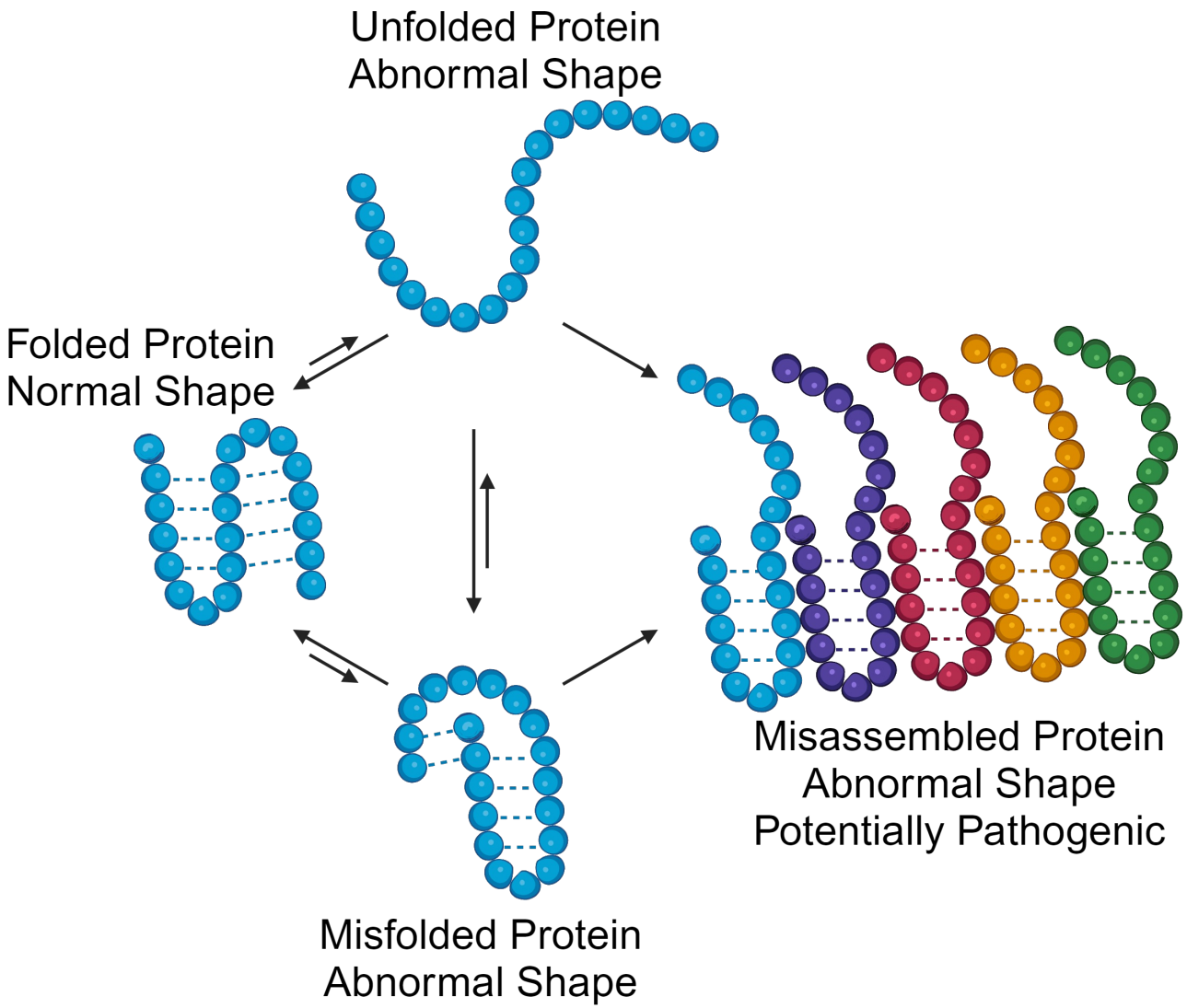
On the Origins of Proteins
DNA to RNA to Protein

DNA is transcribed into RNA. RNA is translated into proteins.

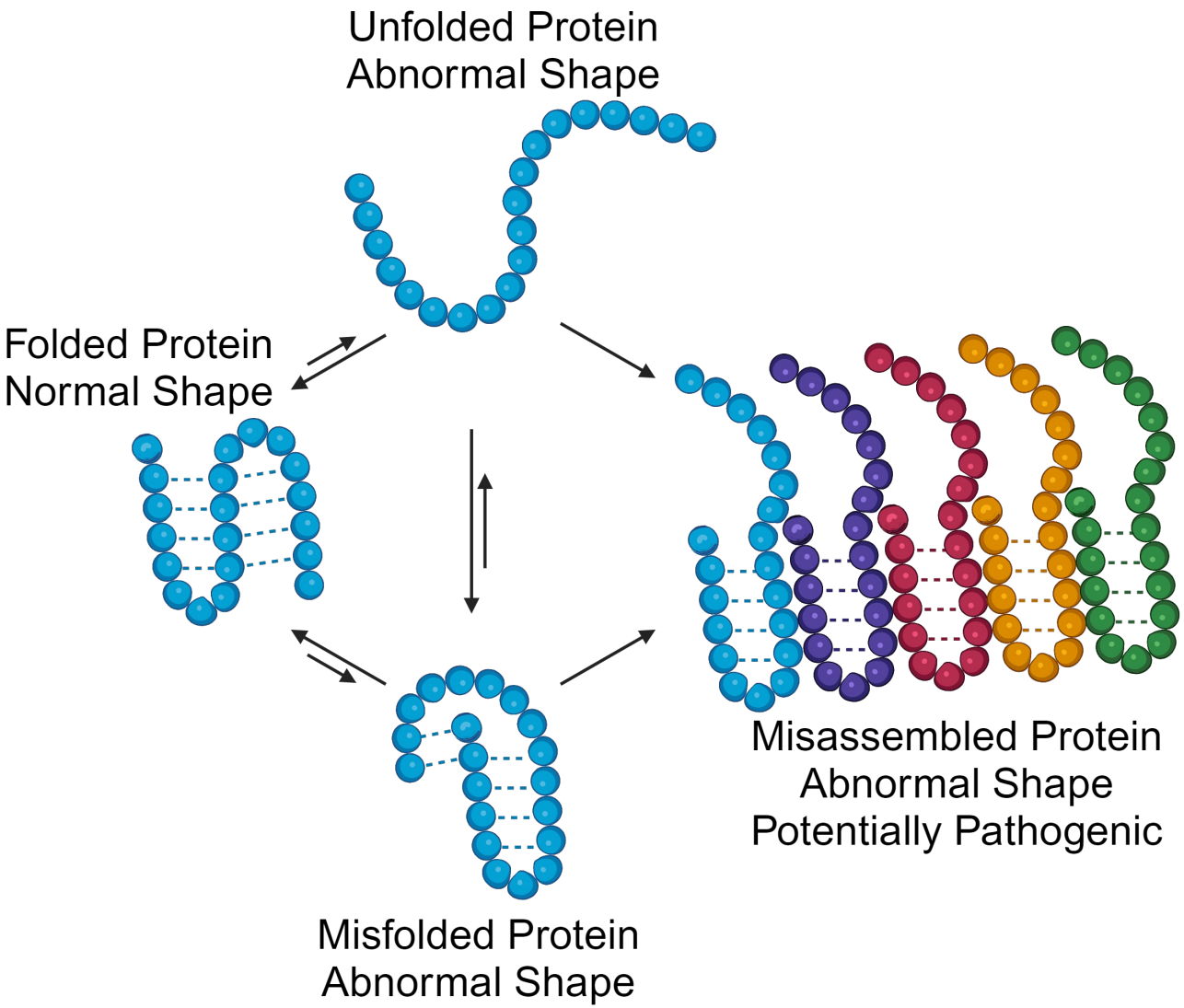
Proteins are best thought of as an unlatched pearl necklace, composed of twenty different types of “pearls” or amino acids with distinct chemical properties.

Because of the affinity of a given amino acid for a subset of the twenty other amino acids, proteins adopt shapes by a process known as protein folding that can be spontaneous

Protein Folding is often Spontaneous—Misassembly Competes



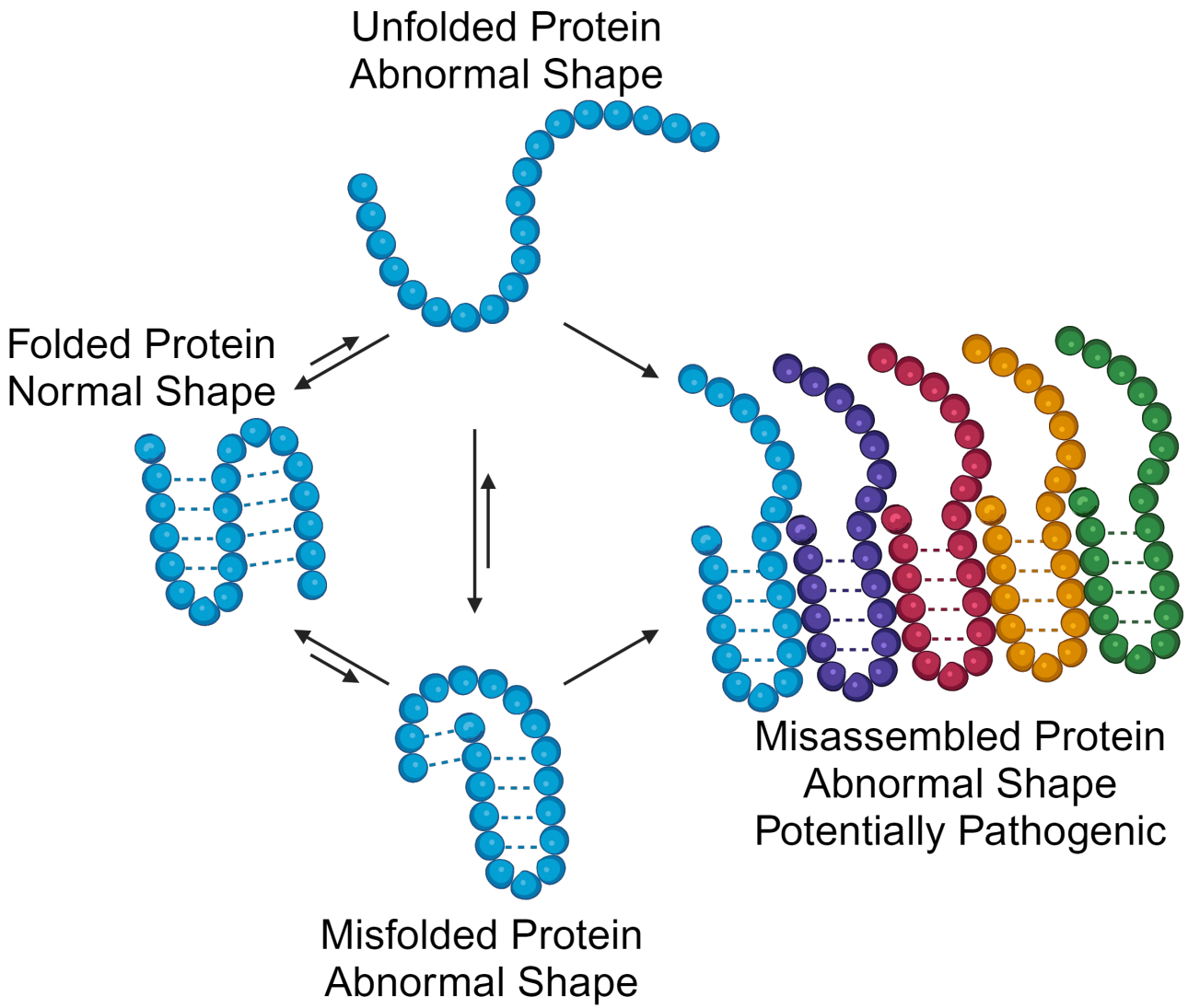
Intracellular Protein Folding & Protein Degradation Compete



Cellular Degradation

- Protein folding often inefficient
- Cellular degradation decreases with aging
- Aging is the dominant risk factor for neurodegeneration

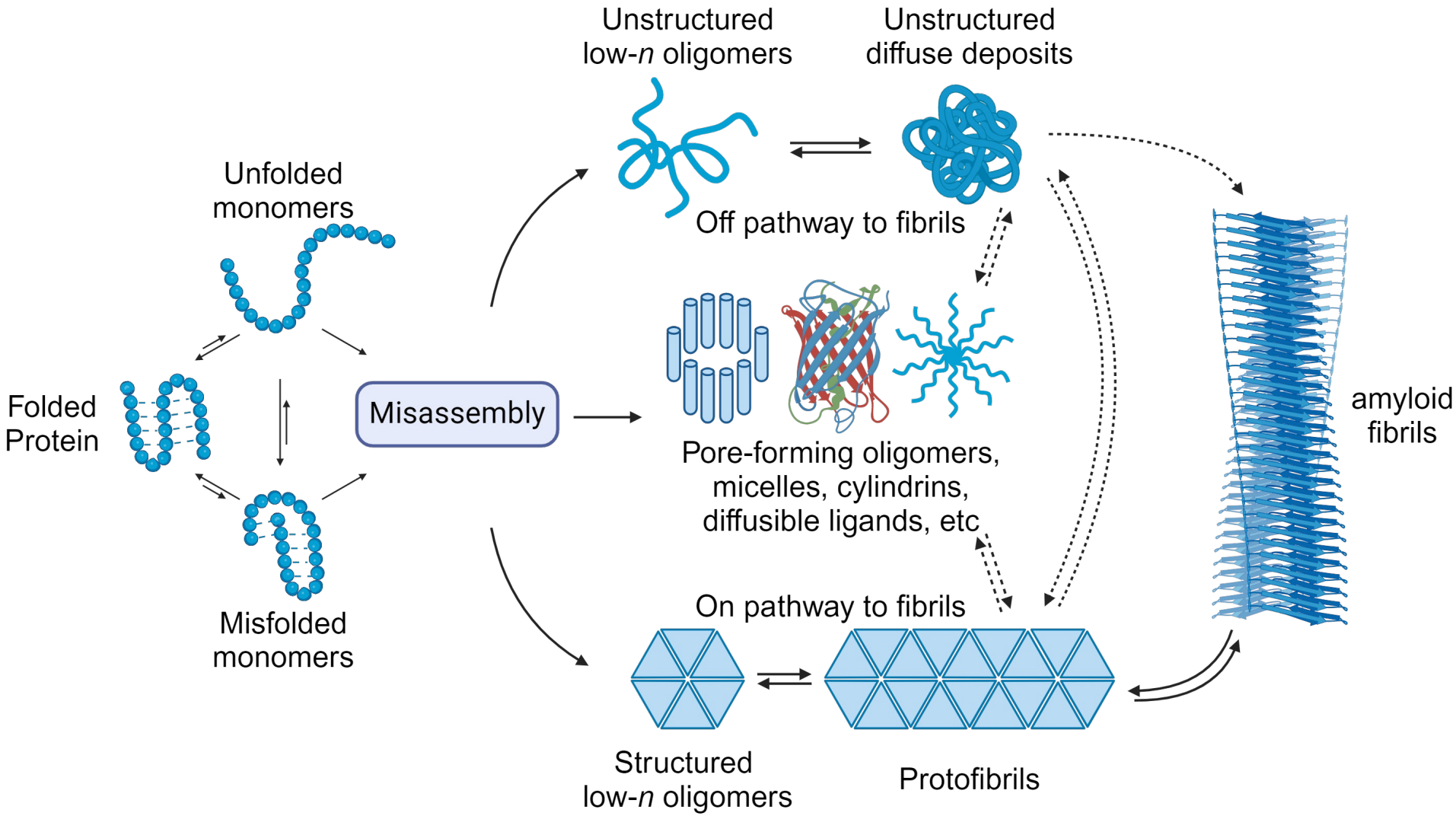
Inability to Maintain the Extracellular Folded State Leads to Misfolding and Misassembly and the formation of Many Abnormal Shapes



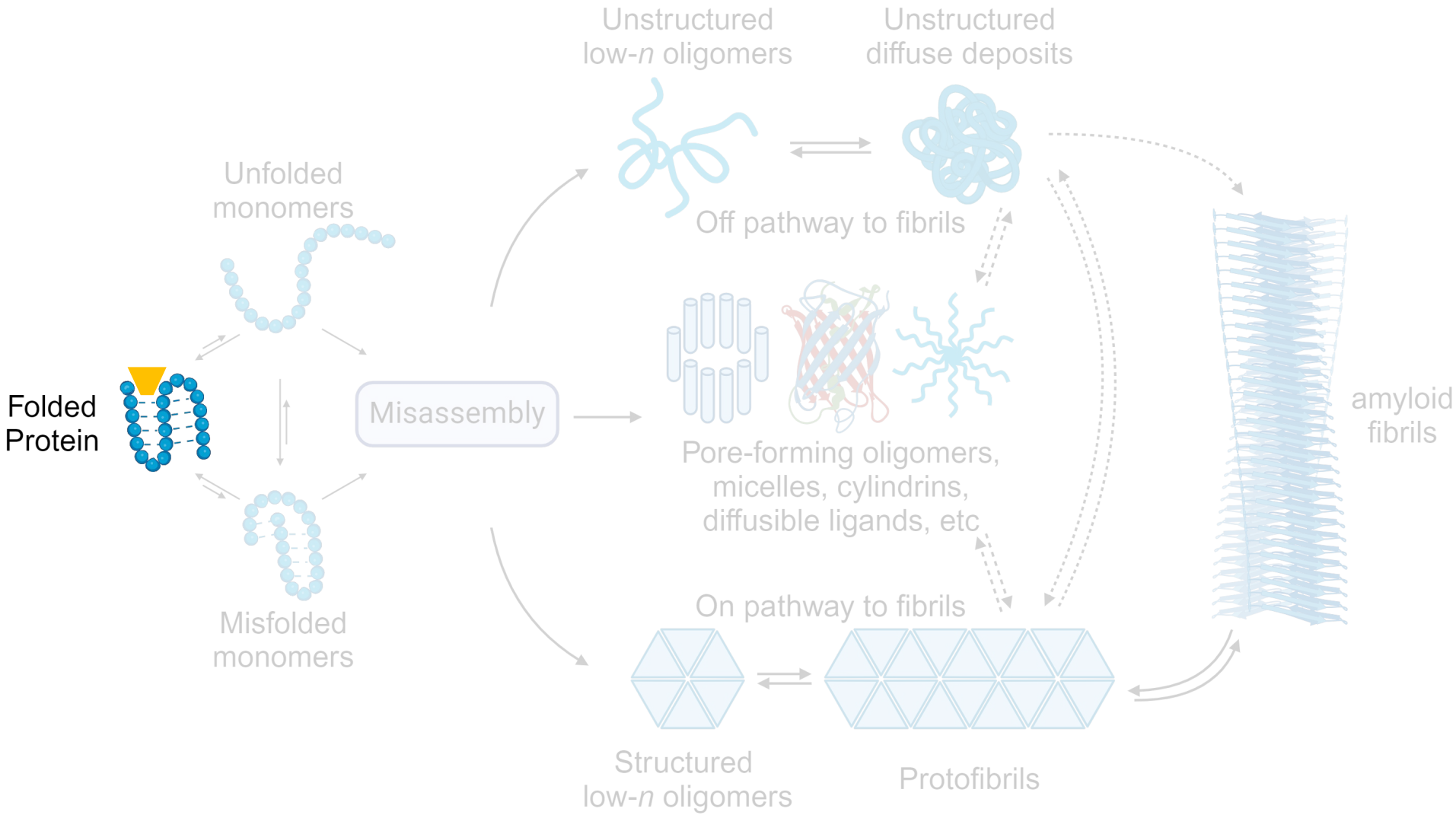
Shape Conversion

Amyloid Fibrils

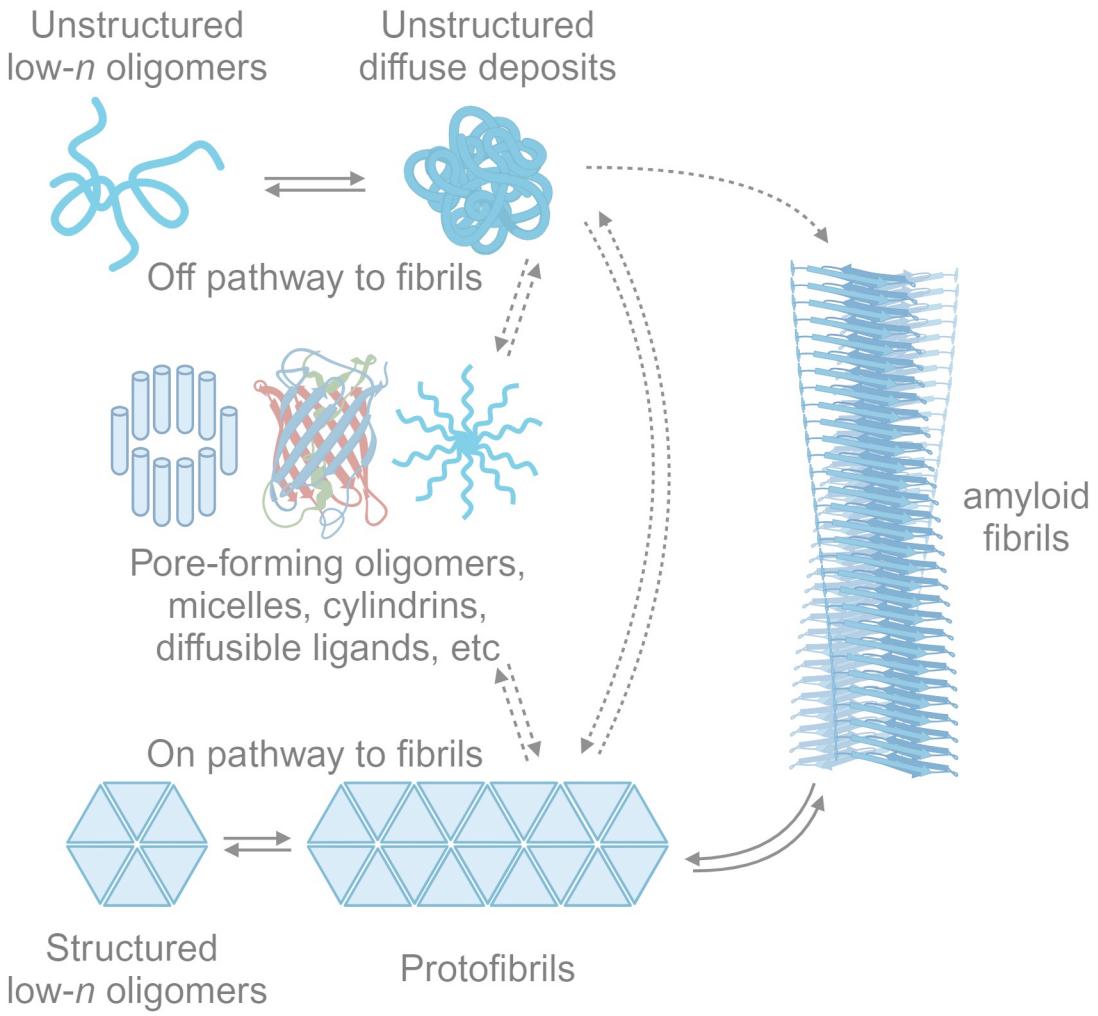
Since We Do Not Know Which Abnormal Protein Structures Drive Degeneration, We Posited that Inhibiting All Aggregation of Newly Synthesized Protein Would be Key to Clinical Success

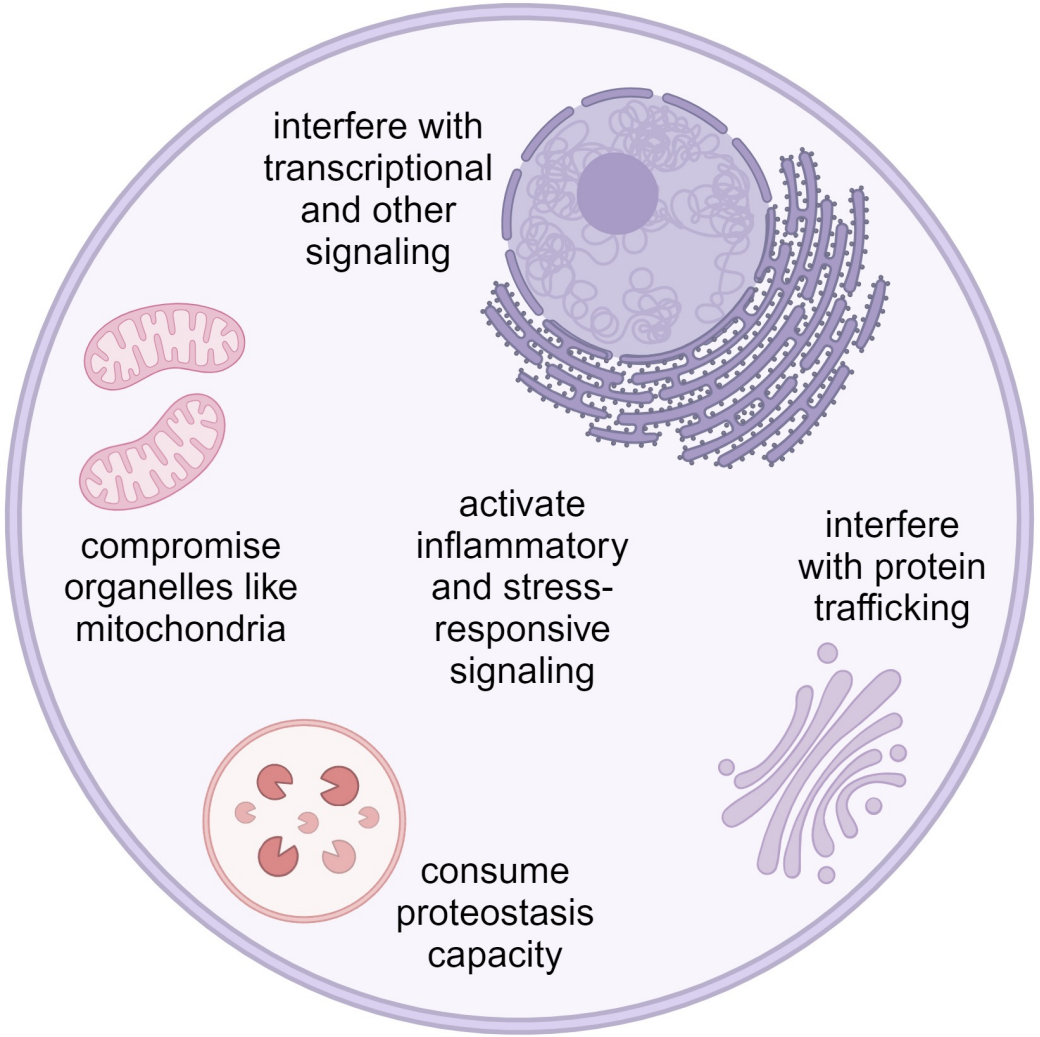


Stabilizer Binding to the Properly Folded Protein Maintains the Extracellular Folded State Leading to Less Misfolding and less formation of many misassembled or abnormal Shapes

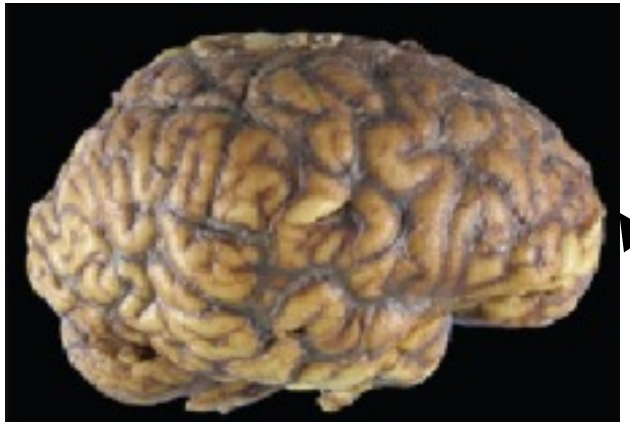


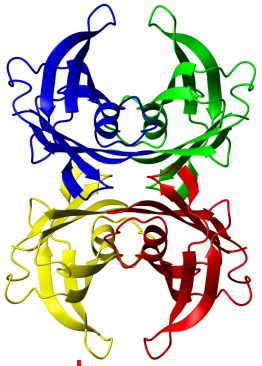
Abnormal shapes confer abnormal functions that damage tissue

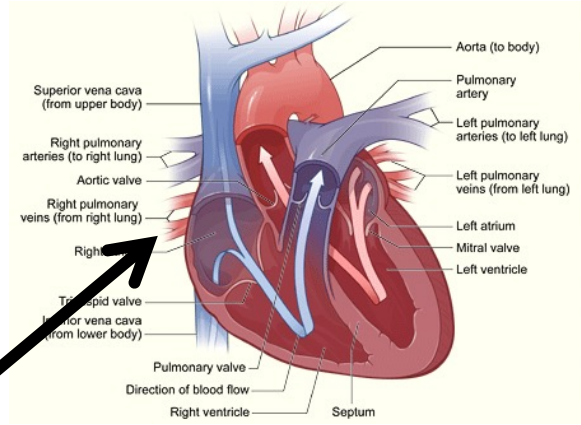


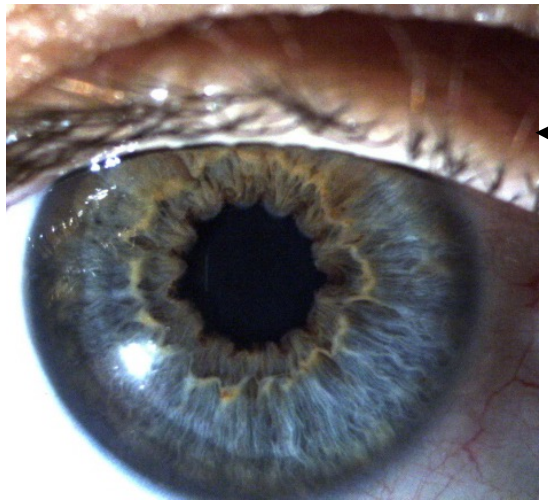


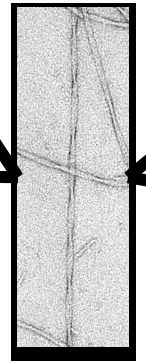
The Transthyretin (TTR) Amyloidoses Are *in trans* Gain-of-Proteotoxicity Diseases—Sporadic and Autosomal Dominant

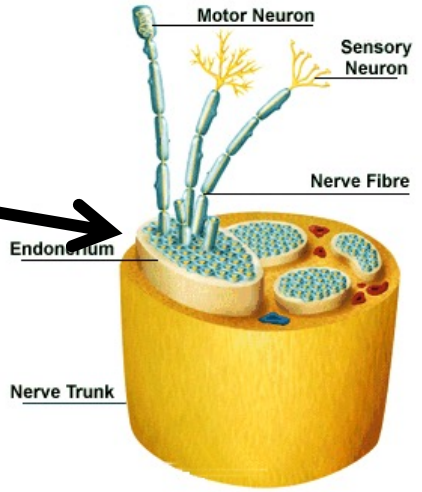






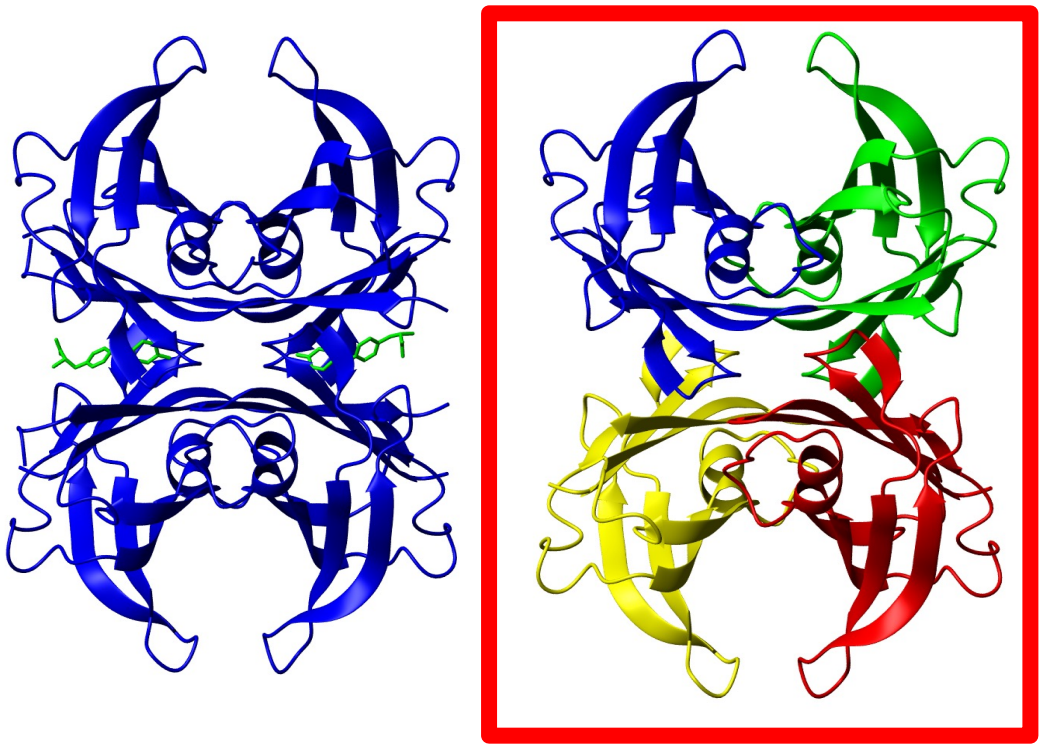






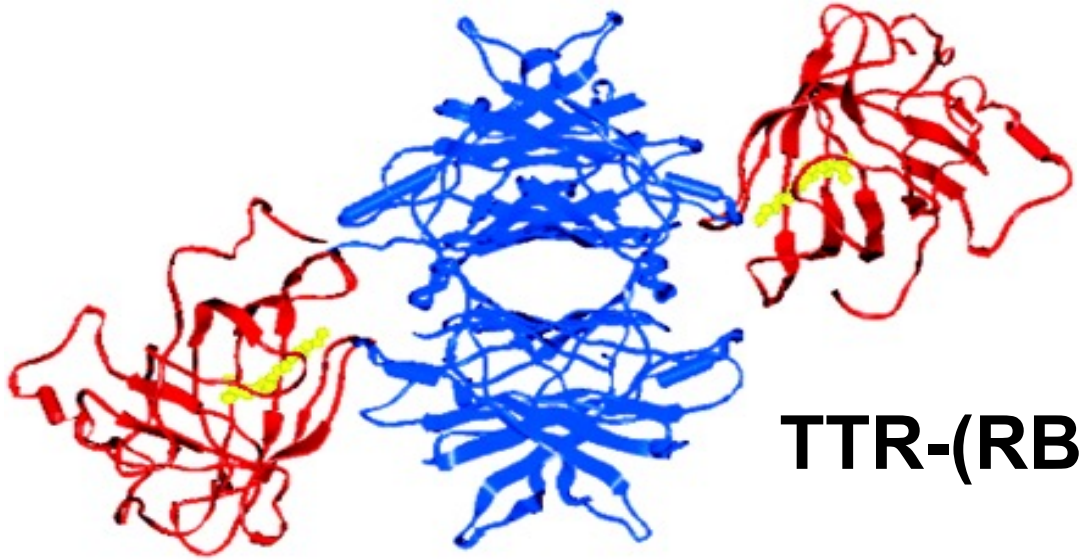
Transthyretin (TTR)–Extracellular Circulatory Protein

Transport Thyroxine Retinol Binding Protein



TTR

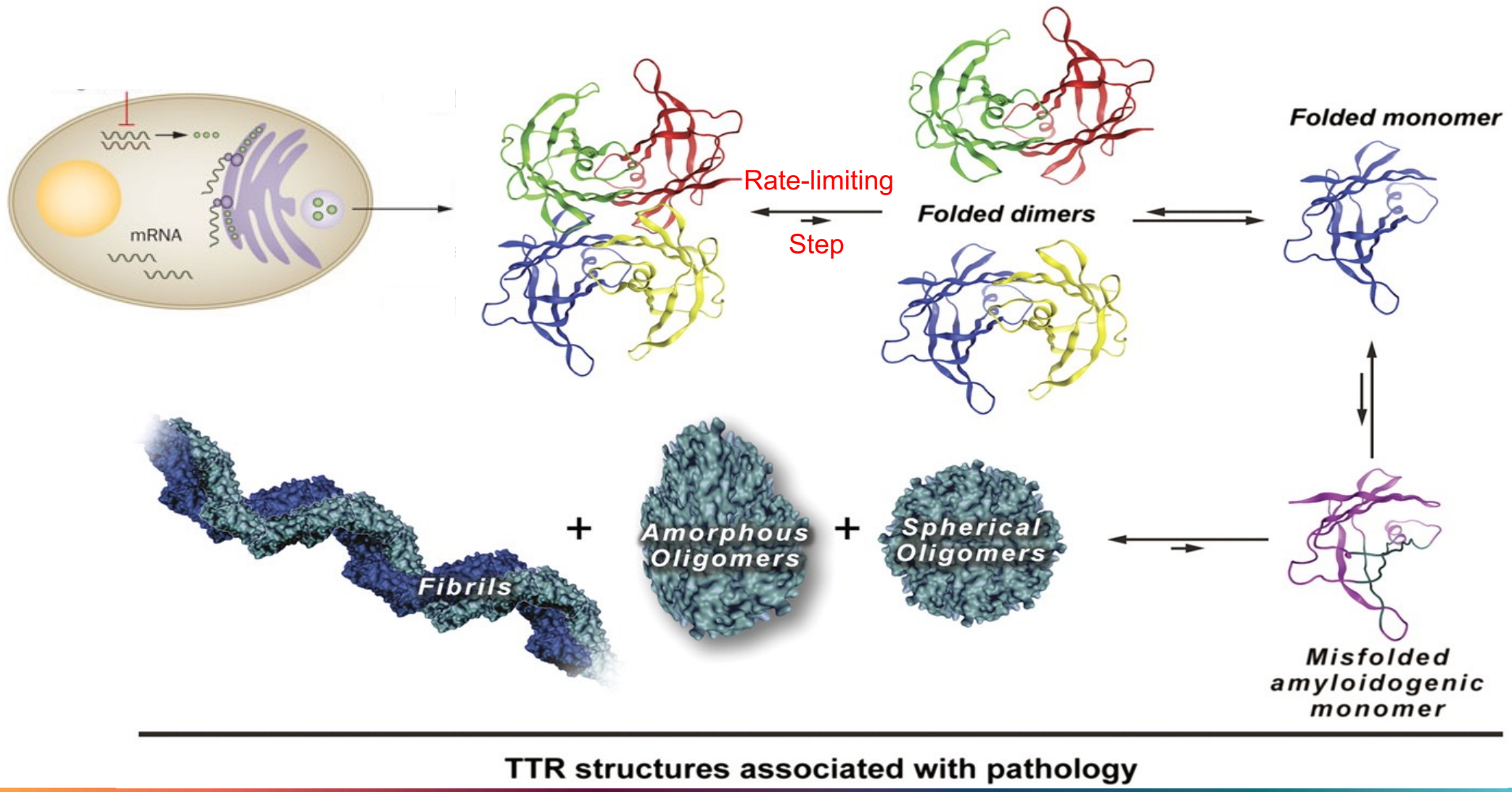
Thyroxine



$TTR-(RBP)_2$

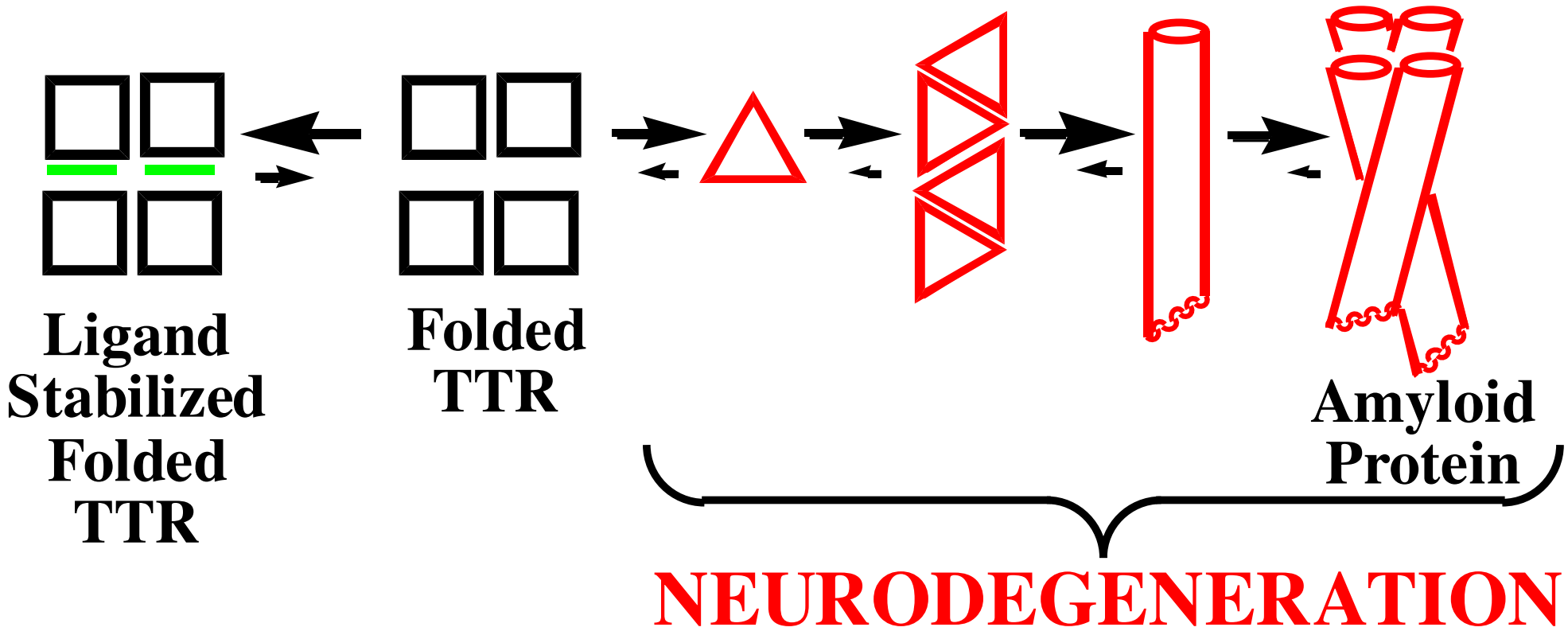
- 127AA β-sheet rich 55 kDa homotetramer
- Present in serum & cerebral spinal fluid
- Ligand-less TTR is the form that aggregates

We Investigated the Detailed Mechanism by Which Transthyretin (TTR) Aggregates–Basic Knowledge Needed for Interventions



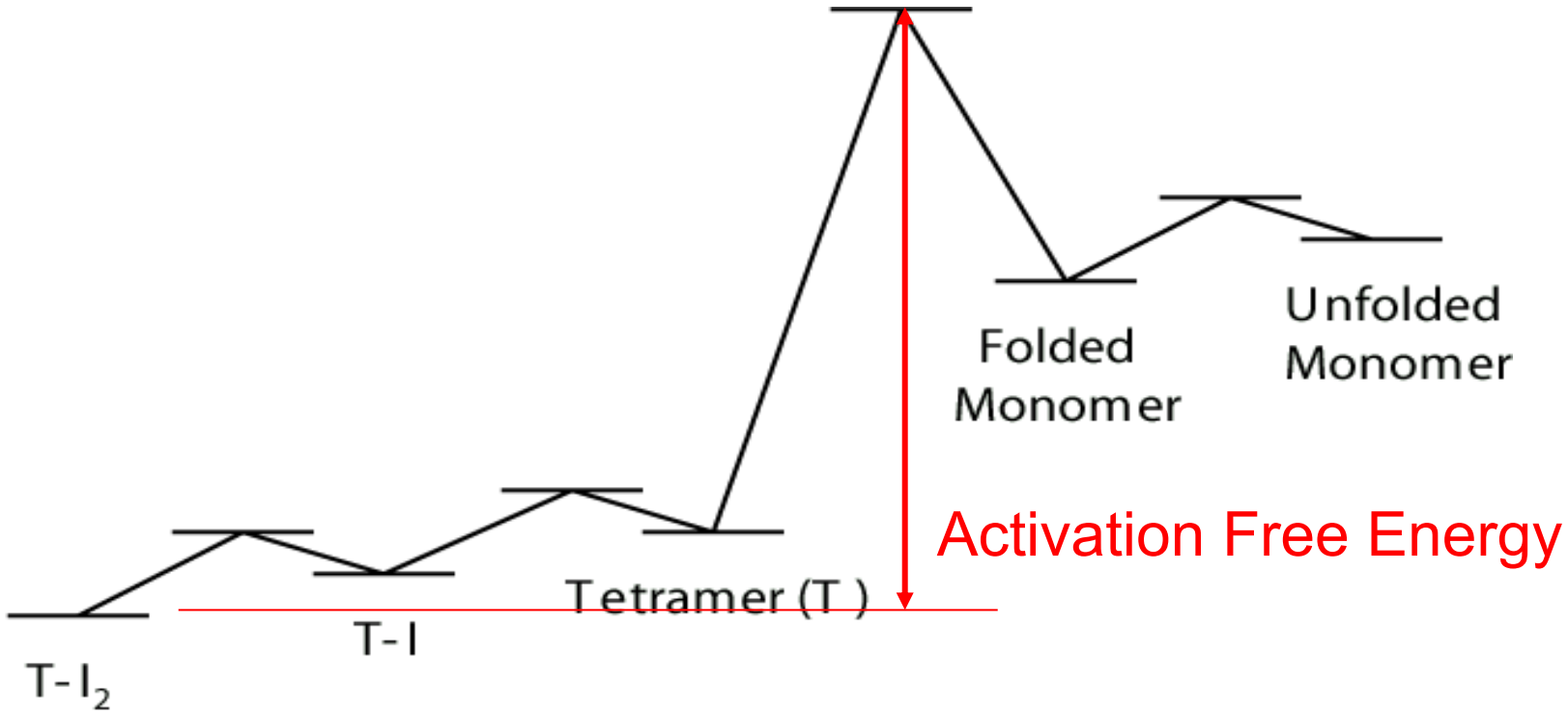
Colon, W.; Kelly, J.W. "Partial Denaturation of Transthyretin is Sufficient for Amyloid Fibril Formation In Vitro." *Biochemistry*, 1992, 31, 8654-8660; Sekijima, Y., Wiseman, R.L., Matteson, J., Hammarström, P., Miller, S.R., Balch, W.E., Kelly, J.W. "Biological and Chemical Basis for Tissue Selective Amyloid Disease" *Cell* 2005 121, 73-85.

Ligand Binding Can Prevent The Tetramer-Amyloidogenic Intermediate Transition Into Misfolded Transthyretin Assemblies



Most Conservative Approach as Clinical Success Dose not Presuppose What the Toxic Species is, Unless its....

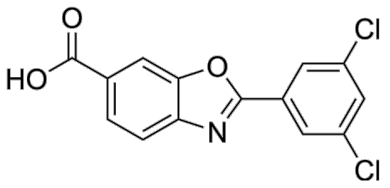
Native State Kinetic Stabilization Mediated by Activation Barrier Tuning w Small Molecules



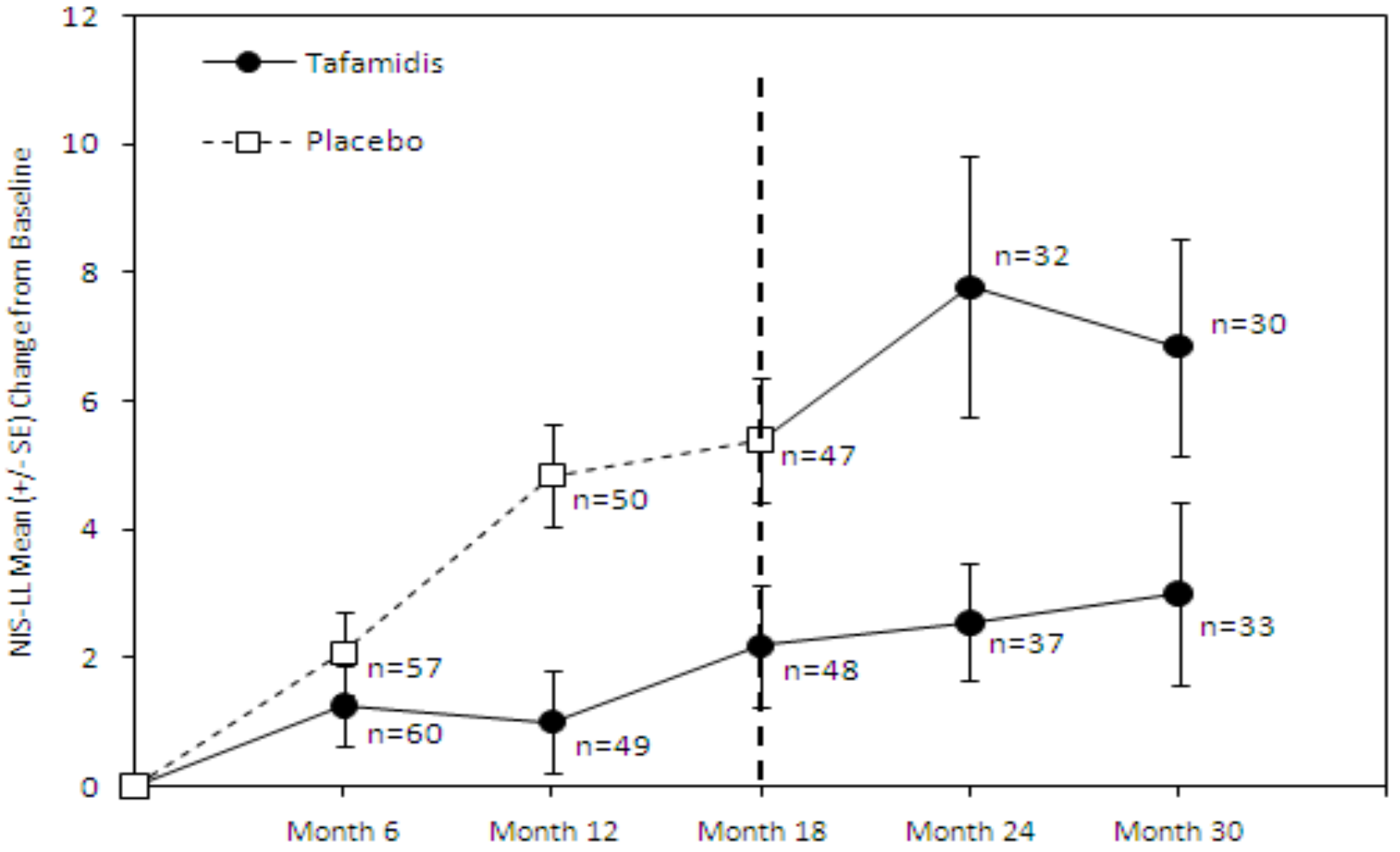
Science 2003, 299, 713-716; *Angew. Chem. Int. Ed.* 2003, 42,2758-276

Neurologic Impairment Score-Lower Limb Neurological Exam—Sensation, Muscle Strength and Lower Limb Reflexes–First Clinical Trial

Change From Baseline, 2011



Tafamidis
20 mg
once daily



- Dr. Richard Labaudiniere
- Dr. Teresa Coelho et al.
- Dr. Donna Grogan

FoldRx

Starting Tafamidis Early in the course of TTR Peripheral and Autonomic Neuropathy offers a substantial advantage to the patient

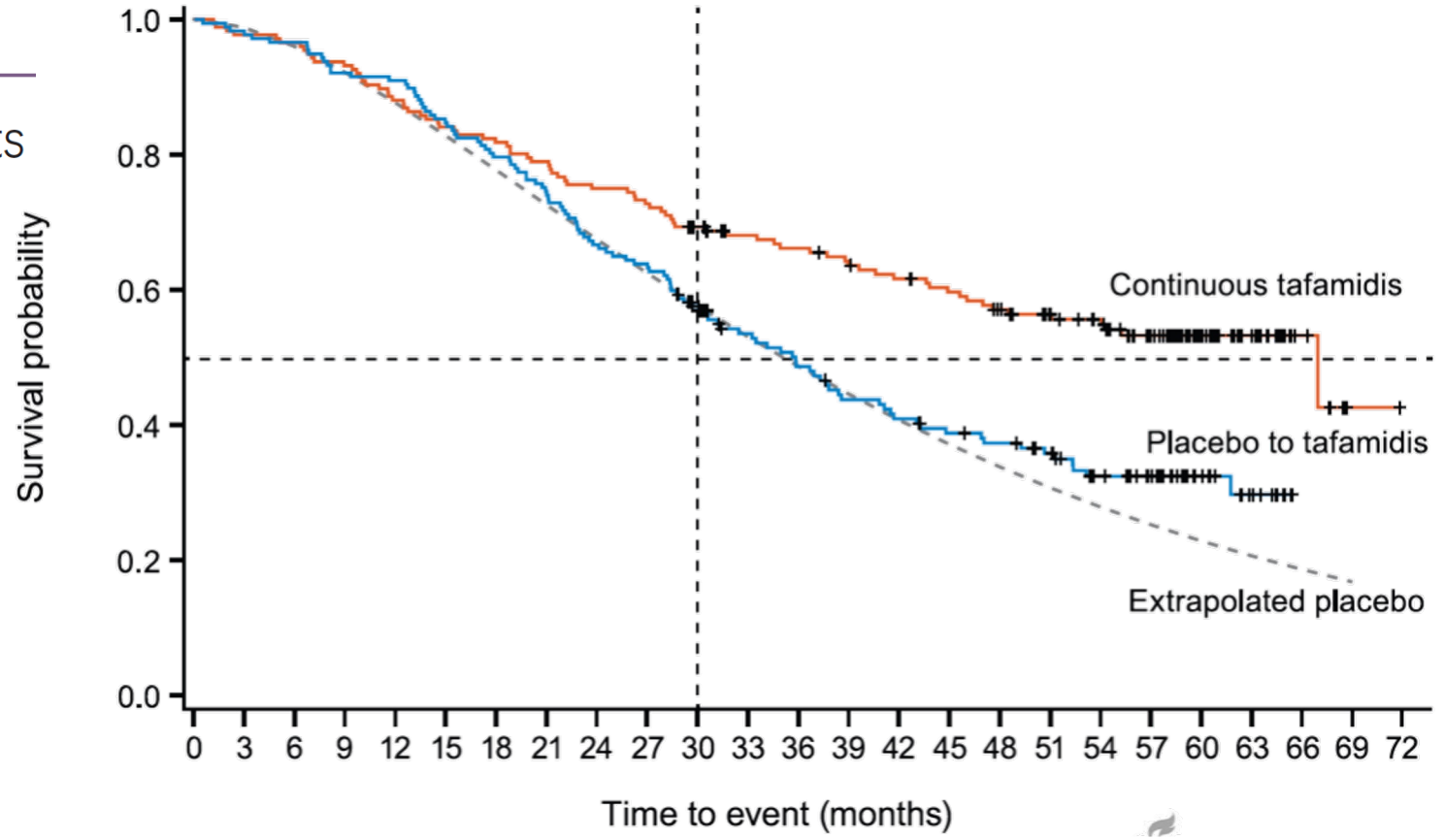
	Stable or improved	Progressing at a slow rate (mean progression of NIS-score is 1.1 / year)
Started on tafamidis (n=22)	68%	22%
Started on placebo (n=22) **18 Month Delay in Start of Treatment**	46%	27%

Indicates that the earlier patients go on Tafamidis the better; prophylaxis when generic

Circulation: Heart Failure

ORIGINAL ARTICLE

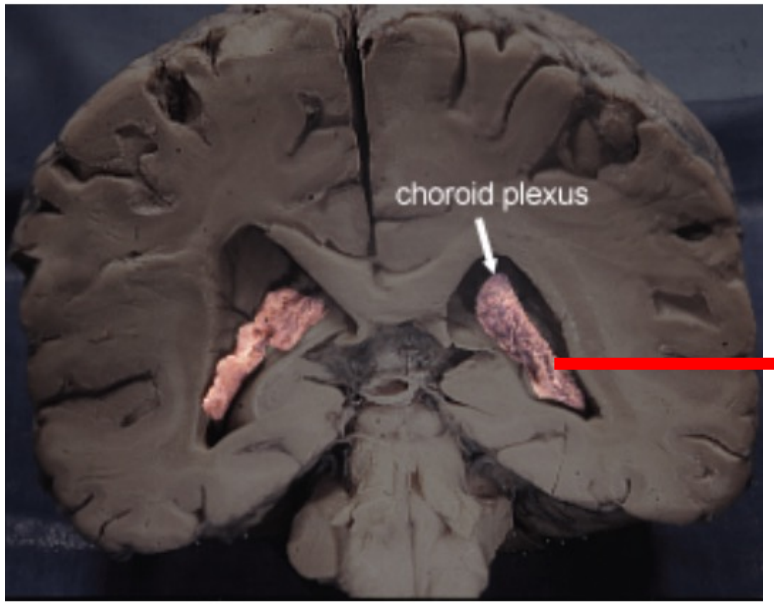
Long-Term Survival With Tafamidis in Patients With Transthyretin Amyloid Cardiomyopathy

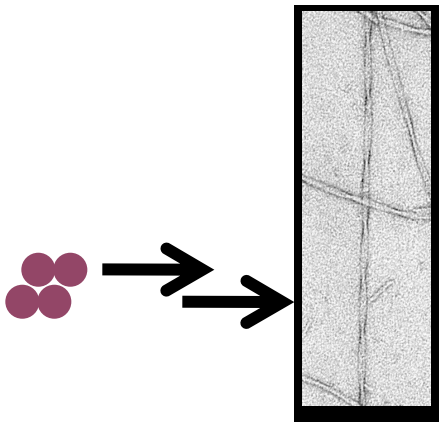


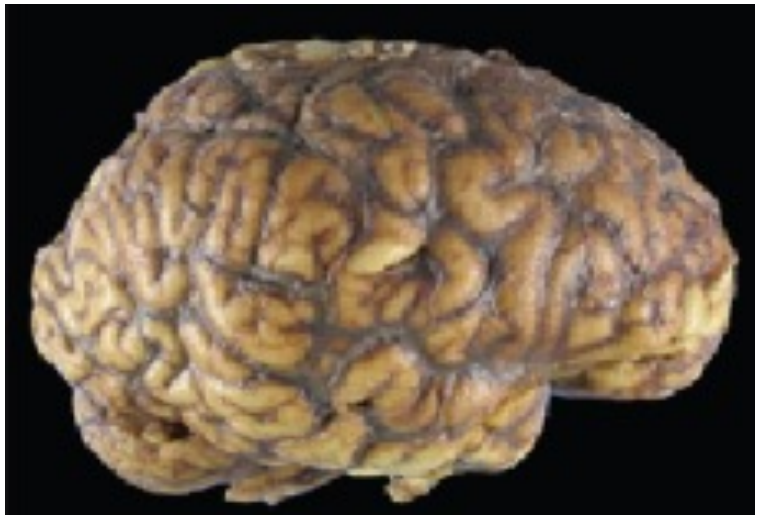
Maurer, M.S., et al., *Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy.* New England Journal of Medicine, 2018. **379**(11): p. 1007-1016.

Transthyretin Amyloidosis Lead to Dementia, Focal Neurologic Episodes, Cerebral Vascular Bleeding

The Choroid Plexus Secretes TTR
Into the Cerebral Spinal Fluid







TTR Aggregation in the CSF Destroys the Central Nervous System

TTR Concentration in Blood ≈ 4 μM
TTR Concentration in CSF ≈ 200 nM

Category 1 Drugs Stop Newly Synthesized Proteins from Aggregating, **But do Not Clear Amyloid**

- **Transthyretin Kinetic Stabilizers**
  - Tafamidis (Regulatory Agency Approval; 2011)
  - Diflunisal (Merck NSAID repurposing as TTR Stabilizer; 2013)

- **Transthyretin mRNA Degraders (Ionis Pharmaceuticals)**

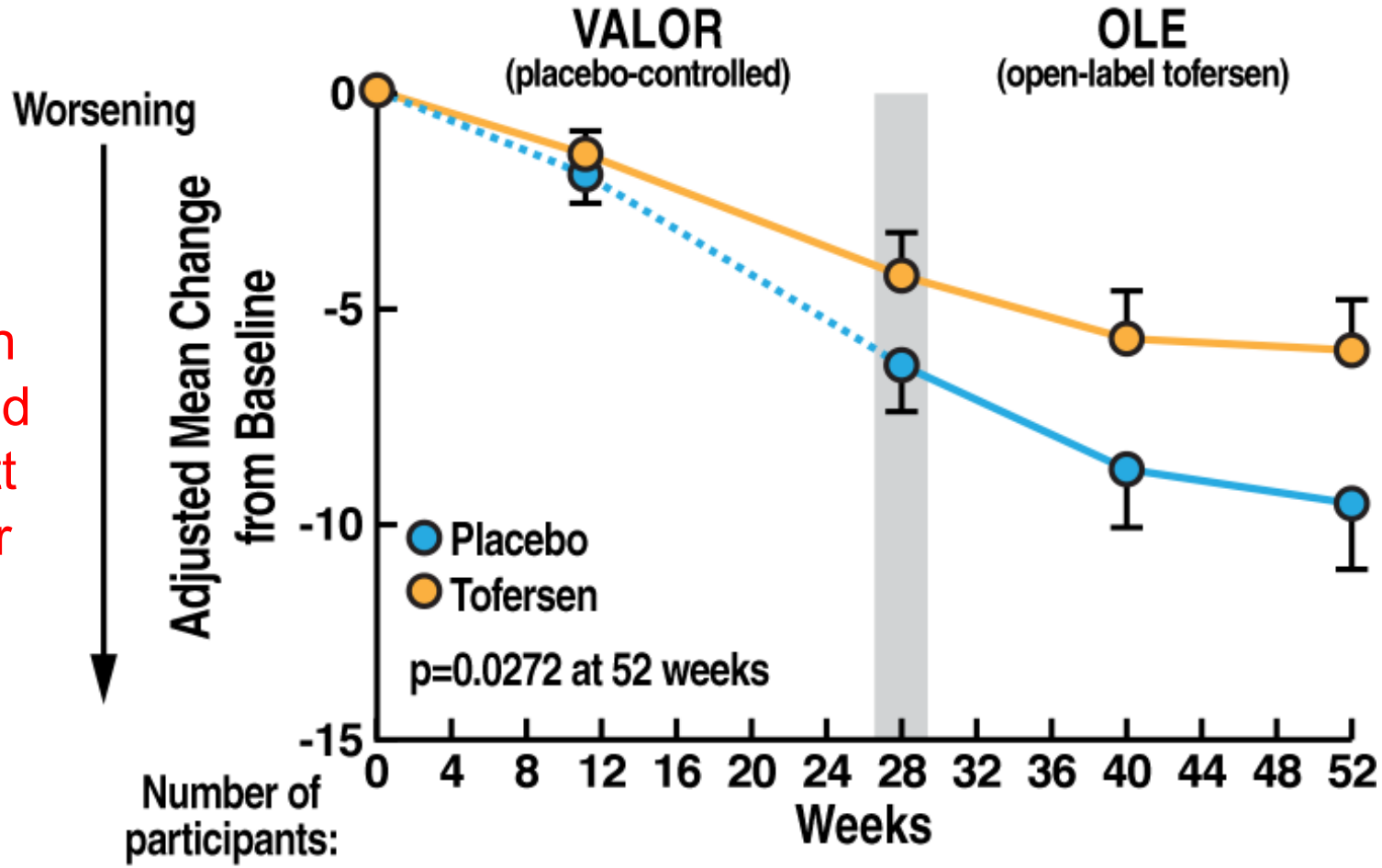
  Inoteresen, and Eplontersen–Antisense Oligonucleotides (2018)

  Patisiran and Vutrisiran–RNAi-based drug (2018)

- **Superoxide Dismutatse Amyotrophic Lateral Sclerosis**
  - Tofersen Antisense Oligonucleotide (2023)

Antisense Oligonucleotide Against SOD, Tofersen, to Ameliorate SOD-Amyotrophic Lateral Sclerosis

Richard Smith
Don Cleveland
Frank Bennett
Timothy Miller

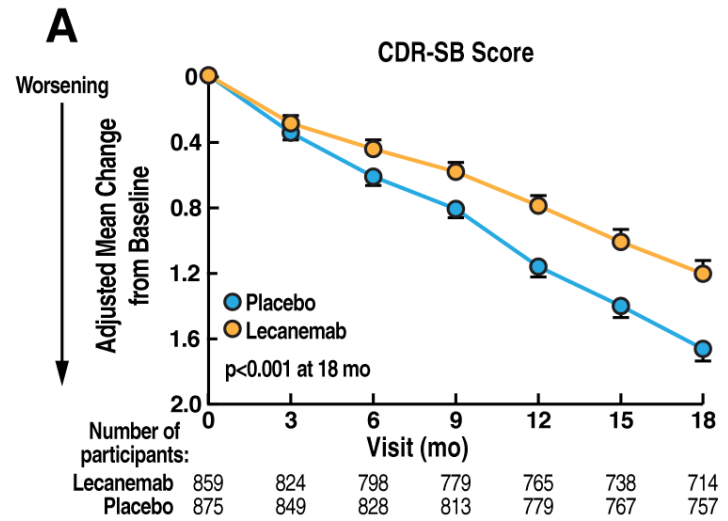


Category 2 Drugs Clear Amyloid Fibrils, and May Slow the Aggregation of Newly Biosynthesized Proteins

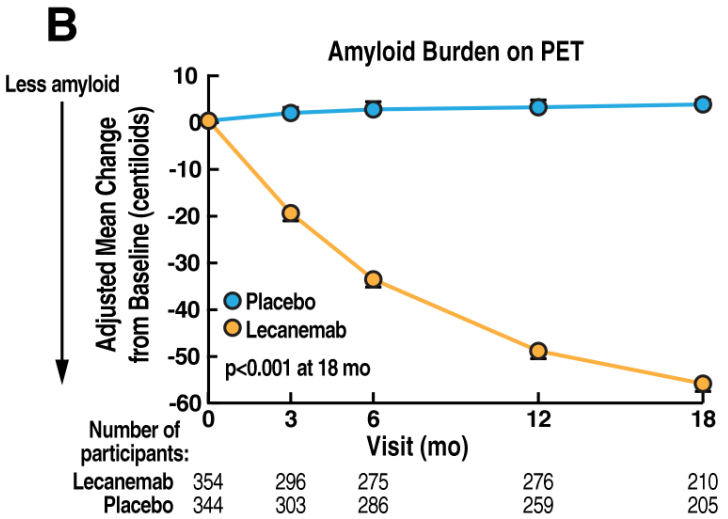
- **Alzheimer's Aβ Aggregate Seeking Monoclonal Antibody**
  - Aducanumab (2021; Marketing Withdrawl)
  - Lecanemab (2023)
  - Donanemab (Not an Approved Drug)
- **Parkinson's α-Synuclein Aggregate Seeking Antibody**
  - Prasinezumab (Not an Approved Drug, Clinical Results Promising

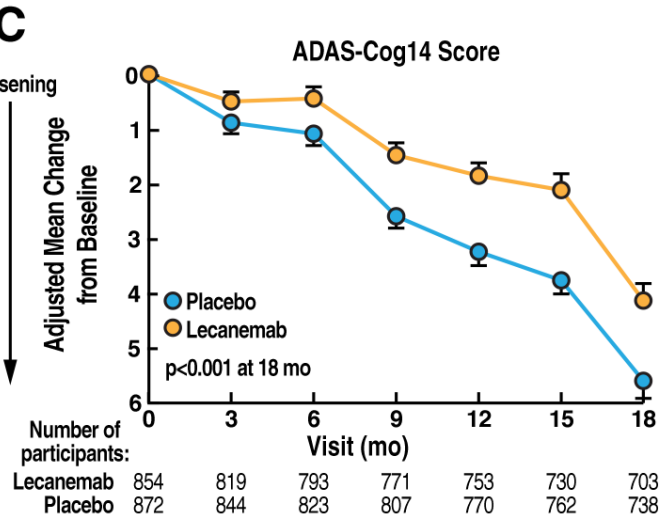
These Antibodies recruit Microglial Cells to the cross-β-sheet amyloid fibrils and in some cases other aggregates mediating cellular endolysosomal uptake and an autophagy-mediated degradation

Lecanemab, an Aβ Oligomer & Amyloid Fibril Removing Antibody, Significantly Slowed Cognitive and Functional Decline



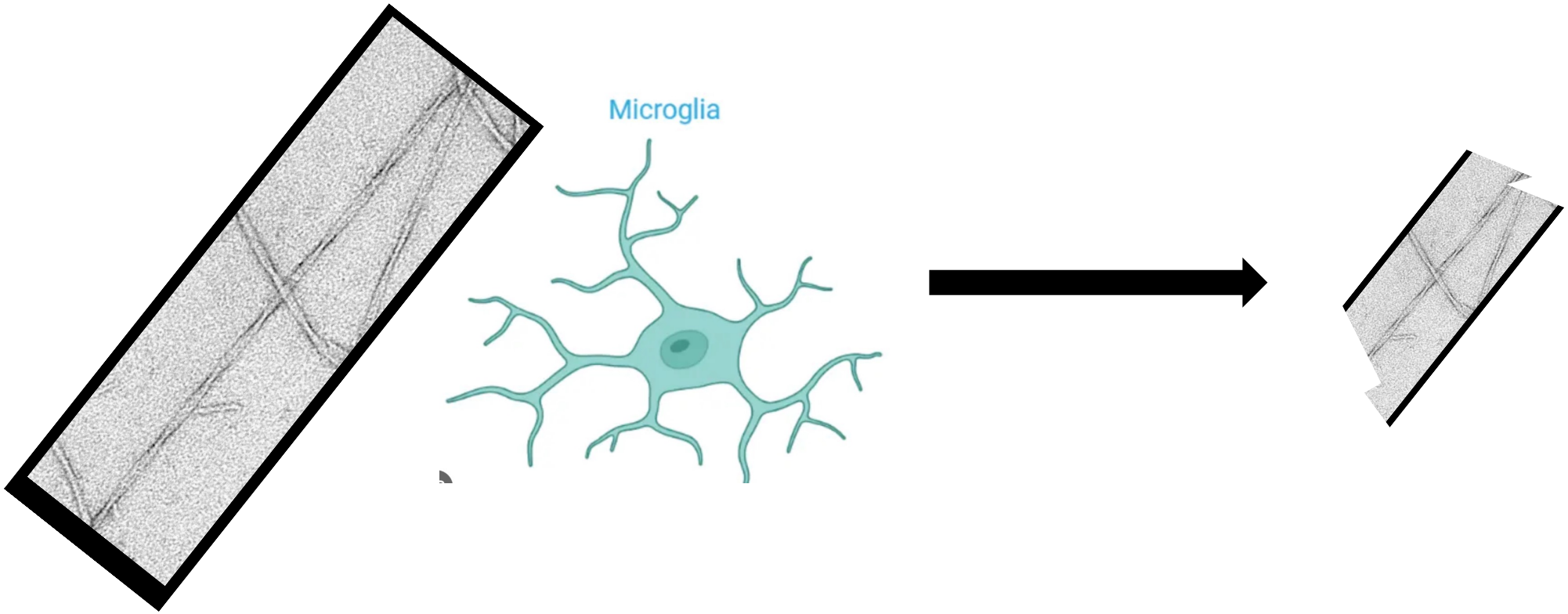
Lars Lannfelt Discovered Arctic and Swedish Hereditary AD Mutations & Lecanemab in his academic lab





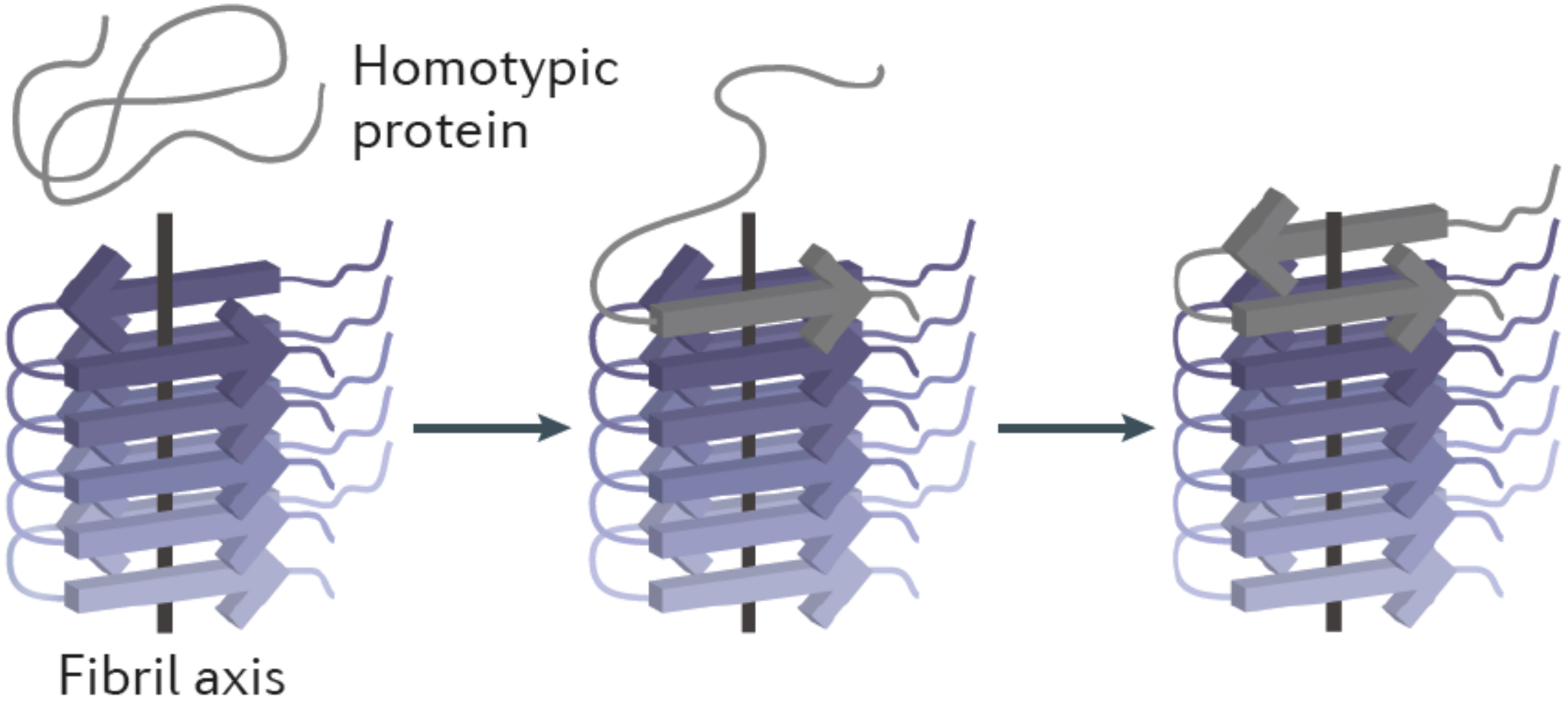
Unifying Hypothesis for how the Dozen Regulatory Agency Approved Neurodegeneration Drugs Function

Step 1: Creating Naked Amyloid Fibrils Inside and Outside of Cells



Goate, Glass, Barres, Cleveland, Holtzman

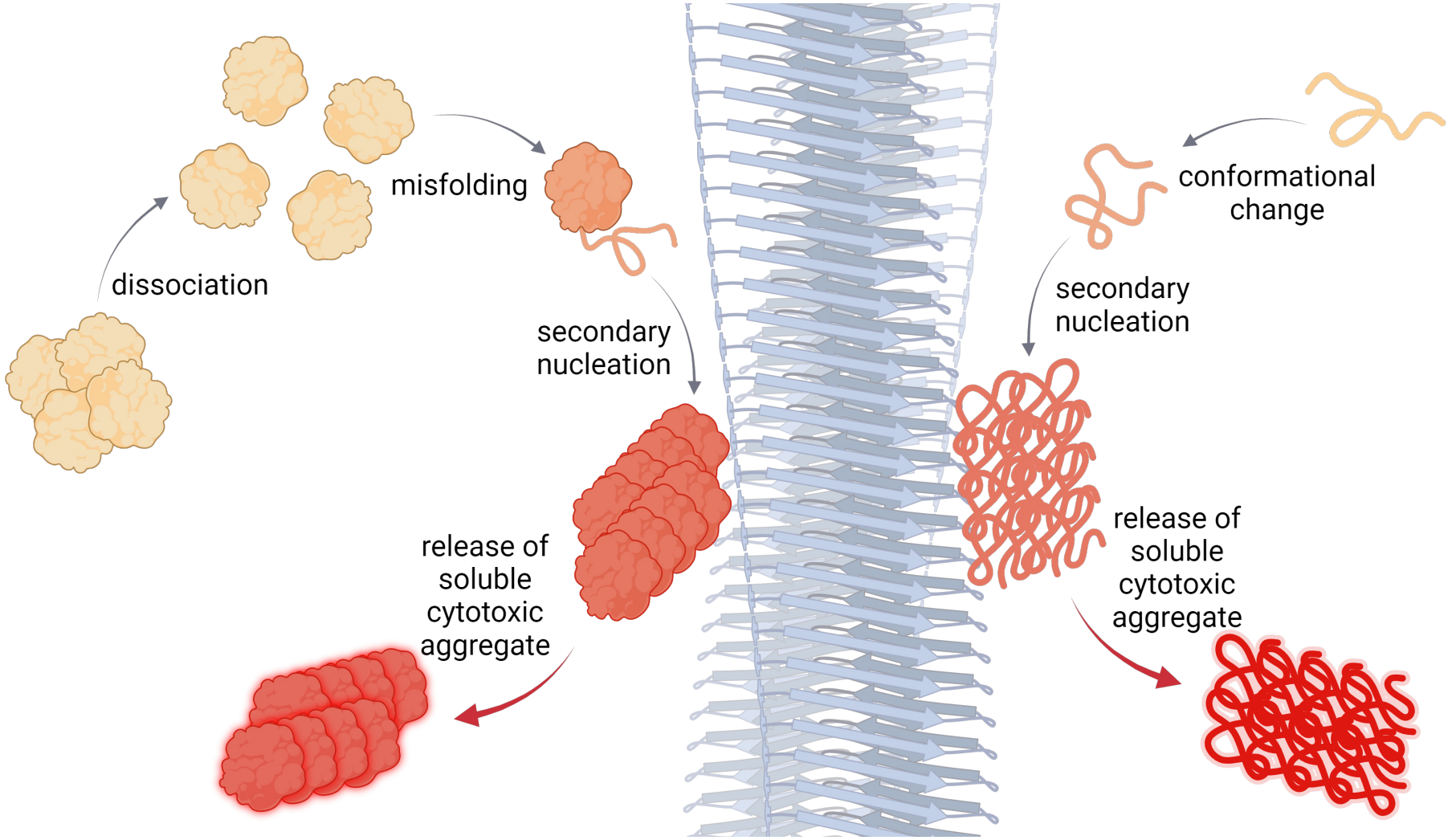
Step 2: Cell-to-Cell Spreading of Amyloid by Primary Nucleation or Templated Misfolding Increases Naked Amyloid Levels



Jucker, Collinge, Westermark, Diamond, Knowles

Step 3. Secondary Nucleation

Secondary nucleation converts the misfolding-prone proteome into highly dynamic non-amyloid aggregates that dissociate from amyloid and remain soluble



Protein Aggregation is a Main Driver of Morbidity and Mortality in Amyloid Diseases

- Genetic data in Support of the Aggregation Hypothesis to explain neurodegeneration in the Literature for Decades
- Starting about 10 years ago widespread skepticism owing to clinical trial failures (predominantly in Alzheimer's disease)
- The hypothesis that protein aggregation causes neurodegeneration lacked substantial support by the scientific and medical communities before the pharmacological clinical trial data was generated

Thank You

Acknowledgments

- Dr. Per Hammarstrom
- Dr. Hans Purkey
- Prof. Luke Wiseman
- Prof. Evan Powers
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- Prof. Ian Wilson
- Prof. Joel Buxbaum
- Dr. Hossein Razavi
- Dr. Ted Foss
- Dr. Steven Johnson
- Dr. Wilfredo Colon
- Dr. Xin Jiang
- Dr. Vicki Lai
- Dr. Greta Miroy
- Dr. Michael Petrassi
- Dr. Stephen Connelly
- Mr. Jeff Packman
- Dr. Donna Grogan
- Dr. Richard Labaudiniare

$$

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