Precision Therapies for Aging-associated Neurodegenerative Diseases

Jeffery W. Kelly

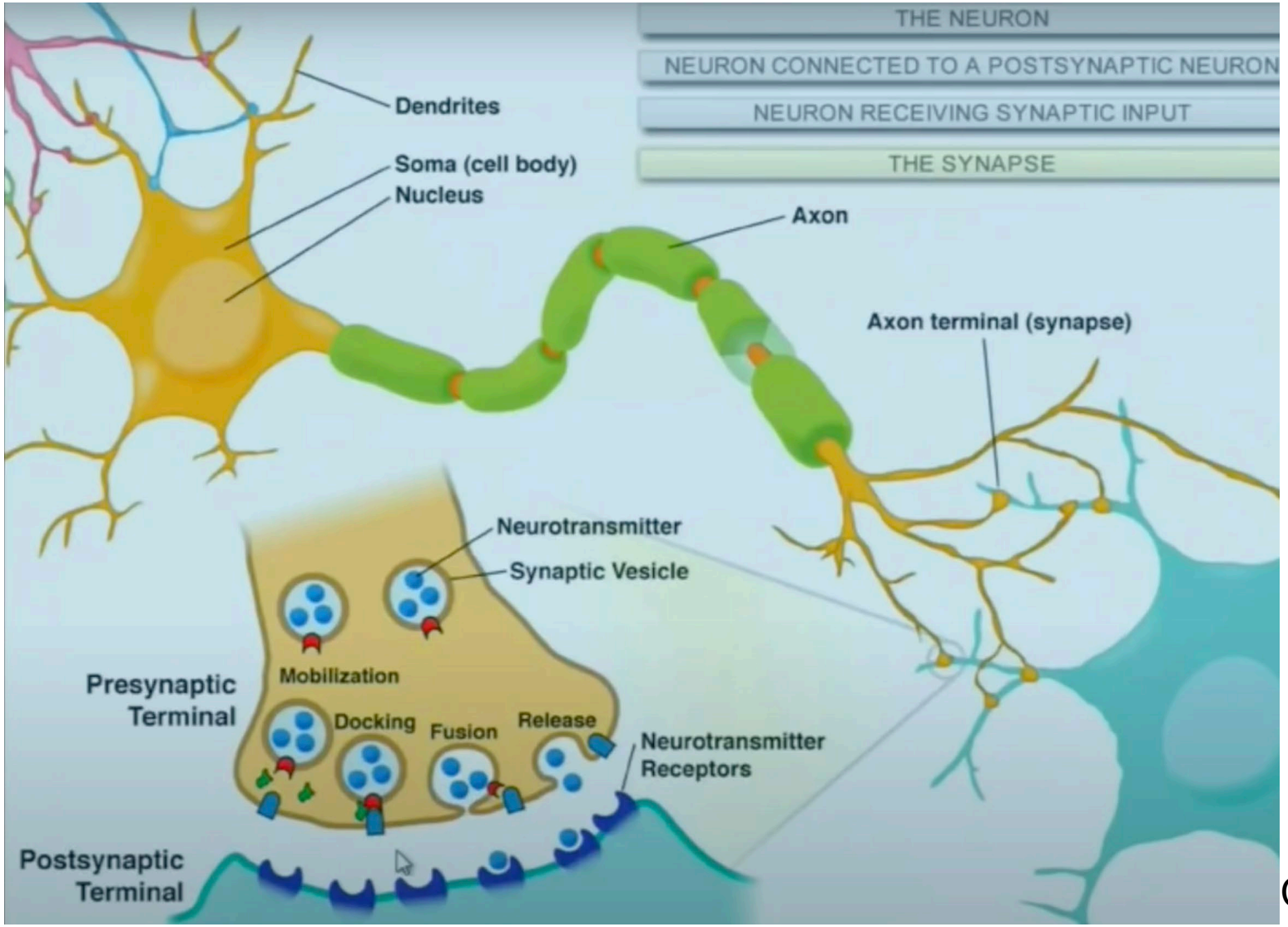
Lita Annenberg Hazen Professor of Chemistry

Wednesday September 15, 2021 1:00 PM PT

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, ≈ 1 million Patients worldwide

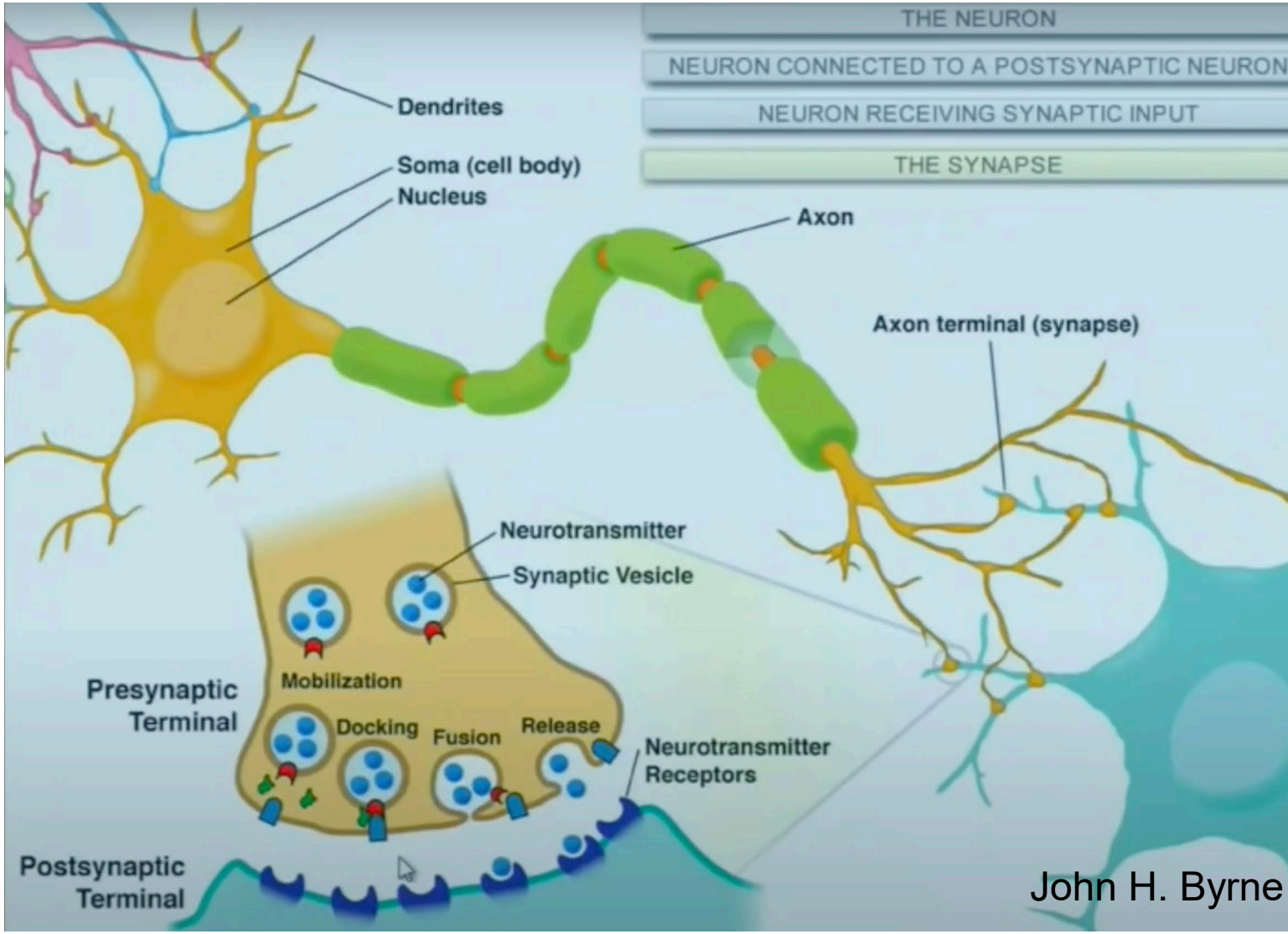
Introduction to Neurons



Credit: John H. Byrne

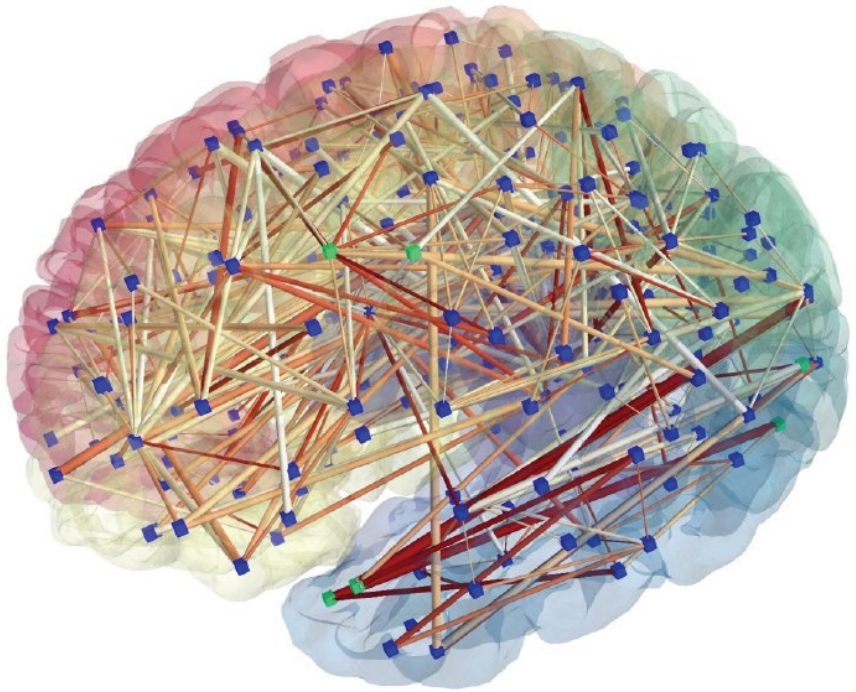
Neurodegenerative Diseases

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

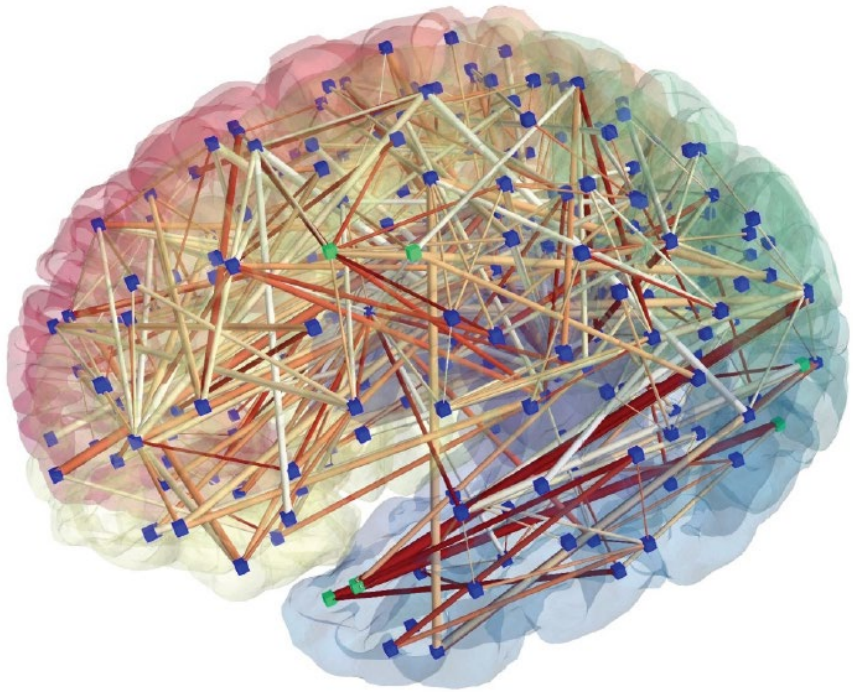


Brain Function Requires Neuronal Communication

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

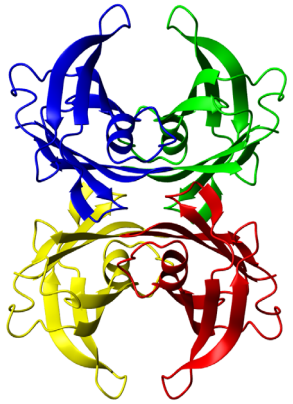


Brain Function Requires Neuronal Communication

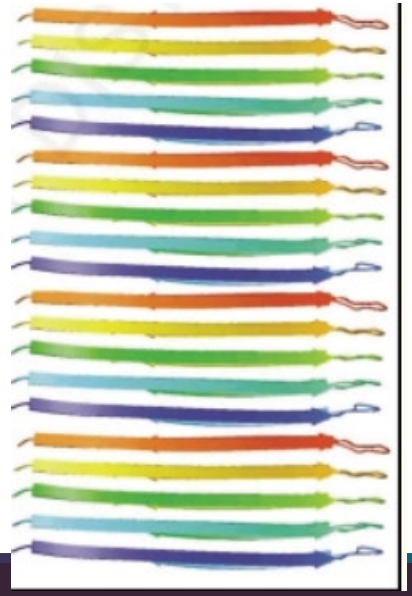


Several Organ Systems are Compromised!

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)

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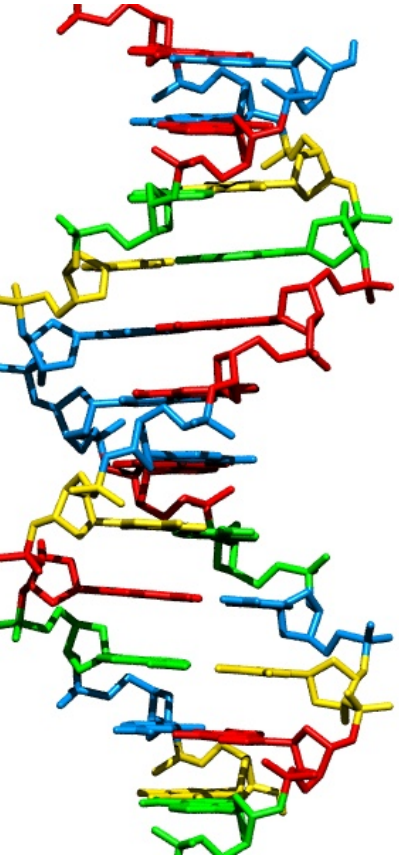
A primer on how normal protein shapes are attained

Cellular Protein Folding



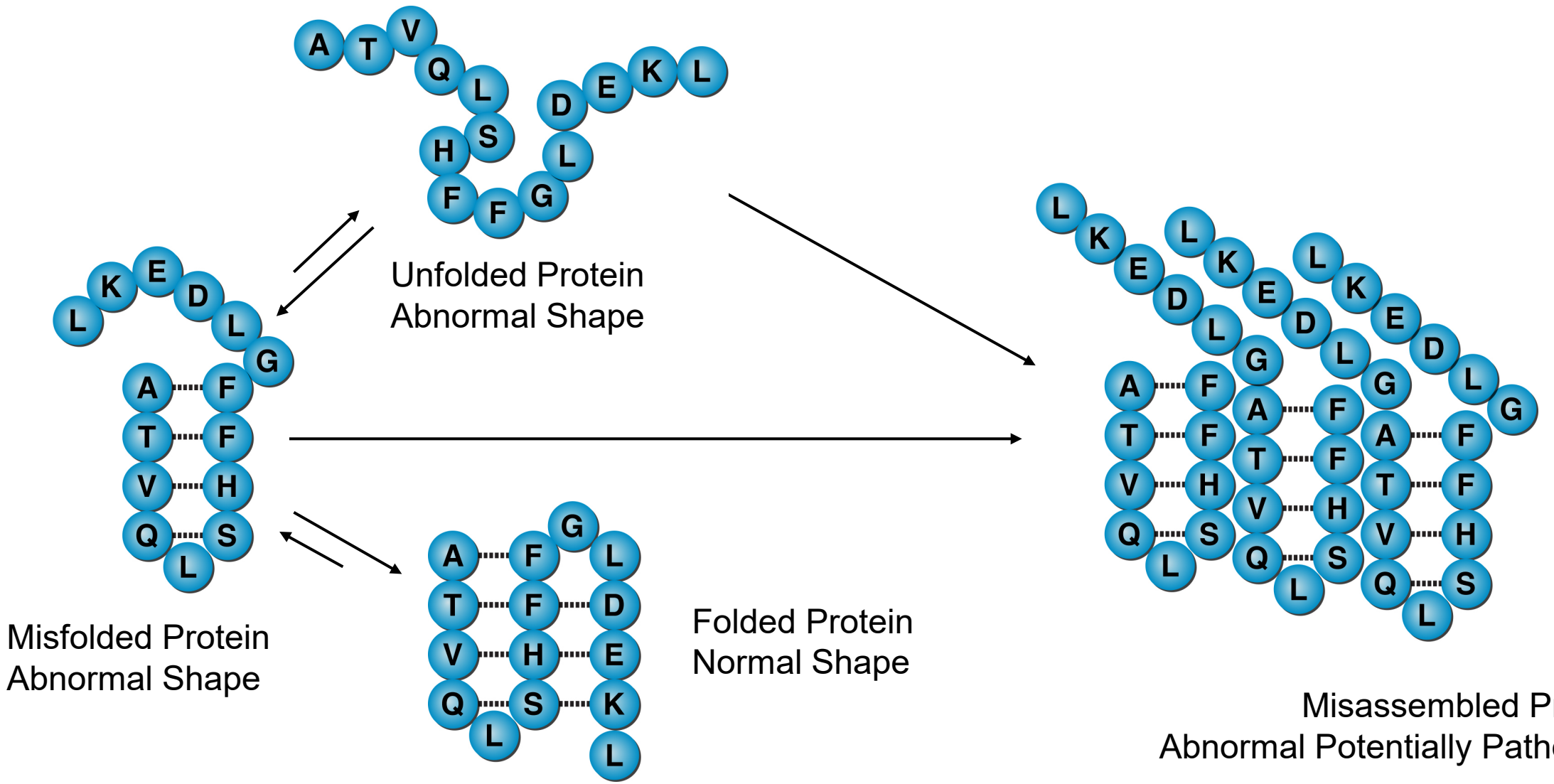
DNA to RNA to Protein

DNA is transcribed into RNA, RNA is translated into Proteins

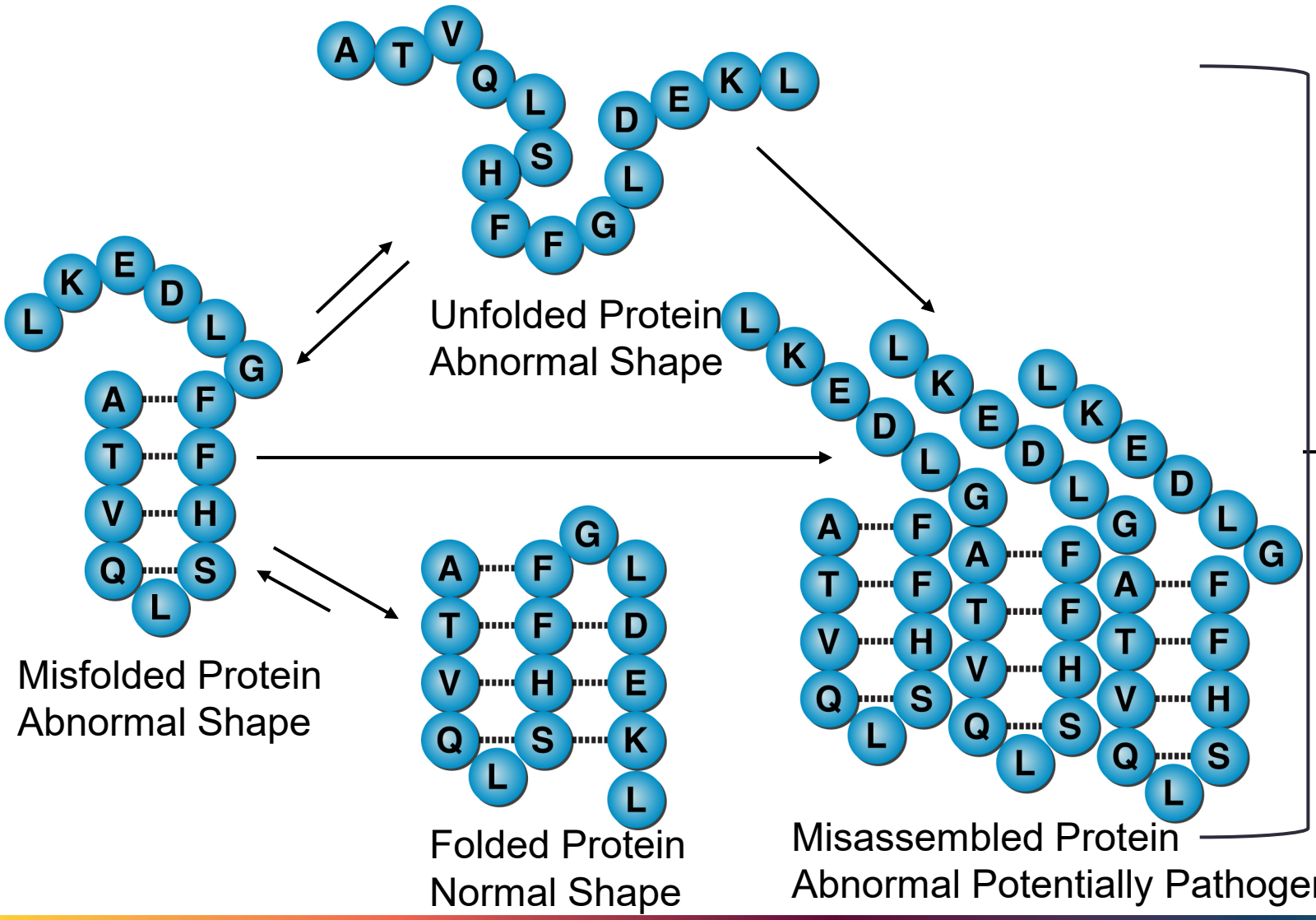
Proteins are best thought of as a unlatched Pearl Necklace, composed
Of twenty different colored pearls or amino acids owing to their distinct
chemical properties

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

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

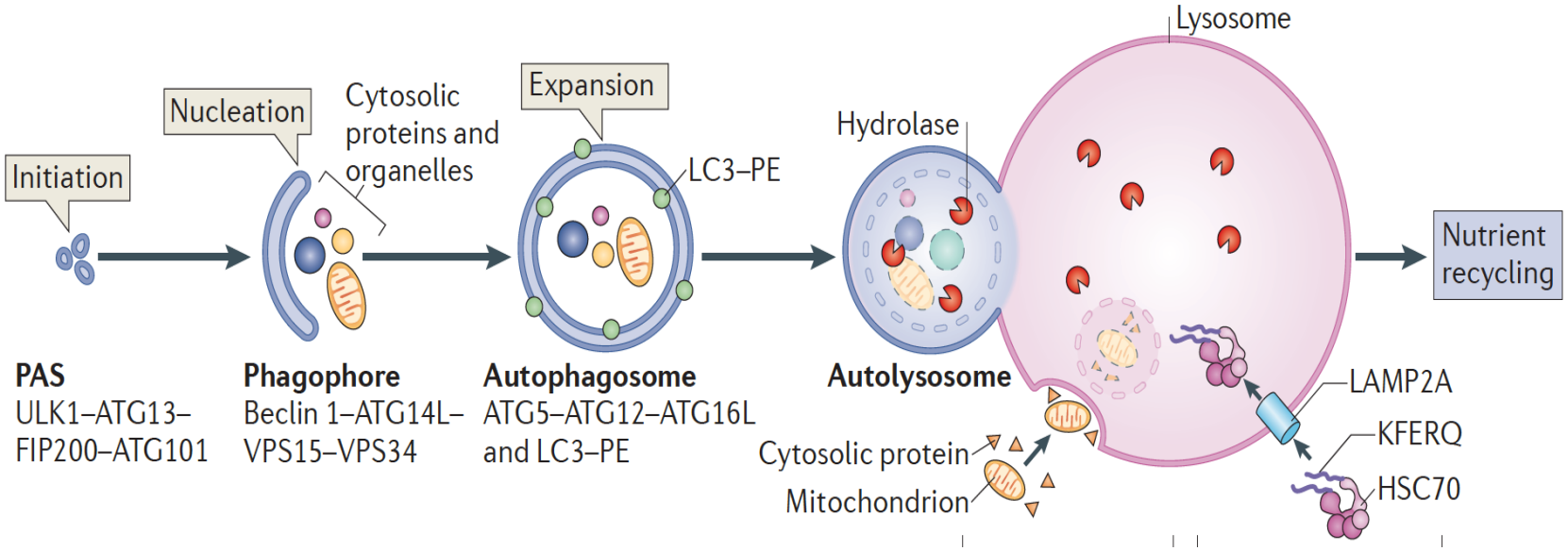
Conclusion of Introduction

Intracellular Protein Folding, Mis-shapen Protein Formation are Competitive Processes

- Cellular degradation competes with misfolding and misassembly and prevents myriad abnormally shaped proteins for accumulating when we are young
- Cellular degradation can become less efficient after age 65, thus abnormally shaped proteins increasingly accumulate
- Abnormally shaped protein accumulation instead of degradation or folding can lead to neurodegeneration–very relevant in Parkinson's Disease

Since Intracellular Degradation Capacity Wanes with Aging, We Seek Degradation (Autophagy) Activators

Lysosomal degradative process used to recycle obsolete cellular constituents and eliminate damaged organelles, protein aggregates, and lipids–there is also constitutive turnover of cellular constituents



Nat Rev Drug Disc 2007, *6*, 304-312.

Nat Rev Mol Cell Bio 2015, *16*, 461-472.

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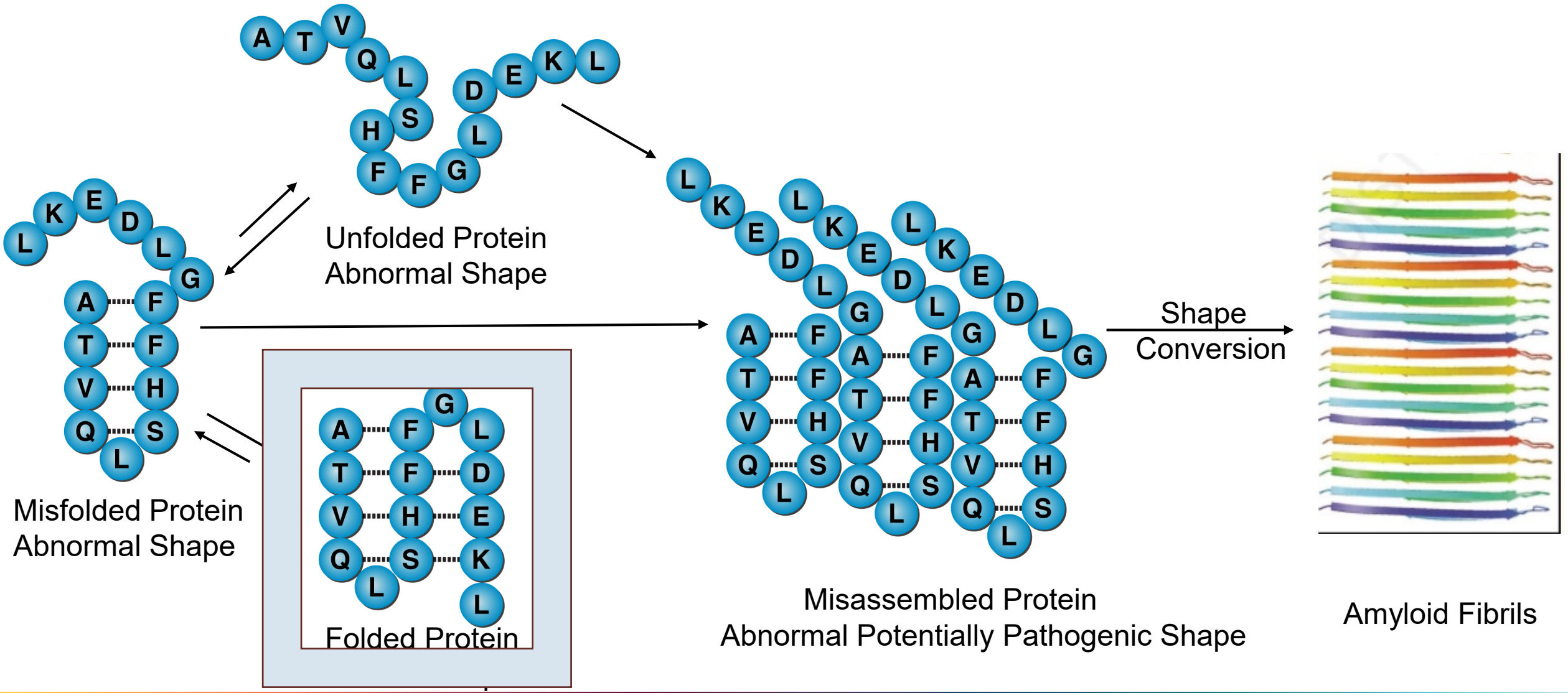
After Folding About 30% of human Proteins Are Sent Outside of the Cell

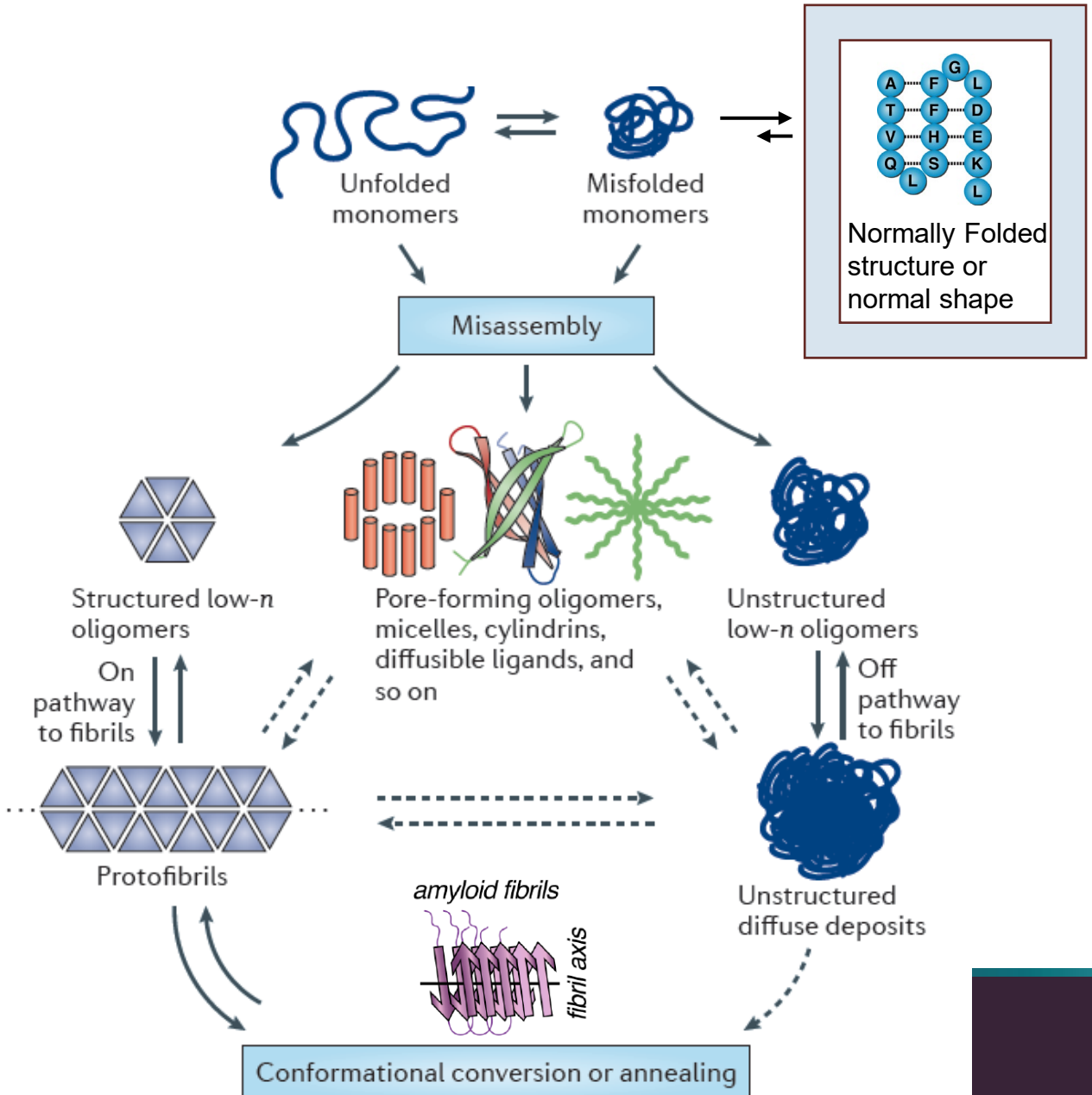
Inability to Maintain Normal Protein Shapes in the extracellular space causes major neurodegenerative diseases-Alzheimer's & Transthyretin Amyloidosis




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



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



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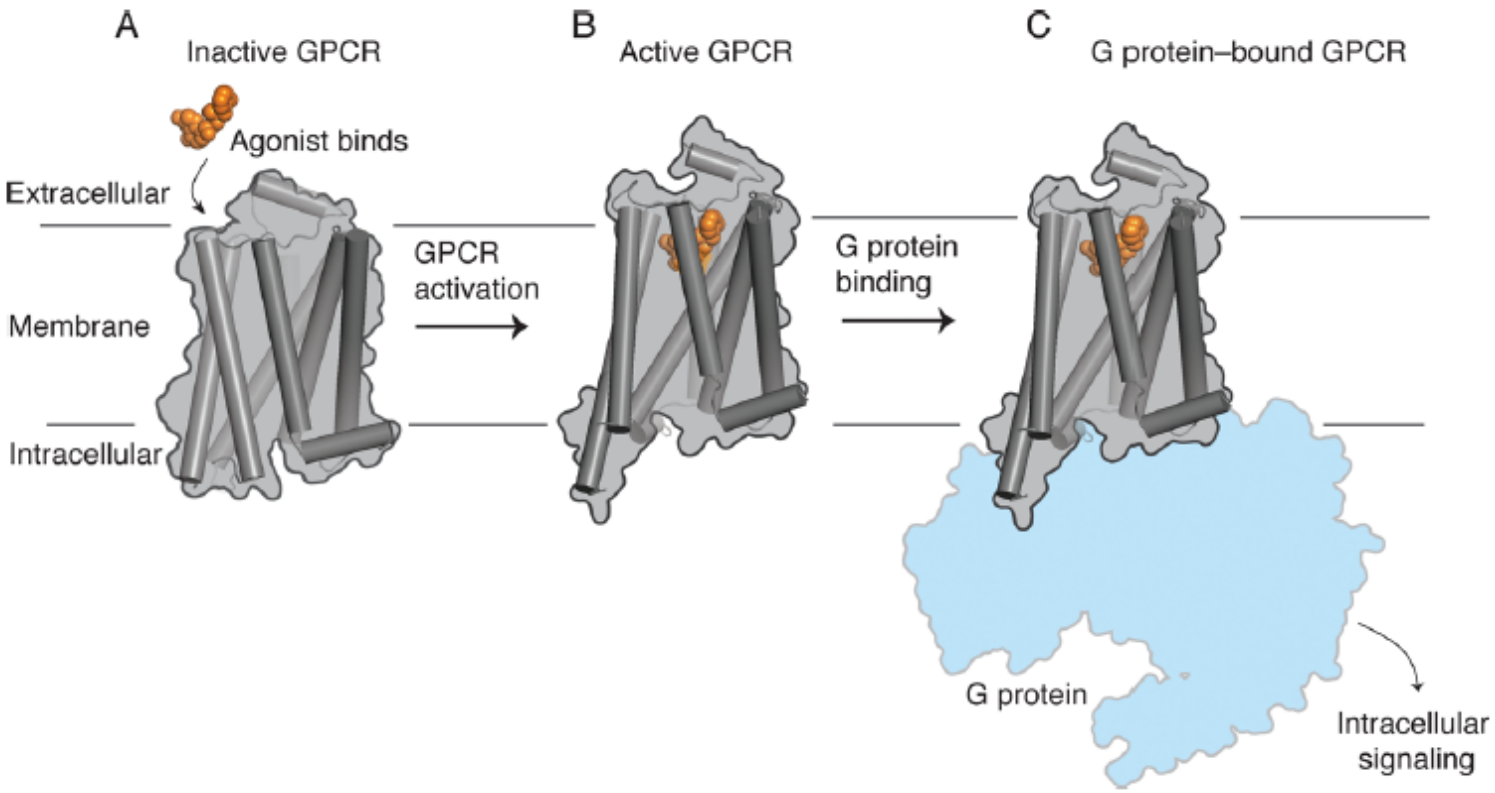
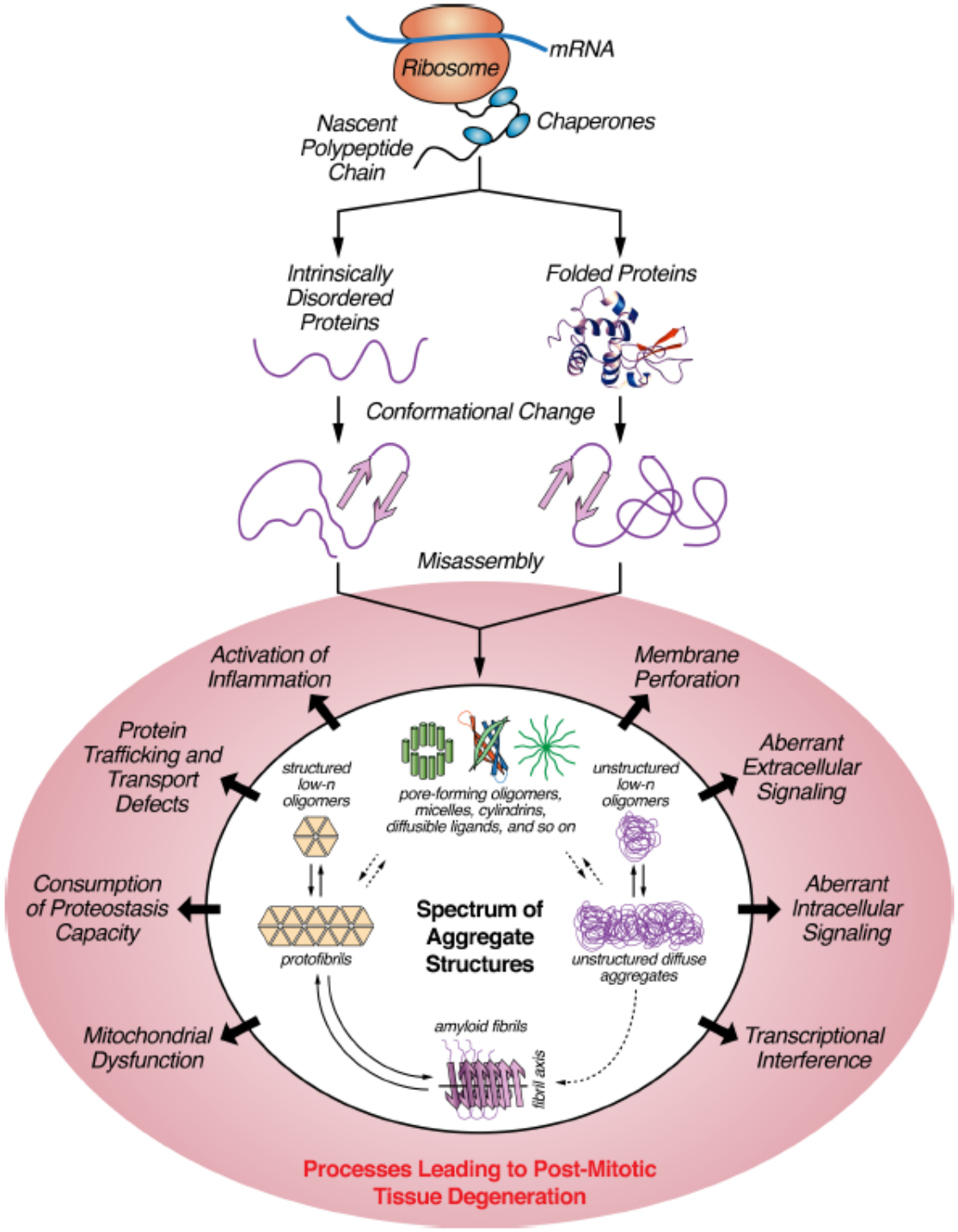
So Why do Abnormal Protein shapes Lead to Neurodegenerative Diseases ?

Protein shapes or structures enable their functions

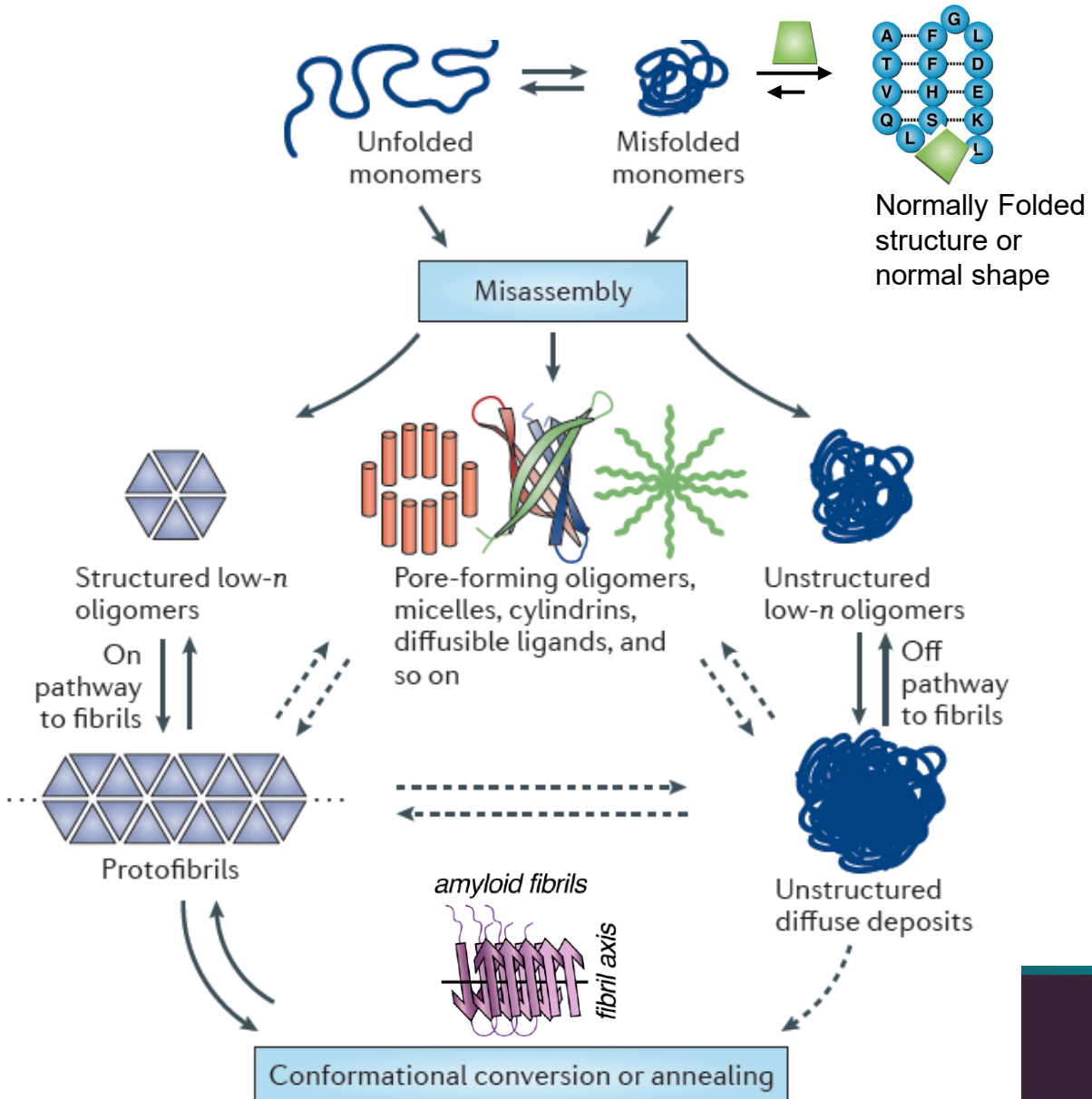


Mechanism of Tissue Degeneration

Hence abnormal shapes confer abnormal functions that ultimately damage the tissue in contact with these Abnormal Protein Shapes



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



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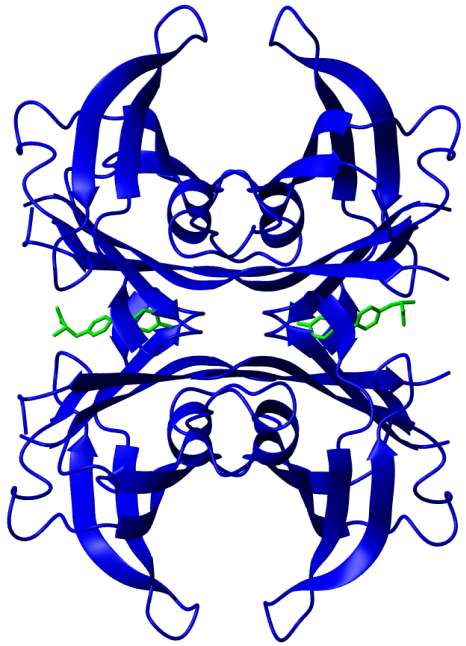
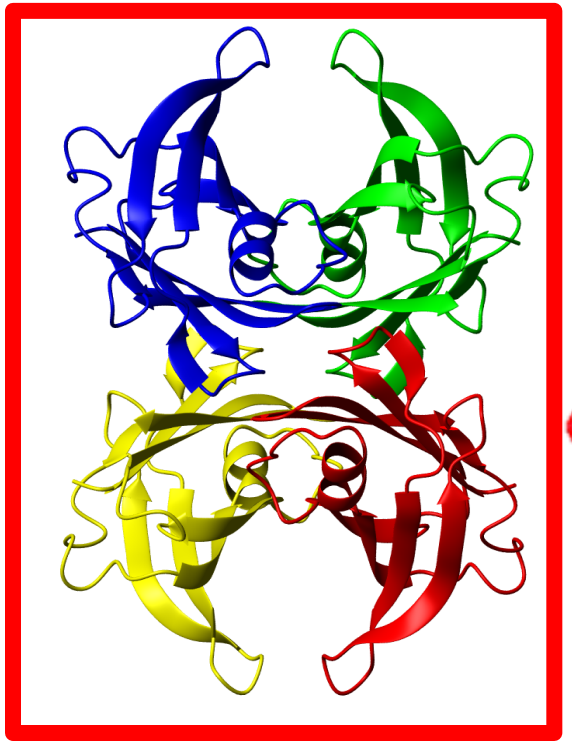
Transthyretin Amyloidosis

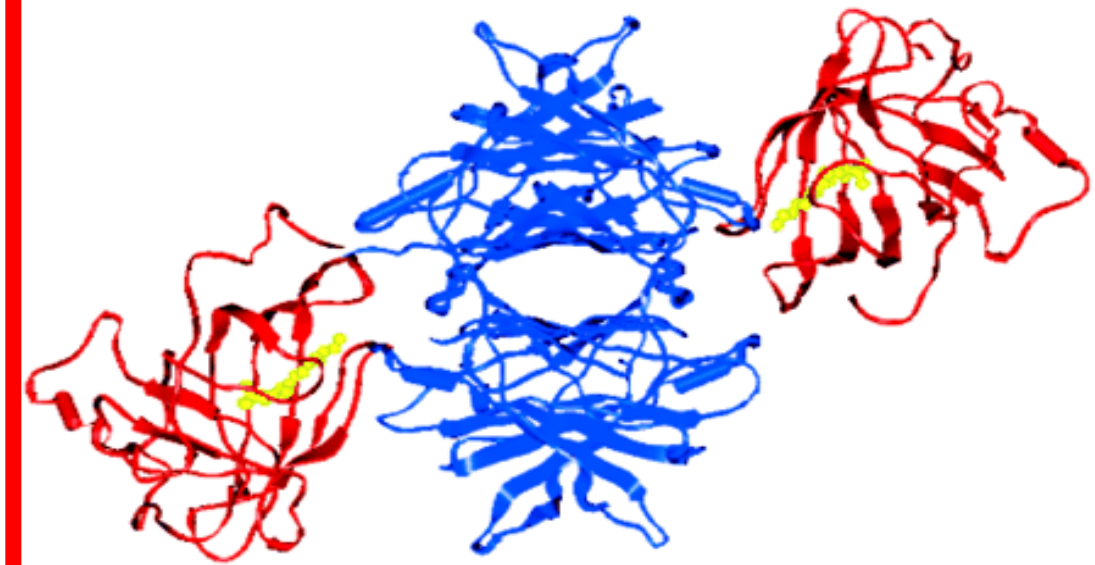
Peripheral, autonomic and central nervous system degeneration and/or cardiac degeneration

Transthyretin (TTR)

Transport Thyroxine Retinol Binding Protein







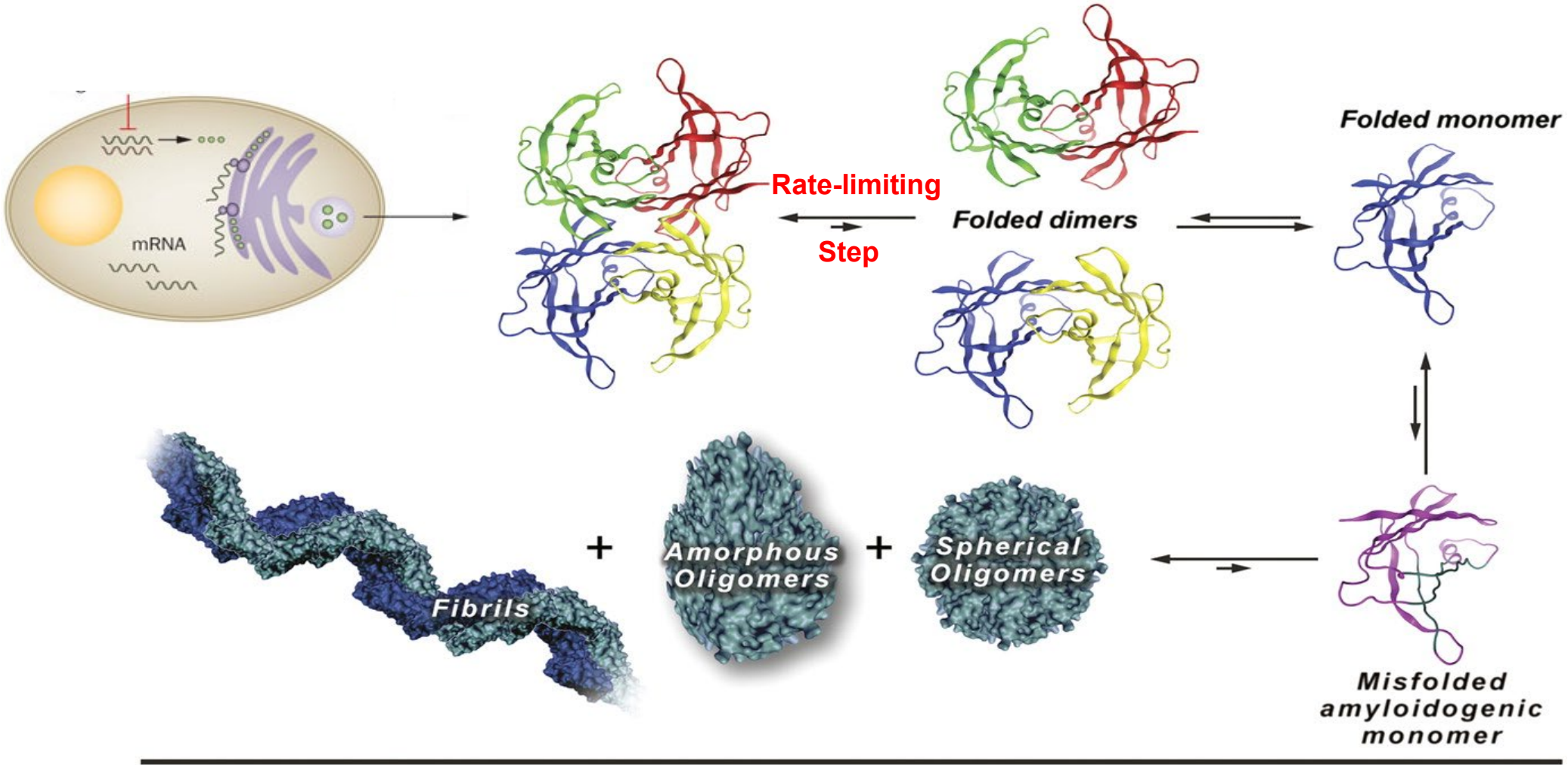
$TTR\text{-}(RBP)_2$

TTR

Thyroxine

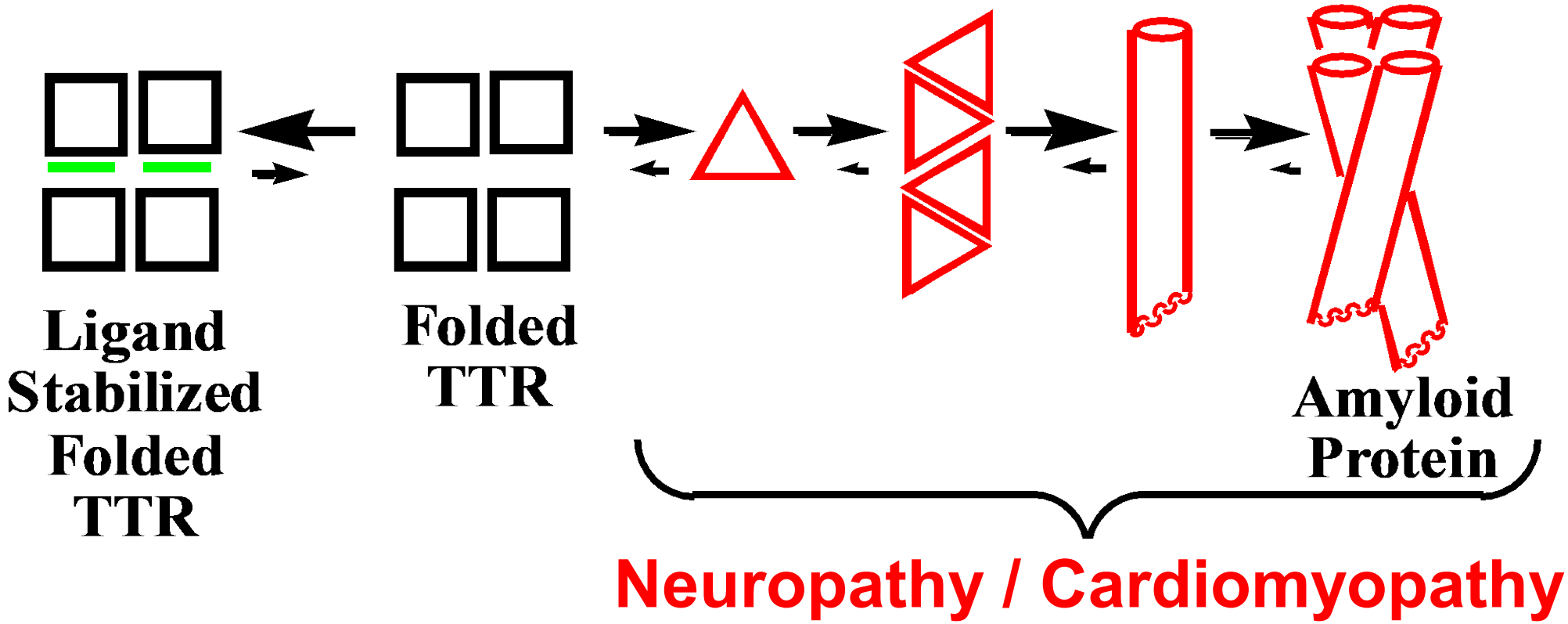
- 127AA β-sheet rich 55 kDa homotetramer
- Present in serum & cerebral spinal fluid
- Ligand-less TTR is the form that aggregates

Human Genetic Evidence Suggested Inability to Maintain the Extracellular Folded State Leads to More Misfolding & Misassembly



So we performed a decade + of Careful Research to Understand the Pathway By Which the Transthyretin Protein Undergoes Shape Changes that lead to Abnormal Protein Shape Formation

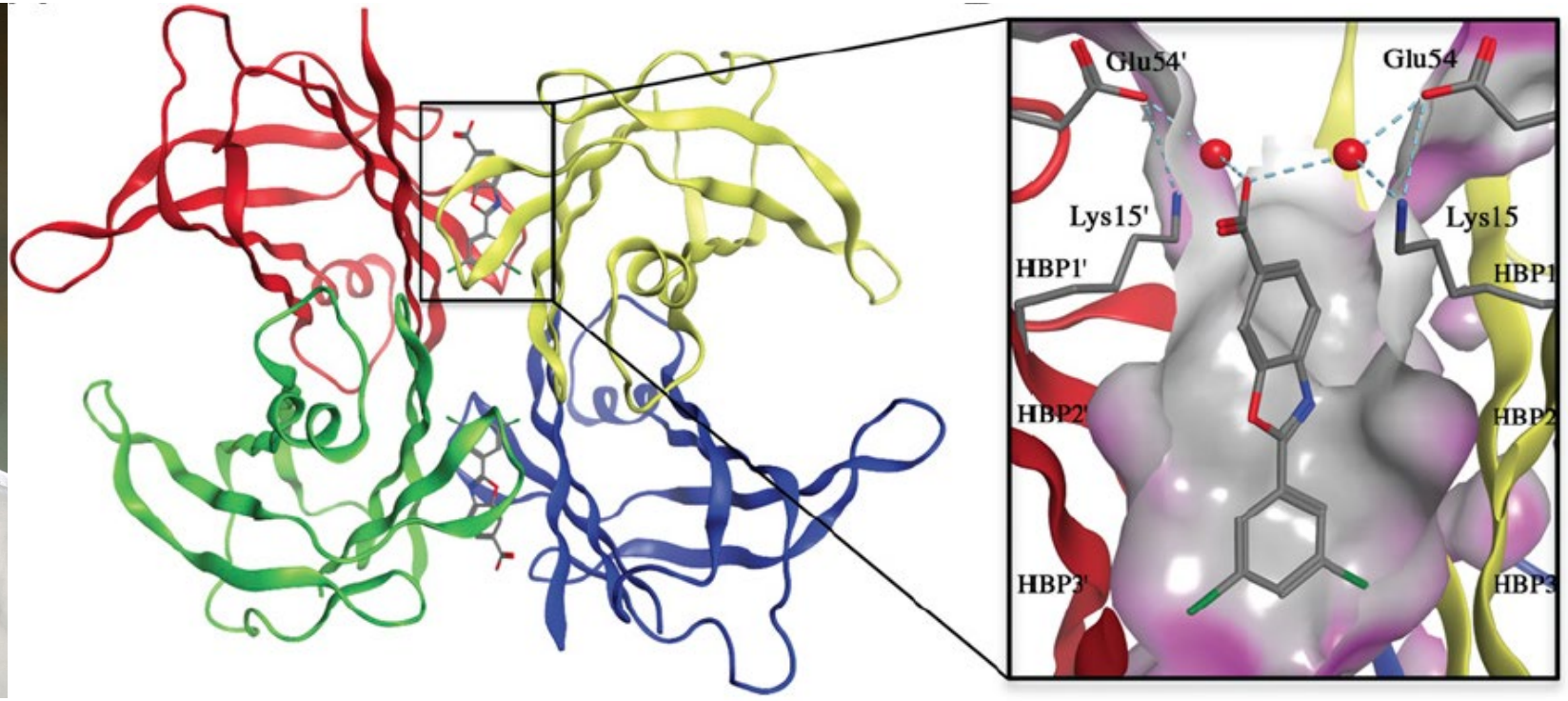
Stabilizer Binding Maintains the Extracellular Folded Shape Preventing Abnormal Shape Formation



Most Conservative Approach as it Dose not Presuppose What the Toxic Species is !

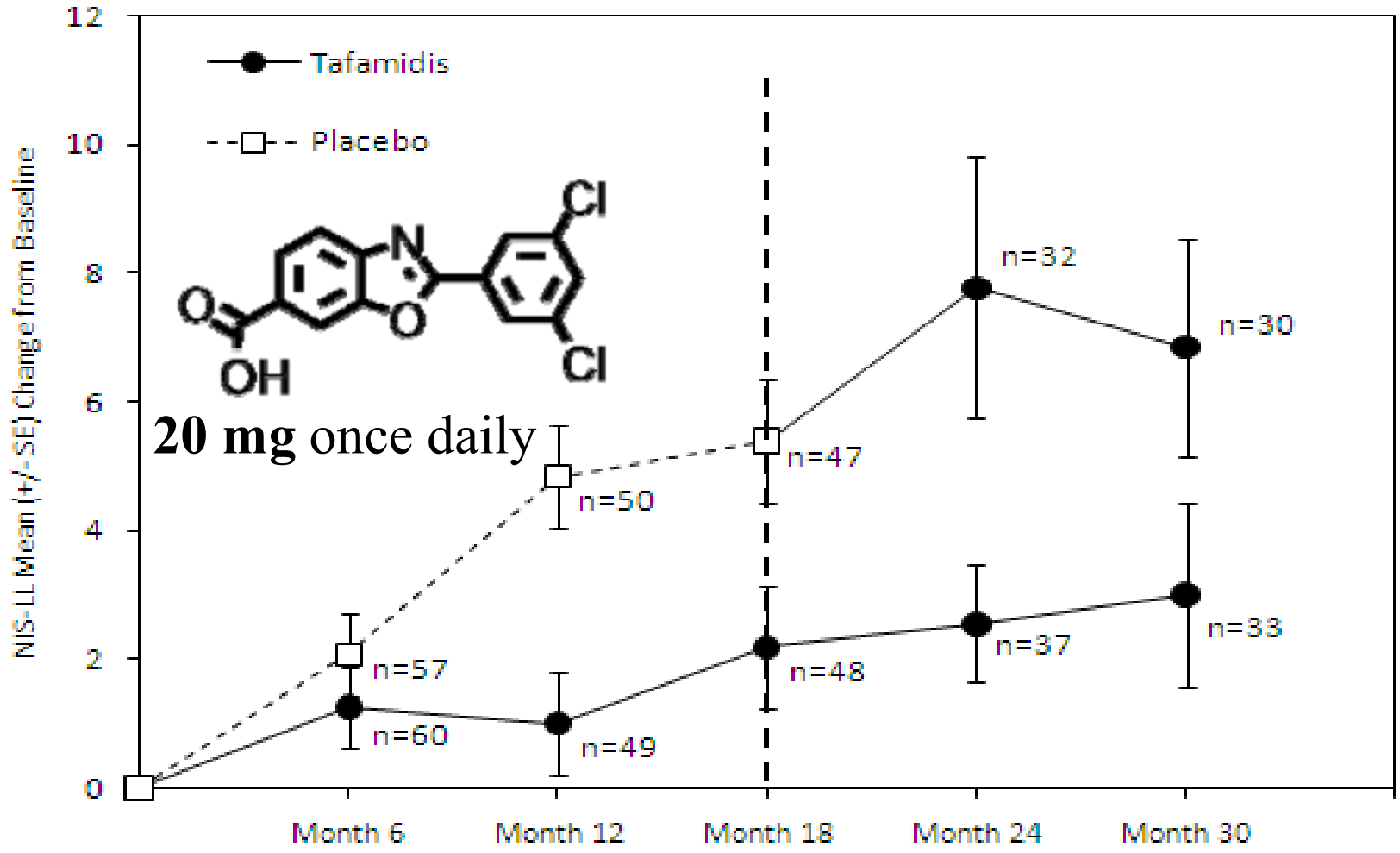
Structure-based Drug Design Played an Important Role in the Conception of Tafamidis

Evan Powers



Connelly, S.; Choi, S.; Johnson, S. M.; Kelly, J.W.; Wilson, I.A. "Structure-Based Design of Kinetic Stabilizers That Ameliorate the Transthyretin Amyloidoses" ***Curr. Op. Struct. Biol.*** **2010, 20, 1-9; Klabunde, T.; Petrassi, H. M.; Oza, V.B.; Raman, P.; Kelly, J.W.; Sacchettini, J.C.; "Rational Design of Potent Human Transthyretin Amyloid Disease Inhibitors"** ***Nature Struct. Biol.*****., 2000, 7, 312-321.**

Human Clinical Trial–Neurologic Impairment Score Lower Limbs, a Neurological Exam–Sensation, Muscle Strength and Lower Limb Reflexes-Change From Baseline



Dr. Teresa Coelho

FoldRx

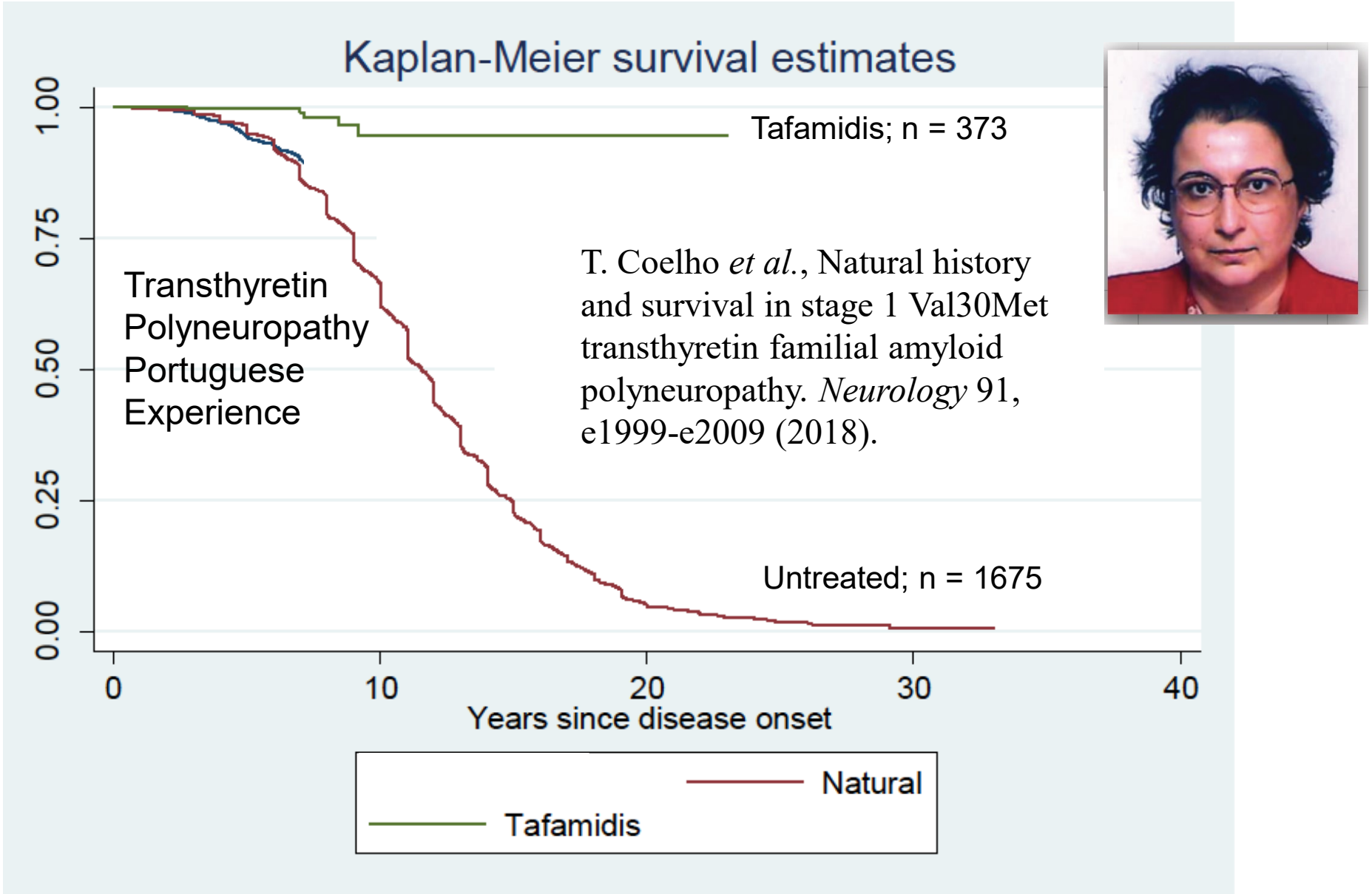
Pfizer

Clinical Trial Evidence that Starting Tafamidis Early in the Course of TTR Peripheral and Autonomic Neuropathy offers a Substantial Advantage to the Patient

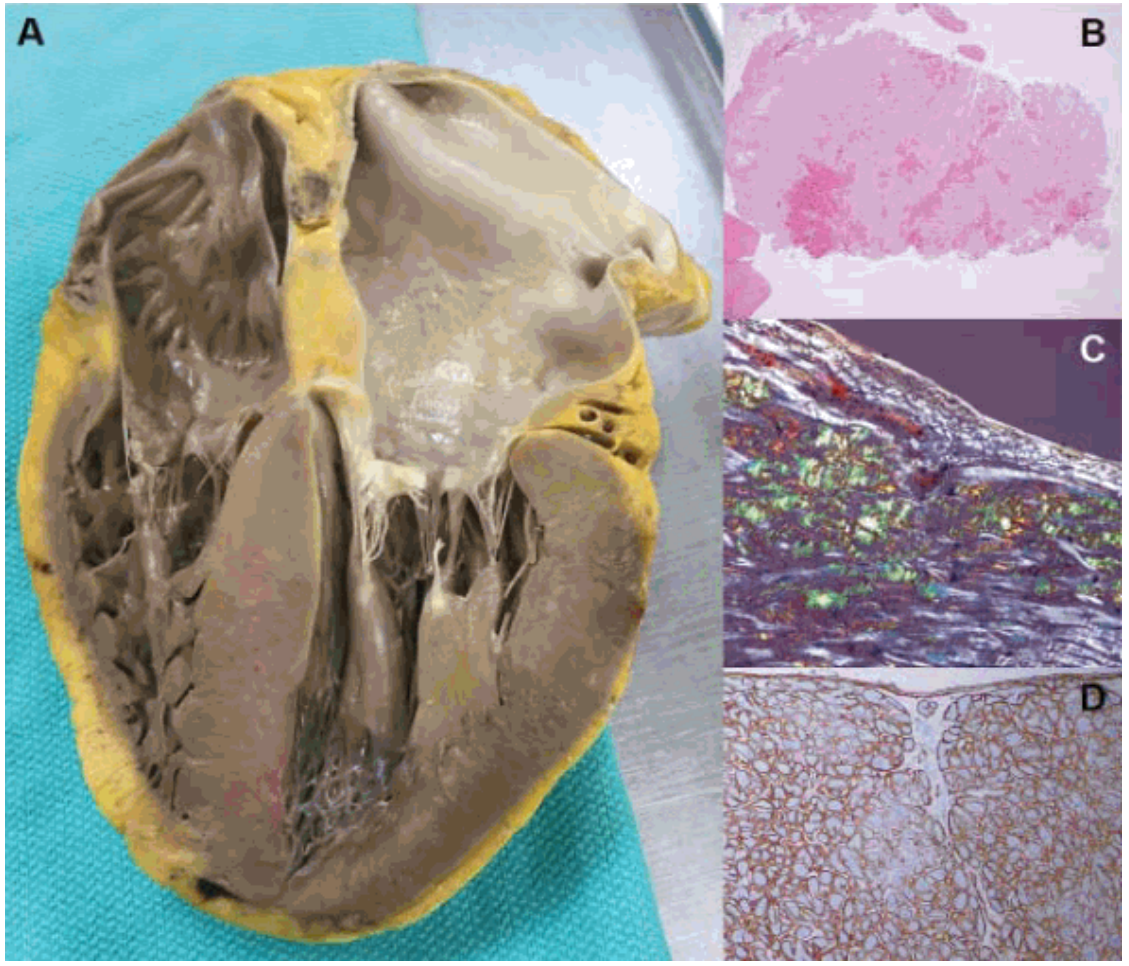
	Stable or improved	Progressing at a slow rate (mean progression of NIS-score is 1.1 / year)
Started on tafamidis (n=22)	68%	22%
Started on placebo (n=22) **18 Month Delay in Start of Treatment**	46%	27%

Indicates that the earlier patients go on Tafamidis the Better; Ultimately Prevention?

Portuguese Experience With Tafamidis vs. Untreated



Pathology of WT TTR Cardiomyopathy (CM)
Cardiac Tissue Dosen’t Easily Regenerate after Abnormal Shapes of Transthyretin Compromise Function

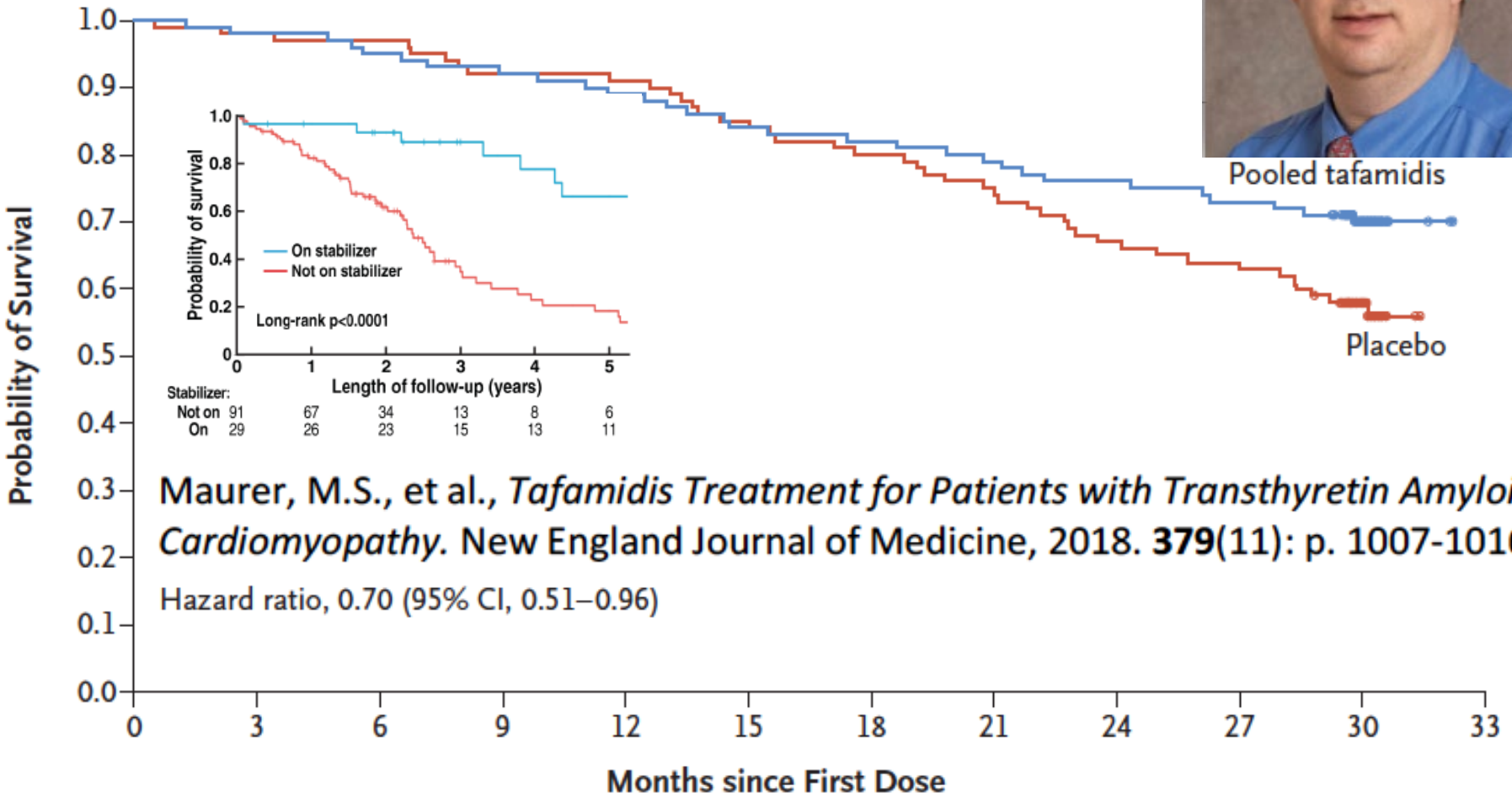


Tafamidis Cardiomyopathy Trial Completed Successfully

- 441 patients
- Tafamidis vs. Placebo
- **Result: Statistically Significant Reduction in the Combination of all-cause Mortality and the Frequency of Cardiovascular-related Hospitalizations vs. Placebo at 30 Months P=0.0006**

Tafamidis Slows Progression of Cardiomyopathy

Analysis of All-Cause Mortality



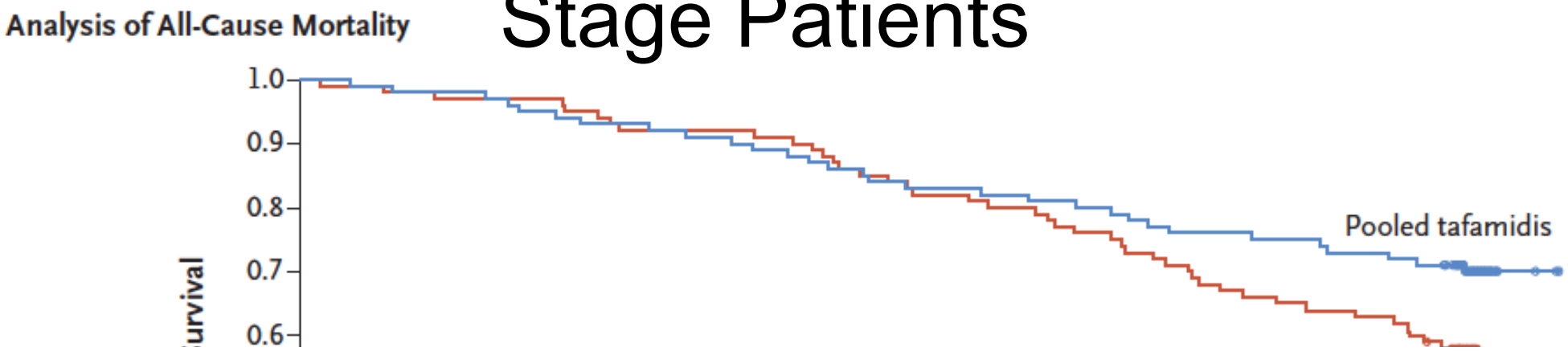
Maurer, M.S., et al., *Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy.* New England Journal of Medicine, 2018. **379**(11): p. 1007-1016.

Hazard ratio, 0.70 (95% CI, 0.51–0.96)

No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

Tafamidis is More Effective In Early Stage Patients



Tafamidis treatment of wild type and familial TTR cardiomyopathy in subjects in NYHA class I heart failure (n=37) was associated with a reduction in the risk of death of 64.4%, compared with 39.6% for NYHA class II subjects (n=263) and 16.3% for NYHA class III subjects.

0 3 6 9 12 15 18 21 24 27 30 33

Months since First Dose

No. at Risk (cumulative no. of events)												
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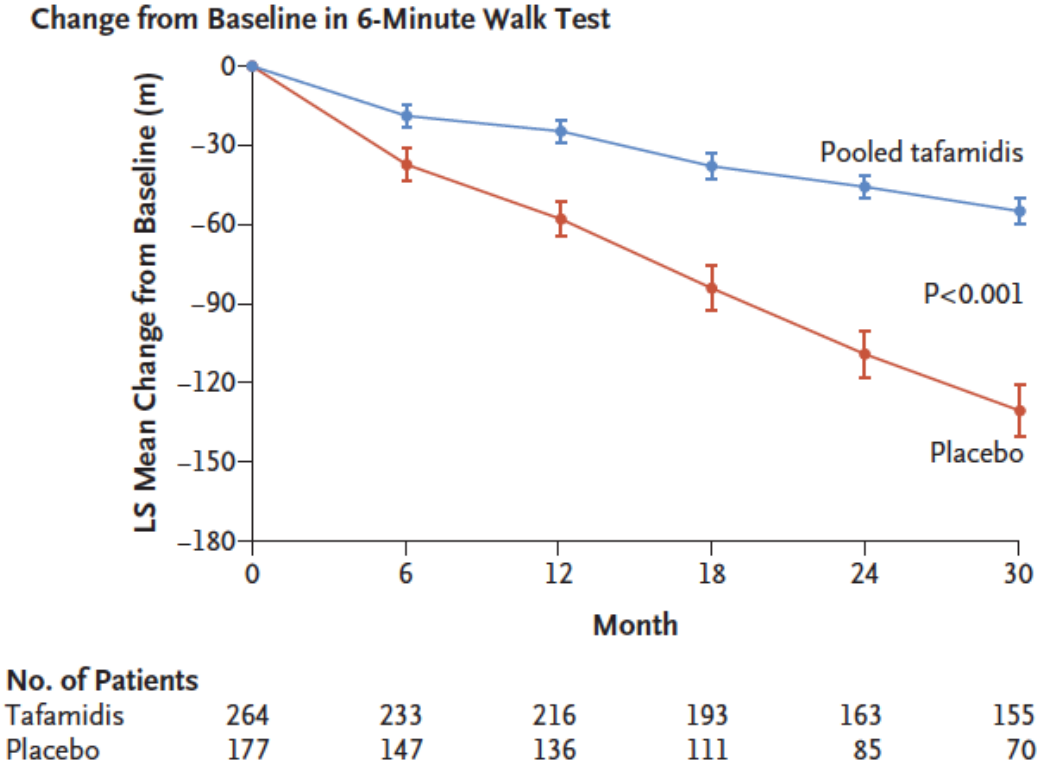
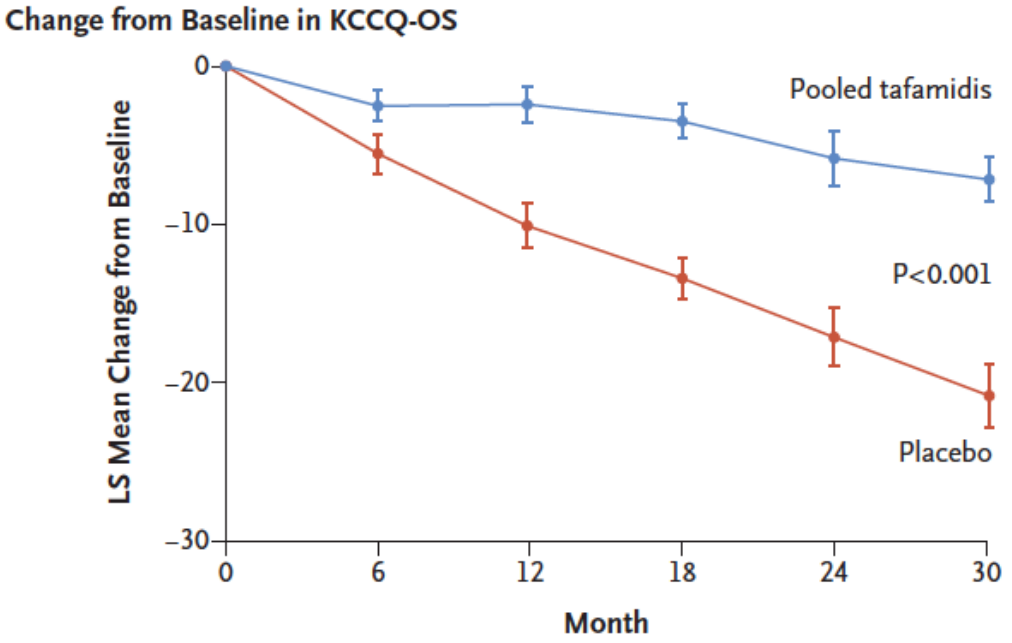
Tafamidis Slows Progression of Cardiomyopathy



No. of Patients						
Tafamidis	264	233	216	193	163	155
Placebo	177	147	136	111	85	70



No. of Patients						
Tafamidis	264	241	221	201	181	170
Placebo	177	159	145	123	96	84

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

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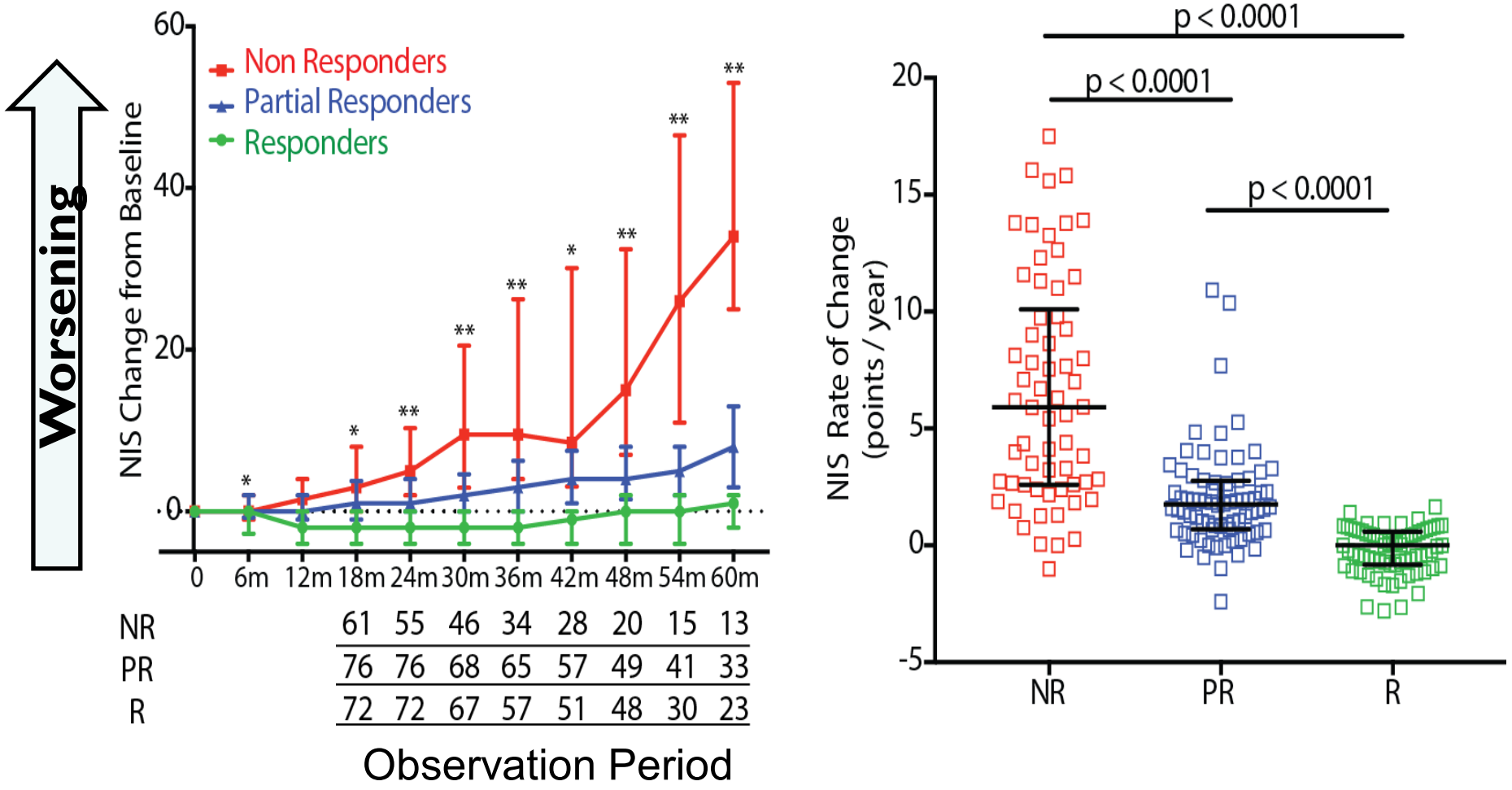
30 % of Polyneuropathy Patients Do Not Respond to Tafamidis in spite of Demonstrated TTR Stabilization

Is Immune Cell Activation Driving TTR Amyloidoses in the Non-responder Patients ?

Neuropathy Impairment Arrested or Slowed in 2/3 of Polyneuropathy Patients Taking Tafamidis



Cecilia Monteiro, Teresa Coelho et al. *J. Clin Inv Insight* **2019** 4(12) e126526

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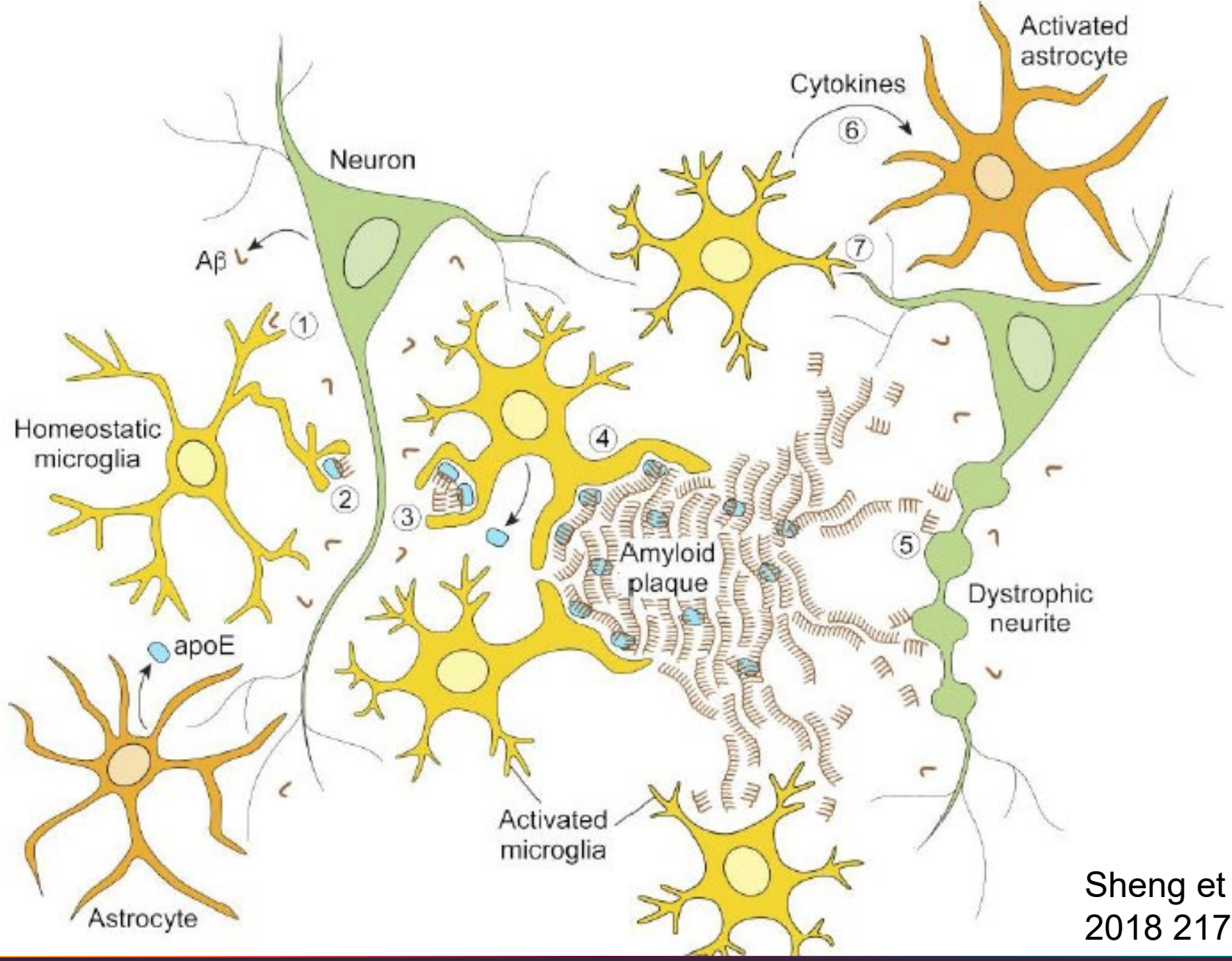
There is Emerging Evidence That Immune Cell Overactivation Takes over and Becomes a Major Driver of Neurodegeneration As the Disease Progresses

Initially immune cell activation is beneficial, but sustained activation can lead to neuronal death



Sheng et al. J. Cell Biol. 2018 217, 469-472

UPCOMING LECTURE

Unlocking new insights into brain-gut communication, metabolism and longevity

Supriya Srinivasan, PhD
Associate Professor
Department of Neuroscience

Wednesday, October 13, 2021
1:00 PM PT/4:00 PM ET

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Thank You

Acknowledgments

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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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