Precision Therapies for Aging-associated Neurodegenerative Diseases

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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
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.
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).
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

- Folded Protein: Normal Shape
- Unfolded Protein: Abnormal Shape
- Misfolded Protein: Abnormal Shape
- Misassembled Protein: Abnormal Potentially Pathogenic Shape
Intracellular Protein Folding & Protein Degradation Compete

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

Folded Protein
- Normal Shape

Misfolded Protein
- Abnormal Shape

Unfolded Protein
- Abnormal Shape

Misassembled Protein
- Abnormal Potentially Pathogenic Shape

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

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

Folded Protein
Normal Shape

Misfolded Protein
Abnormal Shape

Unfolded Protein
Abnormal Shape

Misassembled Protein
Abnormal Potentially Pathogenic Shape

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.
So Why do Abnormal Protein shapes Lead to Neurodegenerative Diseases?
Protein shapes or structures enable their functions
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
Transthyretin Amyloidosis

Peripheral, autonomic and central nervous system degeneration and/or cardiac degeneration
Transthyretin (TTR)

Transport Thyroxine Retinol Binding Protein

- 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 Does not Presuppose What the Toxic Species is!

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

Evan Powers

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

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

<table>
<thead>
<tr>
<th></th>
<th>Stable or improved</th>
<th>Progressing at a slow rate (mean progression of NIS-score is 1.1 / year)</th>
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<tbody>
<tr>
<td>Started on tafamidis (n=22)</td>
<td>68%</td>
<td>22%</td>
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<tr>
<td>Started on placebo (n=22)</td>
<td>46%</td>
<td>27%</td>
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<td><strong>18 Month Delay in Start of Treatment</strong></td>
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Indicates that the earlier patients go on Tafamidis the Better; Ultimately Prevention?
Portuguese Experience With Tafamidis vs. Untreated

Kaplan-Meier survival estimates

Pathology of WT TTR Cardiomyopathy (CM)
Cardiac Tissue Doesn’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


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

<table>
<thead>
<tr>
<th>Months since First Dose</th>
<th>Pooled tafamidis</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0</td>
<td>264 (0)</td>
<td>177 (0)</td>
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<tr>
<td>3</td>
<td>259 (5)</td>
<td>173 (4)</td>
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<td>51 (75)</td>
</tr>
<tr>
<td>33</td>
<td>0 (78)</td>
<td>0 (76)</td>
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</tbody>
</table>
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
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
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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THE FRONT ROW
at Scripps Research
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