Rationale for and Development of IONIS-MAPT Rx, the First Tau-lowering Antisense Oligonucleotide, in Patients with Mild AD

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BACKGROUND

Microtubule Associated Protein Tau (MAPT)

An Important Protein in Neurodegenerative Diseases

MAPT gene, previously known as P301, encodes tau, a protein that

- Fibrillates in the spinal cord in adult brains (Serrano et al., 1989)
- Tau proteins form three isoforms in adult brains (Serrano et al., 1989)
- Normal human brains maintain a 1:16:46 T1/T2 ratio
- Isoform expression and phosphorylation states are developmentally regulated and important for cytoskeletal plasticity during embryogenesis and early development

CHARACTERISTICS OF TAU

- Highly stable protein, with a disorder structure, able to undergo end-to-end conformations
- Expanded central core and peripheral domains
- Highly flexible in neuronal states, axonemotility compartment and in oligodendrocytes
- Cellular compartmentalization change in disease

MAPT post-translationally modified proteins (Serrano et al., 1989; Goedert et al., 1989; Qiang et al., 2006; Lei et al., 2008; Lei et al., 2016; Zhou et al., 2008; Serrano et al., 1989; Qiang et al., 2006; Lei et al., 2008; Lei et al., 2016; Zhou et al., 2008)

- Tauopathies involve Soluble and Membranous Tau Protein Becoming Hypophosphorylated, Insoluble & Filamentous

Primary taupathies

- FTLD: frontotemporal lobar degeneration
- SFTLD: semantic sensory motor degeneration
- GSS: Guam-type familial progressive supranuclear palsy
- argyrophilic grain disease
- Pick's disease

Secondary taupathies

- AD: Alzheimer's disease
- PD: Parkinson's disease
- ALS: amyotrophic lateral sclerosis
- AD/FTLD: amyotrophic lateral sclerosis, frontotemporal lobar degeneration

Tau (not Aβ) Aggregate and Deposition Corelate with Alzheimer Disease Progression

- Tau accumulation increases in density in females with FAD compared to early-onset Alzheimer Disease

- Tau aggregation and clearance products point cognitive status in AD (a decline on a MMSE score of 80/100 on normal level, and a 10 year lifespan)
- Neurofibrillary tangles range explains 44% of the neuronal loss in degenerating and atrophic regions of Alzheimer Disease patient brains (Brink and Danks, Human Aging, 1991; Mandei and Nupponen, 2003)

In Alzheimer disease tau is not mutated, yet neurofibrillary tangle form and tau pathology is prominent

- Tau spreading correlates with disease progression, and tau loss critical role in neurofibrillary tangle formation

- Tau spreading and neurofibrillary tangles predict cognitive status in AD (a decline on a MMSE score of 80/100 on normal level, and a 10 year lifespan)

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