POSTER #M158

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

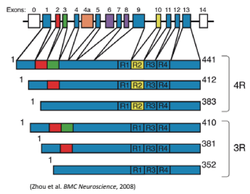
Roger M. Lane[1], Holly B. Kordasiewicz[1], Anne E. Smith[1], Laurence Mignon[1], Timothy Miller[2], Padma Narayanan[1], Eric E. Swayze[1], Daniel A. Norris[1], Bethany Fitzsimmons[1], C. Frank Bennett[1]

[1]Ionis Pharmaceuticals, Inc., 2855 Gazelle Court, Carlsbad, CA 92010 [2]Biogen, St. Louis, MO

BACKGROUND

Microtubule Associated Protein Tau (*MAPT*) An Important Protein in Neurodegenerative Diseases

MAPT gene, 16 exons, chromosome 17, 6 tau isoforms in adult brain (Goedert et al. *Neuron,* 1989)



(Zhou et al. *BMC Neuroscience*, 2008)

- Tau isoforms contain 3 (3R splice variant) or 4 (4R splice variant) microtubule binding domains, depending on inclusion of exon 10
- Adult human brains maintain a 1:1 3R:4R TAU ratio
- Isoform expression and phosphorylation status are developmentally regulated and important for cytoskeletal plasticity during embryogenesis and early development

Characteristics of Tau

- Highly soluble protein, with a disordered structure, able to undergo myriad of conformational changes
- Expressed in central and peripheral nervous systems,
  - mainly in neuronal axons, somatodendritic compartment and in oligodendrocytes
  - cellular compartment/localization changes in disease
- **Modified post-translationally via phosphorylation** (Lee et al. *J Neurosci*, 2004), **acetylation** (Min et al. *Neuron,* 2010), **glycation** (Ledesma et al. *J Biol Chem,* 1994), **isomerization** (Miyasaka et al. *J Neuropahtol Exp Neurol*, 2005), **nitration** (Reyes et al. *Neurobiol Dis*, 2008), **sumoylation** (Dorval and Fraser, *J Biol Chem,* 2006), **ubiquitination** (Cripps et al. *J Biol Chem,* 2006) **and more**
  - Suggests tau activity is highly regulated
- Not clear which isoforms, post-translational modifications and conformations are toxic or if toxicity varies by localization

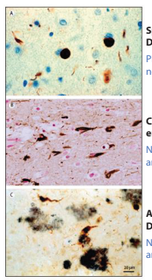
Tauopathies Involve Soluble and Monomeric Tau Protein Becoming Hyperphosphorylated, Insoluble & Filamentous

Primary tauopathies

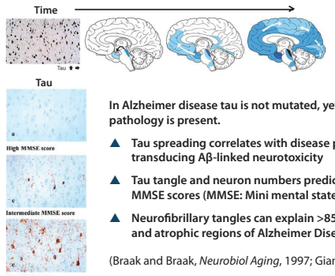
- 4R
  - Frontotemporal lobar dementia with *MAPT* mutation (some mutations associated with 3R and 3R/4R)
  - Progressive supranuclear palsy
  - Corticobasal degeneration
  - Argyrophilic grain disease
- 3R
  - Pick's disease

Secondary tauopathies

- 3R/4R
  - Chronic Traumatic Encephalopathy
  - Alzheimer's disease (all tau isoforms in neurofibrillary tangles)
    - Early Onset (include APP, PS1, PS2 mutations)
    - Late Onset (>60 years)
  - Down's Syndrome



Tau (not Aß) Aggregation and Deposition Correlate with Alzheimer Disease Progression



Tau accumulations increase in density (darker blue) and spread throughout the Alzheimer Disease brain over time

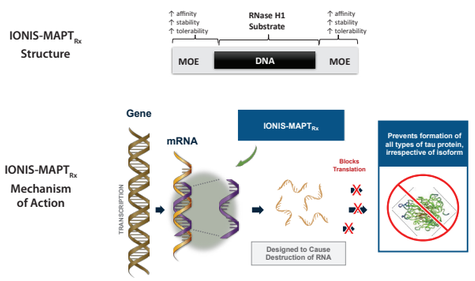
In Alzheimer disease tau is not mutated, yet neurofibrillary tangles form and tau pathology is present.

- Tau spreading correlates with disease progression, and tau has critical role in transducing Aβ-linked neurotoxicity
- Tau tangle and neuron numbers predict cognitive status in AD [i.e. declines on MMSE scores (MMSE: Mini mental state examination)]
- Neurofibrillary tangles can explain >85% of the neuronal loss in degenerating and atrophic regions of Alzheimer Disease patient brains

(Braak and Braak, *Neurobiol Aging*, 1997; Giannakopoulos et al., *Neurology*, 2003)

BACKGROUND *continued*

IONIS-MAPT$_{Rx}$ – Elegant Solution to Reducing all Forms of Tau by Targeting RNA



Reduction of Tau Does Not Result in Loss of Normal Function in Animal Models

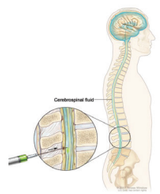
- *Tau*$^{+/-}$ mice not associated with any phenotype even with aging
  - Indicates that down-regulation of *Tau* gene expression by 50% should not pose a safety concern
- Lack of overt phenotype in most *Tau*$^{-/-}$ mouse models
  - Complete ablation of Tau gene expression in adult life (after the completion of neurodevelopment) does not appear to pose a significant safety concern
  - Mild motor phenotype emerging in older (≥1 yr) *Tau*$^{-/-}$ mice in some studies (Lei et al. *Nat Med*, 2012; Lei et al. *Mol Neurodegen*, 2014), but no replication in other large studies (Li et al. *Neurobiol Aging*, 2014; Morris et al. *Neurobiol Aging*, 2013)
- Microtubule stabilization and axonal transport may not be critical functions of *tau*
  - Likely redundancy with other microtubule-associated proteins such as MAP1B (Lei et al. *Mol Neurodegen*, 2014)
  - Reduction of tau by siRNA not lethal to primary neurons in culture and does not decrease the number of microtubules or their polymerization state (King et al. *JCB*, 2006; Qiang et al. *J Neurosci*, 2006)
  - Ablation of tau does not alter axonal transport in primary neuronal culture (Vossel et al. 2010) or *in vivo* (Yuan et al. 2008)

Ionis' Experience with Intrathecal Delivery

- Spinal Muscular Atrophy (SMA) (Spinraza) altering SMN2 mRNA splicing to increase functional survival motor neuron protein; approved on Dec 23, 2016 by FDA

SPINRAZA™ (nusinersen) injection 12 mg/5 mL

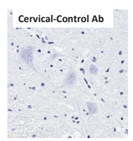
- Huntington's disease (NCT02519036) targeting HTT mRNA to reduce huntingtin protein expression
- Mutant SOD1 ALS (NCT02623699) targeting SOD1 mRNA to reduce SOD1 protein expression

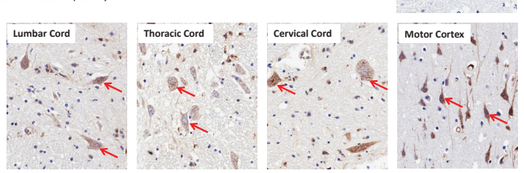


Confirmation of Antisense Oligonucleotide Distribution in CNS after Intrathecal Delivery

- Autopsy material obtained from infant in Phase 2 open-label trial of Spinraza: Study drug was given on days 1, 15, and 85; autopsy done on day 163
- Immunohistochemical staining confirms drug in all levels of spinal cord and in specific brain regions

(Finkel et al. *Lancet*, 2016)





*ISIS-SMN$_{Rx}$ in neurons indicated by red arrows; brown staining indicates ISIS-SMN$_{Rx}$ in cells

PRE-CLINICAL DATA

Reduction of Tau Does Not Result in Loss of Normal Function in Animal Models

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

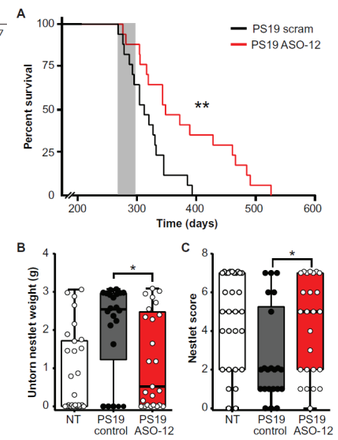
ALZHEIMER'S DISEASE *Sci. Transl. Med.* **9**, eaag0481 (2017) 25 January 2017

Tau reduction prevents neuronal loss and reverses pathological tau deposition and seeding in mice with tauopathy

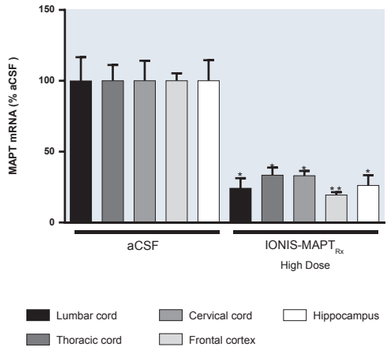
Sarah L. DeVos,[1] Rebecca L. Miller,[1]* Kathleen M. Schoch,[1]* Brandon B. Holmes,[1] Carey S. Kebodeaux,[1] Amy J. Wegener,[1] Guo Chen,[1] Tao Shen,[1] Hien Tran,[2] Brandon Nichols,[2] Tom A. Zanardi,[2] Holly B. Kordasiewicz,[2] Eric E. Swayze,[2] C. Frank Bennett,[2] Marc I. Diamond,[3] Timothy M. Miller[1]†

Results

- ASO reduced human tau and prevented tau pathology in PS19 mice (ICV infusion for 1 month)
- Even in aged PS19 mice, reduction of human tau reversed tau pathology
- Reduction of human tau prevented hippocampal neuron loss in PS19 mice
- Tau seeding activity was reversed after human tau reduction
- Human tau reduction extended PS19 mouse survival and prevented nesting behavioral deficits



Mean *MAPT* mRNA Knockdown in Nonhuman Primates



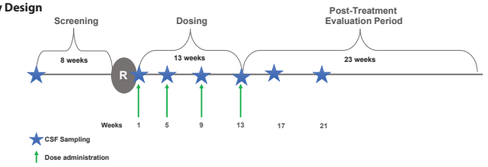
CLINICAL STUDY

IONIS-MAPT$_{Rx}$ Clinical Study (NCT03186989)

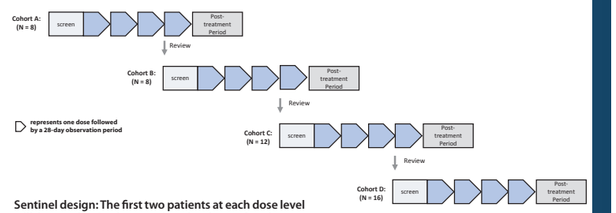
First-in-human study

- Double-blind, placebo-controlled study in patients with mild AD (n=44)
- Multiple-ascending dose study (4 dose levels tested)
- Primary endpoints: safety and tolerability
- Secondary endpoints: CSF pharmacokinetics
- Exploratory endpoints: Pharmacodynamic biomarkers and clinical outcomes

Study Design

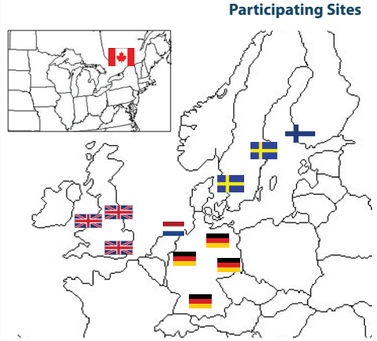


Escalation Through Multiple-Ascending Doses



Sentinel design: The first two patients at each dose level will be randomized 1:1 active:placebo and at least 1 week must elapse between dosing in these two patients and dosing in any other patients at this dose level.

Participating Sites



- University College London, Hospital NHS Foundation Trust, Dr. Mummery
- Royal Liverpool University Hospital, Dr. Fitzgerald
- Sheffield Institute for Translational Neuroscience (SITraN), Dr. Blackburn
- Goteborgs Universitet-Sahlgrenska Akademin, Dr. Borjesson-Hanson
- Karolinska University Hospital Huddinge, Dr. Andreasen
- St Josef Hospital, Dr. Muhlack
- MZV Mittweida, Dr. Bodenschatz
- Universittsklinikum, Dr. von Armin
- Charite-Universitaetsmedizin Berlin, Dr. Priller
- Clinical Research Center Turku, Dr. Rinne
- Faculty Medical Sciences UMGG Neurology, Dr. De Deyn
- Montreal Neurological Hospital, Dr. Genge

Press Release - October 13, 2017

IONIS PHARMACEUTICALS

IONIS PHARMACEUTICALS INITIATES CLINICAL STUDY OF IONIS-MAPT$_{Rx}$ IN PATIENTS WITH ALZHEIMER'S DISEASE

Antisense drug designed to reduce tau protein in the CNS

Ionis earns $10 million milestone payment from Biogen

Carlsbad, Calif., October 13, 2017 –Ionis Pharmaceuticals, Inc. (NASDAQ: IONS) today announced that it has initiated a Phase 1/2a clinical study of IONIS-MAPT$_{Rx}$ in patients with mild Alzheimer's disease (AD). Ionis earned a $10 million milestone payment from Biogen related to the initiation of this study.

Partnered with: Biogen

More information on IONIS-MAPT$_{Rx}$ clinical trials can be found at www.clinicaltrials.gov

More information on Ionis and antisense oligonucleotide drugs can be found at www.ionispharma.com

Contact: LMignon@ionisph.com