Novel Compounds for Treating MSA Patients

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Disclosure

- Dr. Perez has filed a patent for the drugs she will be talking about today: "Compositions and Methods for the Treatment of Parkinson's Disease", US 20150290145, CA 2888634
- Her patent further claims the drugs may also be useful for MSA and other synucleinopathies

OUTLINE OF PRESENTATION

- Background
  - Ataxia and MSA
  - What causes problems
    - α-Synuclein (αSyn) aggregation in glia and neurons
  - What does αSyn normally do?
  - αSyn function lost when it aggregates
  - Could a drug take αSyn's place?
  - Evaluation in cell and mouse models
  - Potential Benefits for MSA patients

What is Ataxia?

- Ataxia patients have clumsy movement, but not due to weakness
- Ataxia can be caused by problems in
  - Cerebellum of brain
  - Balance system in the inner ear
  - Nerves outside the brain
- Symptoms include problems with
  - Speech
  - Eye movements
  - Arm & Leg movements
  - Balance - Leads to Falls

Multiple System Atrophy (MSA)

- An adult onset progressive ataxia
- Damage to nerves in brain and body
- Symptoms include
  - Stiffness of muscles
  - Jerky movement
  - Lightheadedness, Heart rate problems
  - Bladder, Sexual, and Bowel problems

MSA

- Most is sporadic
  - This means there is NO genetic cause
  - Possibly due to infection or toxin exposure
- A tiny number of MSA families exist
  - These have a genetic cause
  - Mutations in SNCA, the α-synuclein gene
α-Synuclein (aSyn) Protein

- Amphipathic repeats
- NAC
- Acidic region
- 140 amino acid long protein

aSyn takes this shape if it associates with lipid vesicles inside cells.

Image by Dr. Elizabeth Rhodes, University of Pennsylvania

Synucleinopathies

Are diseases with aSyn aggregation inside cells
- Parkinson’s disease (PD, neurons)
- Multiple System Atrophy (MSA, oligodendroglia)

Image by Spillantini, 1997 - Lewy bodies, Lewy Neurites

Image by Ahmed, 2012 - Glial inclusions

aSyn is normally soft and fluid, like an uncooked egg white.

Aggregated aSyn forms a solid clump, like hard boiled egg white.

What does aSyn Normally Do?

- Regulates neuron & pancreas vesicles
- Regulates synthesis, release, and uptake of neurotransmitter
- Activates PP2A phosphatase protein

aSyn Problems in MSA Lead to Brain Damage

PP2A removes phosphate from a protein

This helps regulate signaling and other proteins in cells.
aSyn increases PP2A activity

Our data published in:
- Peng 2005
- Lou 2010
- Farrell 2014
- Vargas-Medrano 2014

PP2A activity goes down in brains with aSyn aggregates

We found FTY720
- FTY720 increases PP2A activity
- Enters brain after taking it as a pill
- Used to treat multiple sclerosis (MS), another demyelinating disorder
- Novartis owns patent until 2018 and call their drug Gilena™

Could we modify FTY720 to be even safer or more potent?

Worked with medicinal chemist, Dr. Jeffrey Arterburn, and biochemist, Dr. Donald Moss to create two new FTY720 compounds.

Are there medications that can restore PP2A activity?

Made FTY720 Derivatives
- FTY720-C2
- FTY720-Mitoxy
All 3 FTY720s Stimulate PP2A

All 3 FTY720s enhance metabolism, increase protective factors, and block inflammation in neuronal cells

aSyn Mice Have Constipation & Gut aSyn Aggregation

FTY720 Reduces Gut aSyn Aggregation in Mice

FTY720 Blocks Constipation and Improves Gut Motility

Just published FTY720 mouse data in the Journal of Biological Chemistry

FTY720/Fingolimod Reduces Synucleinopathy and Improves Gut Motility in A53T Mice

CONTRIBUTIONS OF PRO-BRAIN-DERIVED NEUROTROPHIC FACTOR (PRO-BDNF) AND MATURE BDNF

Vidal-Martinez et al, JBC, 2016

FTY720 Reduces Gut aSyn Aggregation in Mice

Vidal-Martinez et al, JBC, 2016
Blocking neuroprotection increases constipation and aSyn aggregation, which can be reversed by FTY720

New FTY720s Rapidly Enter Brain and Do Not Make Toxic Metabolites

What does this mean for those suffering from MSA?

FTY720s could help by:
- stopping aSyn aggregation
- reducing inflammation
- optimizing PP2A activity
- slowing or halting MSA progression

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