

Novel Compounds for Treating MSA Patients

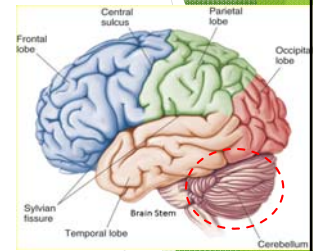
Dr. Ruth G. Perez, Ph.D.



MSA Coalition Patient & Family Conference
New Orleans LA - October 15, 2016

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



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

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

OUTLINE OF PRESENTATION

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

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

Exon 3 Exon 4 Exon 5 Exon 6 Exon 7

140 amino acid long protein

aSyn takes this shape if it associates with lipid vesicles inside cells
Image by Dr. Elizabeth Rhoades, University of Pennsylvania

Synucleinopathies

Are diseases with aSyn aggregation inside cells

- Parkinson's disease (PD, neurons)
- Multiple System Atrophy (MSA, oligodendroglia)

Spillantini, 1997 - Lewy bodies/Lewy Neurites

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

Neuron Glia

α-syn cell-to-cell propagation

Loss of trophic support

Abnormal myelin accumulation

Altered myelination

Brain Neurodegeneration

Myelin Demyelination

Normal MSA

Ubhi, Low and Masliah, 2011

PP2A removes phosphate from a protein

Protein

Phosphatase

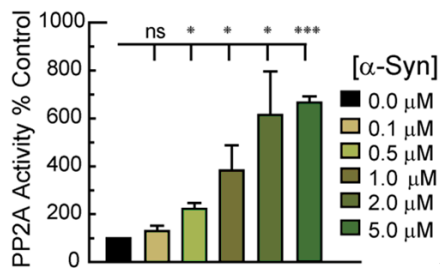
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Protein

Kinase

This helps regulate signaling and other proteins in cells

aSyn increases PP2A activity

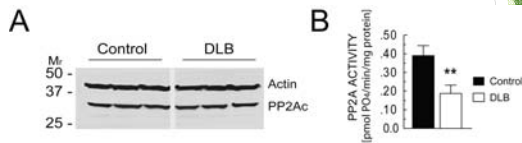


Our data published in:
Peng 2005
Lou 2010
Farrell 2014
Vargas-Medrano 2014

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 *Gilenya™*

PP2A activity goes down in brains with aSyn aggregates



Wu et al. 2012

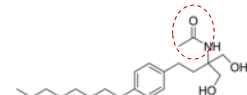
Could we modify FTY720 to be even safer or more potent?

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

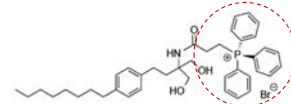
Are there medications that can restore PP2A activity?

Made FTY720 Derivatives

FTY720-C2

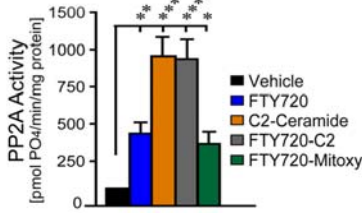


FTY720-Mitoxo



Vargas-Medrano 2014

All 3 FTY720s Stimulate PP2A



Vargas-Medrano 2014

Just published FTY720 mouse data in the Journal of Biological Chemistry

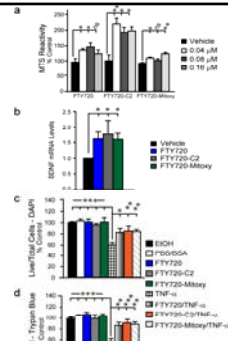
FTY720/Fingolimod Reduces Synucleinopathy and Improves Gut Motility in A53T Mice

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

Received for publication, July 6, 2016, and in revised form, August 11, 2016. Published, JBC Papers in Press, August 15, 2016; DOI:10.1074/jbc.M116.744029
 Guadalupe Vidal-Martinez, Javier Vargas-Medrano, Carolina Gil-Tommee, David Medina, Nathan T. Garza, Barbara Yang, Ismael Segura-Ulate, Samantha J. Dominguez, and Ruth G. Perez
 From the Center of Emphasis in Neurosciences, Graduate School of Biomedical Sciences, Texas Tech University Health Sciences Center El Paso, Paul L. Foster School of Medicine, El Paso, Texas 79965

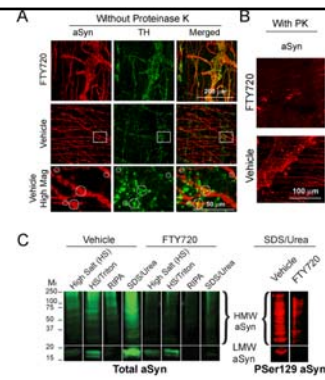
Vidal-Martinez et al, JBC, 2016

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



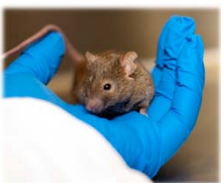
Vargas-Medrano 2014

FTY720 Reduces Gut aSyn Aggregation in Mice



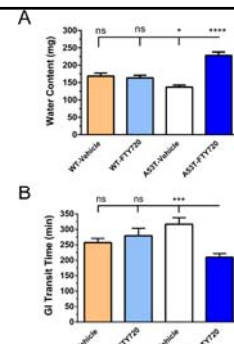
Vidal-Martinez 2016

aSyn Mice Have Constipation & Gut aSyn Aggregation

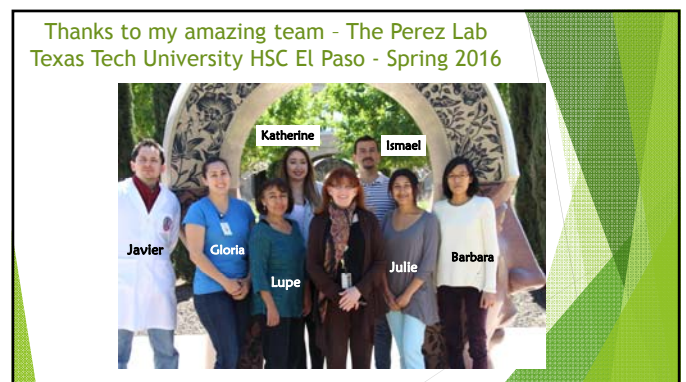
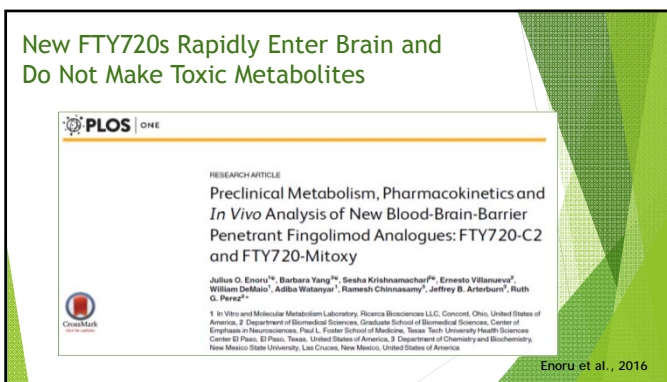
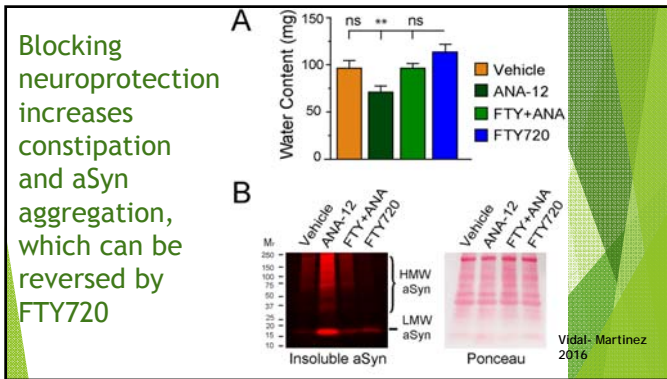


Farrell 2014

FTY720 Blocks Constipation and Improves Gut Motility



Vidal-Martinez 2016



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



