Seminar

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Reducing Synucleinopathy with FTY720 - Closing in on Cures

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Synucleinopathies are progressive neurodegenerative disorders of aging in which the small chaperone-like protein, alpha-synuclein (aSyn), accumulates inside neuronal and/or glial cells of the nervous system. Parkinson's disease (PD) and Multiple System Atrophy (MSA) are two well-characterized types of synucleinopathy. In PD, aSyn pathology affects neurons, while in MSA aSyn pathology occurs in the myelinating oligodendroglial cells, which ultimately leads to neuron loss. While PD patients usually have normal life expectancies, MSA can go from diagnosis to death in less than 10 years. At this time there are no effective treatments for either disease.

My laboratory has been studying normal aSyn function in search of novel therapeutic targets. We discovered that among its normal functions is aSyn's ability to regulate key enzymes, including tyrosine hydroxylase and protein phosphatase 2A. This ultimately led us to identify FTY720 (fingolimod, Gilenya), an FDA-approved drug for multiple sclerosis that can stimulate PP2A activity. We hypothesized that when aSyn aggregated its normal function would be lost, and that FTY720 might restore PP2A activity. We also generated new FTY720 analogues with PP2A stimulatory effects. Data revealed that the concentration of FTY720s required to stimulate PP2A were toxic to neurons and glia, but nanomolar concentrations could effectively increase expression of a potent protective molecule, brain derived neurotrophic factor (BDNF). We have been exploring the preclinical efficacy of all three FTY720 in cells and mice. I will present data showing that FTY720 reduced aSyn pathology and improved function in aSyn transgenic mice. These findings provide preclinical support for repurposing FTY720 for PD and MSA, where it may be able to slow disease progression.