Biomedical Sciences Seminar

Cosponsored by Neuroscience

presents

"Splicing modulation as treatment for spinal muscular atrophy"

Guest Speaker: Dr. Eric Ottesen, PhD
Iowa State University

Thursday, September 17, 2020

WHEN: 12:00pm-1:00pm
WHERE: Vet Med 2226 (Students Only)

You can join the seminar via Zoom. See email for Zoom information.

HOST: Dr. Ravi Singh

Abstract

Spinal muscular atrophy (SMA) is the leading genetic cause of infant mortality. SMA is caused by low levels of the survival motor neuron (SMN) protein due to mutation or deletion of the SMN1 gene and is characterized by progressive deterioration of the motor neurons, leading to muscle weakness and atrophy. In humans, a second copy of the SMN gene, SMN2, cannot compensate for the loss of SMN1 due to a translationally silent mutation that causes predominant skipping of exon 7, producing a truncated and unstable protein. Extensive research into the regulation of SMN2 exon 7 splicing has resulted in multiple treatments that redirect splicing to produce the full-length protein, including two FDA-approved drugs. The first FDA-approved treatment for SMA, Spinraza™ (nusinersen), is an antisense oligonucleotide (ASO) that enhances splicing of SMN2 exon 7 by blocking a negative element in the downstream intron. Alternatively, several small molecules have been identified that redirect splicing of SMN2 exon 7, including the newly FDA-approved Evrysdi™ (risdiplam). Both approaches have advantages and disadvantages, including the potential for off-target effects on the splicing of unrelated genes. We propose that off-target effects of both small molecules and ASOs can be minimized by taking a combinatorial approach and treating with reduced concentrations of each compound together. We show that combination treatment exhibits a synergistic effect on splicing of SMN2 exon 7, allowing for an enhancement of full length SMN2 mRNA and SMN protein levels at greatly reduced dosages of each compound. Examination of several known off-target exons affected by risdiplam and other small splice-modulating compounds reveals a greatly reduced impact on their splicing. Overall, treatment with ASOs and small molecules together is a highly promising approach that allows for much greater specificity than each individual treatment, reducing the potential for deleterious off-target effects.

Next Week: Li Wu, PhD

Title: “SAMHD1-mediated suppression of antiviral immune responses”