MedicalXpress

Orally delivered compounds selectively modify RNA splicing, prevent deficits in SMA models

August 7 2014

Today the journal *Science* published results of a preclinical study demonstrating that treatment with orally available RNA splicing modifiers of the SMN2 gene starting early after birth is preventing deficits in a mouse model of Spinal Muscular Atrophy (SMA). Scientists from Roche Pharma Research and Early Development (pRED), PTC Therapeutics, Inc., the SMA Foundation, the University of Southern California and Harvard University collaborated to demonstrate that continuous treatment of SMA mice with these compounds increased life span, normalized body weight and prevented both disease-related motor dysfunction and neuromuscular deficits.

"Although still preclinical, these results demonstrate how SMN2 splicing modifiers could correct the molecular deficit that causes SMA," said Luca Santarelli, Head of Neuroscience, Ophthalmology and Rare Diseases at Roche. "This study represents an important step towards developing a potential therapeutic option for this devastating and currently untreatable condition. Early clinical trials are currently underway to determine the safety and tolerability of this approach."

"The investigational compounds used in this study represent the first orally available SMN2 splicing modifiers for SMA," commented Stuart W. Peltz, CEO of PTC Therapeutics, Inc. "Using the experience and expertise in RNA biology we have gained at PTC over the last 16 years, we used our alternative splicing technology to identify and subsequently

optimize investigational compounds that target the SMN2 splicing to produce the SMN protein. Our unique partnership with Roche and the SMA Foundation has allowed this project to rapidly move into clinical development."

The study used chemical screening and optimization to identify orally available small molecules that selectively alter the splicing of the SMN2 pre-mRNA to produce stable full-length SMN protein. The SMN2 splicing modifiers described in the *Science* article penetrated into all mouse tissues tested, including brain, spinal cord and muscle, and thus improved SMN2 RNA splicing to increase SMN protein production in these disease-relevant tissues. As a result of the SMN protein increase, the compounds prevented the progression of SMA in a severe mouse model. These compounds also corrected SMN2 RNA splicing and increased SMN protein levels in cell cultures obtained from SMA patients, including stem cell-derived motor neurons. A Phase I clinical program to assess safety and tolerability with investigational compounds was initiated in early 2014.

"The findings of this preclinical study contribute significantly to our understanding of SMA and provide further evidence suggesting that our strategy to upregulate SMN with small molecules could be effective," said Loren Eng, President of the SMA Foundation. "We are proud to have seeded this important work – we believe it could have a meaningful impact on the lives of patients who suffer from SMA."

SMA is a genetic disease caused by mutation or deletion of the SMN1 (survival of motor neuron) gene. It affects one in approximately 10,000 live births and in the most severe forms is associated with a high rate of childhood mortality. SMA is characterized by progressive loss of motor neurons, muscle weakness and atrophy. The disease affects mainly proximal muscles including intercostal muscles (chest muscles), and patients often die due to respiratory complications.

More information: "SMN2 splicing modifiers improve motor function and longevity in mice with spinal muscular atrophy," by N.A. Naryshkin et al *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.1250127

Provided by University of Southern California