Molecular Therapy for Spinal Muscular Atrophy Closer to Clinical Use

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(PhysOrg.com) -- Spinal muscular atrophy, a neurodegenerative disorder that causes the weakening of muscles, is the leading cause of infant death and occurs in 1 in 6,000 live births. While trans-splicing (a form of molecular therapy) has had impressive results as a treatment for spinal muscular atrophy in cell-based models of disease, scientists have been unable to translate the therapy to the human body. A University of Missouri researcher has developed a strategy that will enhance trans-splicing activity and bring it closer to being used in the clinical setting.

Spinal muscular atrophy is caused by the loss of survival motor neuron-1(SMN1). In humans, a nearly identical copy gene is present called SMN2. Because of a single molecular difference, SMN2 alone cannot compensate for the loss of SMN1, but it can be used as a primary target for therapeutics, including trans-splicing. Trans-splicing therapy relies on splicing, or uniting, of mutant RNA and therapeutic RNA in order to correct RNA sequence.

To improve efficiency, the researchers developed a trans-splicing system that uses a strand of RNA that can bind to a gene and inactivate it. Turning the gene "off" reduces competition at splice sites and improves the likelihood of achieving the desired results.

"The key to introducing trans-splicing in clinical settings is developing efficient trans-splicing systems," said Chris Lorson, investigator in the Christopher S. Bond Life Sciences Center; associate professor of veterinary pathobiology in the MU College Veterinary Medicine; and

scientific director for Fight SMA, a private spinal muscular atrophy research foundation in Richmond, Va. "We have found that reducing the competition between the splice sites enhances the efficiency of trans-splicing. This strategy provides insight into the trans-splicing mechanism and significantly improves trans-splicing activity in a mouse model of spinal muscular atrophy."

The study, "Development of a Single Vector System that Enchances Trans-splicing of SMN2 Transcripts," was published in PLoS ONE and was co-authored by Lorson; MU researchers Tristan H. Coady, Travis D. Baughan and Monir Shababi; and Genzyme Corporation neuroscience researcher Marco A. Passini.

Provided by University of Missouri