First treatment for muscular dystrophy in sight: Scientists successfully harness exon-skipping

March 16 2009

Genetic researchers at Children's National Medical Center and the National Center of Neurology and Psychiatry in Tokyo published the results of the first successful application of "multiple exon-skipping" to curb the devastating effects of Duchenne muscular dystrophy in an animal larger than a mouse. Multiple exon-skipping employs multiple DNA-like molecules as a "DNA band-aids" to skip over the parts of the mutated gene that block the effective creation of proteins.

The study, conducted in Japan and the United States, published this month in the peer-reviewed journal of the American Neurological Association, the *Annals of Neurology*, treated dogs with naturally occurring canine X-linked muscular dystrophy, a disease which is genetically homologous to the Duchenne muscular dystrophy that strikes 1 of every 3,500 boys born in the United States and worldwide each year.

Duchenne muscular dystrophy, one of the most common lethal genetic disorders, is an X-linked genetic mutation that causes an inability of the body's cells to effectively create dystrophin—which builds muscle tissue. "Exon-skipping" employs synthetic DNA-like molecules called antisense as a DNA band-aid to skip over the parts of the gene that block the effective creation of dystrophin. Because the gene's mutation could affect any of its 79 exons and sometimes more than one single exon at a time, scientists employed a "cocktail" of antisense called morpholinos to

extend the range of this application. By skipping more than a single exon, this so-called DNA band-aid becomes applicable to between 80 and 90 percent of Duchenne muscular dystrophy patients, including the mutation found in dogs.

"This trial makes the much-talked about promise of exon-skipping as a systemic treatment for Duchenne muscular dystrophy in humans a real possibility in the near term," said Toshifumi Yokota, PhD, lead author of the study. "Of course this success has also introduced even more avenues for investigation, but these findings finally overcome a significant hurdle to our progress—we've solved the riddle of an effective system-wide delivery to muscle tissue, and seen promising results."

A new state-of-the-art facility at the National Center of Neurology and Psychiatry in Japan was utilized to carry out the research.

"This study delivers the proof-of-concept that systemic anti-sense therapy can be done in a large organism, in Duchenne muscular dystrophy or any disease", says Eric Hoffman, PhD, a senior author of the study and director of the Center for Genetic Medicine at Children's National Medical Center.

"Systemic treatment of the majority of Duchenne dystrophy will require multiple sequences to be delivered in the blood, and this study also is the first proof-of-principle of multiple exon-skipping in any organism," Shin'ichi Takeda, MD, another senior author, said. "In order to realize that promise in human trials, it also will be important to re-evaluate current measures of toxicity, efficacy, and marketing that ensure both safety for the patient, as well as rapid development and distribution of life-saving drugs.

The authors do note that significant steps still remain. Successful systemic treatment with morpholinos requires large doses of the

antisense molecules—and the technology is costly and difficult to obtain. Additionally, treatment in this study showed diminished success at curbing muscle deterioration of the heart, meaning that a more effective and specific delivery system is needed to rescue the organ's delicate tissue in Duchenne muscular dystrophy patients. However, these early successes do show much promise for the oft-discussed exon-skipping method as an effective treatment for Duchenne muscular dystrophy and some other genetic disorders.

More information: Efficacy of systemic morpholino exon-skipping in duchenne dystrophy dogs, Toshifumi Yokota, Qi-long Lu, Terence Partridge, Masanori Kobayashi, Akinori Nakamura, Shińichi Takeda, Eric Hoffman, *Annals of Neurology*

Source: Children's National Medical Center (news : web)