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Study leads to a promising first-in-class drug candidate

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Discoveries by Scripps Research Institute scientists have led to a promising new drug candidate--the first in its class--for patients with a genetic protein-misfolding disease. In results announced by the biopharmaceutical firm FoldRx Pharmaceuticals, Inc. today, the new drug tafamidis significantly halts disease progression for patients with a disease called Transthyretin (TTR) amyloid polyneuropathy (ATTR-PN).

"I'm very excited by the prospect of a drug to help patients suffering from TTR amyloid diseases," said Professor Jeffery Kelly, Ph.D., a co-founder of FoldRx. Kelly's Scripps Research laboratory laid the groundwork for this therapeutic strategy and discovered the drug candidate. "Moreover, this is the first pharmacologic evidence that the biomedical researcher communities' hypothesis about the etiology of human amyloid diseases, including Alzheimer's disease, is likely correct. The development of tafamidis—the first disease-modifying agent targeting the underlying cause of a human amyloid disease —was built on years of basic scientific research, funded by institutions including the National Institutes of Health (NIDDK), the Skaggs Institute for Chemical Biology, and The Lita Annenberg Hazen Foundation."

TTR amyloid polyneuropathy, a rare inherited protein misfolding disease also known as Familial Amyloid Polyneuropathy, is a slowly progressive, multifaceted disease that causes loss of sensation, muscle weakness, and autonomic nerve dysfunction (including gastrointestinal disorders and urinary problems), ultimately leading to death. The only treatment

currently available is liver transplantation.

The results from FoldRx's randomized, controlled Phase II/III clinical study show once daily oral treatment with tafamidis significantly halts disease progression and reduces the burden of disease after 18 months compared to placebo. The study also showed that tafamidis appears to be safe and well tolerated.

"We are very excited by the results of the trial and look forward to bringing this innovative therapy to patients worldwide." noted Richard Labaudiničre, Ph.D., President and CEO of FoldRx. "We plan discussions with the U.S. and European regulatory agencies later this year and we anticipate filing marketing applications in 2010."

Following the Path of Positive Results

TTR amyloidosis is a disease caused by the "misfolding" of proteins, which then cluster together in aggregates called amyloid fibrils. These fibrils then deposit in organs, interfering with their normal function. In the case of TTR amyloid polyneuropathy, a protein called transthyretin (TTR) "misfolds" and amyloid fibrils cluster in peripheral nerve tissues that serve limbs and organs. In the case of TTR amyloid cardiomyopathy, amyloid fibrils infiltrate the heart, leading to heart dysfunction. The predominant mutation, V122I, is present in approximately four percent of the U.S. African American population. Wild-type (normal) TTR can also form amyloid fibrils, particularly in the elderly; approximately 15 to 25 percent of individuals over the age of 80 have demonstrable deposition in the heart leading to a cardiomyopathy.

In 2001, Kelly, who is chair of the Department of Molecular and Experimental Medicine, Lita Annenberg Hazen Professor of Chemistry, and member of The Skaggs Institute for Chemical Biology at Scripps

Research, and his colleagues published research showing that a "suppressor" TTR mutant subunit, when incorporated into a TTR protein otherwise composed of amyloid disease-associated TTR subunits, prevents the protein from dissociating, misfolding, and forming fibrils, apparently explaining why patients with a disease-associated TTR mutation and a suppressor mutation exhibit only mild pathology (Science, 293 (5539): 2459 - 2462, September 28, 2001).

A year and a half later, the group published additional research demonstrating the efficacy of using small molecules to stabilize the normal "fold" of TTR, preventing this protein from misfolding by making the barrier for misfolding insurmountable. Using this method, researchers were able to inhibit the formation of amyloid fibrils by a mechanism mimicking that of the suppressor TTR subunit described in the previous study (Science, 299 (5607): 713 - 716, January 31, 2003).

Source: The Scripps Research Institute (news : web)