UMMS and Lundbeck to explore potential targeted therapy for Huntington's disease

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The University of Massachusetts Medical School (UMMS) and Lundbeck Inc. today announced a research collaboration aimed at further development of a targeted therapy to slow or halt the progression of Huntington's disease (HD).

At this time, there is no way to stop or reverse the course of HD, a challenging hereditary neurodegenerative disease characterized by a triad of progressive motor, cognitive and emotional symptoms. This collaboration will support a distinguished group of scientists in the study of RNAi-based therapies as a possible method for selectively suppressing production of mutant huntingtin (mHtt), the abnormal protein that causes HD.

RNA interference, or RNAi, is a natural process that cells use to turn down, or silence, activity of specific genes. HD is mapped to a specific gene, which makes it a promising target for RNAi-based therapy because production of a mutant protein like mHtt can potentially be blocked by knocking down, or reducing, the gene's activity.

"Our core idea is that RNAi can be used to selectively reduce mutant huntingtin production to slow or block the progression of HD, but we also hypothesize that excessive huntingtin silencing may impair neuronal function by interfering with essential signaling events," said Neil Aronin, MD, professor in medicine and cell biology at UMMS and principal investigator of the study. "This research collaboration allows us to test promising RNAi-based therapeutic vehicles to selectively knock down

mutant huntingtin with the goal of restoring normal neuronal function. We've come a long way in pushing this research forward, and this next step with Lundbeck is extremely exciting."

RNAi technology is used to interfere with the expression of a specific gene and, in this case, researchers will apply it to mHtt. This multi-faceted pre-clinical study progresses beyond previously successful mouse studies and could bring RNAi-based therapy one step closer to human clinical trials. The study will evaluate potential dosing regimens of siRNA (small interfering RNA), packaged as short hairpin RNA (shRNA) and transported via the adeno-associated virus (AAV), a promising therapeutic vehicle for siRNA delivery to neurons. Additionally, researchers will work to establish the best brain distribution pattern for potential use of siRNA in clinical HD therapies. More specifically, a major element of the study will be to measure the volume of distribution in brain tissue of AAV-delivered shRNAmir (micro RNA-adapted shRNA).This will permit researchers to evaluate the dosing of AAV-shRNAmir in order to achieve spread throughout the striatum and nearby cortex.

"We've followed Dr. Aronin and his team of researchers at the Medical School for some time and have been inspired by their bold exploration of RNAi technology and its potential use as a therapy for HD," said Stevin Zorn, PhD, executive vice president, Lundbeck Research USA. "Lundbeck is proud to collaborate with such an exceptional group of scientists who are so devoted to those affected by this debilitating condition."

In addition to Dr. Aronin, a talented group of scientists comprise the UMMS research team, including: Guangping Gao, PhD, who brings vast experience in developing adeno-associated virus; Richard Moser, MD, a neurosurgeon with expertise in resection of brain tumors and accessing brain compartments; and Marian DiFiglia, PhD, of Massachusetts

General Hospital, an expert in the neuropathology and mechanisms of HD. Consultants on the project include: Kitty Clarence-Smith, MD, PhD, Lundbeck Inc., a neuro-pharmacologist who was instrumental in the approval process of the first FDA-approved drug for HD chorea; Robert Friedlander, MD, Professor and Chair of Neurosurgery, University of Pittsburgh School of Medicine, who has expertise in the study of neuronal survival in HD; and Michael Levine, MD, Professor and Chair of the Neuro-Psychiatric Institute at UCLA, an expert on HD animal models. The study is expected to be completed in 24 months.

"During my years helping patients who are living with HD, our understanding of the disease has increased dramatically and opened doors for new approaches to treating the condition," said Anne Young, MD, PhD, Chief of Neurology at

Massachusetts General Hospital. "In my opinion, this approach hits the disease right at its core. If this method can reduce the huntingtin protein throughout the brain, it carries the potential to change the course of the disease."

"The Hereditary Disease Foundation recognized the potential of RNA interference to cure Huntington's disease when it was just being discovered," says Nancy Wexler, Ph.D., President of the Hereditary Disease Foundation and Higgins Professor of Neuropsychology, Columbia University. "We organized the first Workshop in the world on this topic: 'RNA Modalities in Huntington's Disease Therapy,' in 2002. The Workshop was led by Phillip Sharp, who won the Nobel Prize in 1993. This was the same year that our research team discovered the HD gene, a breakthrough that made gene silencing possible. Neil Aronin was a critical Workshop participant. The Hereditary Disease Foundation funded the very first research projects proving that RNA inference cures HD in mice. Silencing the abnormal protein gets at the heart of the problem. It is a unique and revolutionary approach to finding

treatments."

This collaboration is part of Lundbeck's Huntington's disease research initiative to identify and ultimately commercialize therapies that may slow or halt the progression of the disease. This research is driven by collaborations with academic institutions and companies with promising compounds in development.

Provided by University of Massachusetts Medical School