Study reports novel drug technology that boosts therapeutic proteins

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(PhysOrg.com) -- A Miller School-led research team has created a groundbreaking drug technology platform that enables the body to increase its protein levels, a novel invention that potentially could usher in treatment for a wide variety of serious diseases resulting from a lack of specific proteins.

Published online March 25 in Nature Biotechnology, the study, "Inhibition of natural antisense transcripts in vivo results in gene-specific transcriptional upregulation," was led by Claes Wahlestedt, M.D., Ph.D., professor of psychiatry and behavioral sciences and associate dean for therapeutic innovation, who is widely known for his research in epigenetics and novel drug therapies to treat diseases such as autism, Alzheimer's, schizophrenia, depression, addiction, Parkinson's and cancer. Mohammad Ali Faghihi, M.D., Ph.D., research assistant professor of psychiatry and behavioral sciences, spearheaded the study with Wahlestedt.

The study is considered a breakthrough because the new drug discovery platform allows researchers to increase, or upregulate, gene expression by coaxing the body to increase the production of proteins that are necessary to ward off certain diseases. The method provides a possible alternative to standard forms of drug therapy where medicines either boost or, more frequently, inhibit genes or proteins.

"What we have discovered is a new way to stimulate the body's own production of therapeutic proteins that could potentially help ward off a

wide variety of illnesses," said Wahlestedt, who undertook much of the research when he and his team worked at the Florida campus of The Scripps Research Institute.

A resounding endorsement for the new research came last year when cuRNA, a Scripps spin-off focusing on Wahlestedt's work in upregulating RNA (ribonucleic acid), was sold to Opko Health Inc. of Miami. Other entities outside Florida also attempted to acquire the technology.

Although there are a number of modern approaches to drug therapy, including RNA interference (RNAi) to inhibit gene expression, scientists have few if any simple and rational pharmacological avenues to upregulate gene expression when there is a shortage of a critical gene product to fight disease. One anticipated solution, gene therapy, which aims to replace a poorly functioning gene, has proven to be challenging and potentially risky in some cases.

The new strategy developed by Wahlestedt and his team uses known drug molecules, known as oligonucleotides, to inhibit natural molecules that normally act as a continuous brake on genes. Thereby the brake "releases" one gene at a time in a reversible manner, potentially allowing for precise medication of patients.

While this new approach can be applied to a vast number of genes, the published study focuses on upregulating Brain-Derived Neurotrophic Factor (BDNF) gene. BDNF is essential for neuronal growth, maturation, differentiation and maintenance and increased levels of BDNF is thought to be beneficial in treating several human disorders, including Alzheimer's disease, Huntington's disease, Rett syndrome and depression. The study shows increased levels of brain BDNF in an animal model after upregulation.

"This new technology, which upregulates the functional endogenous proteins in their natural environment—correctly folded with the appropriate post-translational modifications—could provide advantages over administering recombinant proteins or viral vectors supporting protein expression," Faghihi said. "This technology could be a major advance in medical research as many diseases could be treated by increasing the availability of a protein in the body."

Provided by University of Miami

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