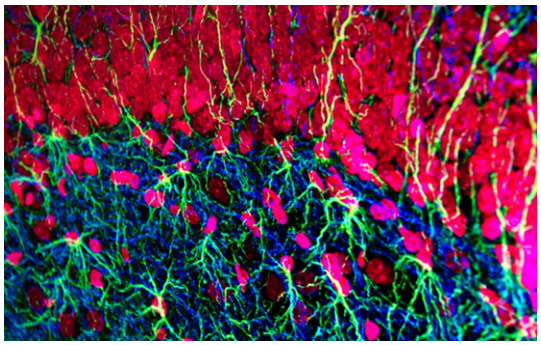
UC San Diego
UC San Diego News Center

June 20, 2012 | By Scott LaFee

Proposed Drug May Reverse Huntington's Disease Symptoms

Single treatment produces long-term improvement in animal models

With a single drug treatment, researchers at the Ludwig Institute for Cancer Research at the University of California, San Diego School of Medicine can silence the mutated gene responsible for Huntington's disease, slowing and partially reversing progression of the fatal neurodegenerative disorder in animal models.



Stained mouse neurons. Image courtesy of Taylor Bayouth.

The findings are published in the June 21, 2012 print issue of the journal *Neuron*.

Researchers suggest the drug therapy, tested in mouse and non-human primate models, could produce sustained motor and neurological benefits in human adults with moderate and severe forms of the disorder. Currently, there is no effective treatment.

Huntington's disease afflicts approximately 30,000 Americans, whose symptoms include uncontrolled movements and progressive cognitive and psychiatric problems. The disease is caused by the mutation of a single gene, which results in the production and accumulation of toxic proteins throughout the brain.

Don W. Cleveland, PhD, professor and chair of the UC San Diego Department of Cellular and Molecular Medicine and head of the Laboratory of Cell Biology at the Ludwig Institute for Cancer Research, and colleagues infused mouse and primate models of Huntington's disease with one-time injections of an identified DNA drug based on antisense oligonucleotides (ASOs). These ASOs selectively bind to and destroy the mutant gene's molecular instructions for making the toxic huntingtin protein.

The singular treatment produced rapid results. Treated animals began moving better within one month and achieved normal motor function within two. More remarkably, the benefits persisted, lasting nine months, well after the drug had disappeared and production of the toxic proteins had resumed.

“For diseases like Huntington’s, where a mutant protein product is tolerated for decades prior to disease onset, these findings open up the provocative possibility that transient treatment can lead to a prolonged benefit to patients,” said Cleveland. “This finding raises the prospect of a ‘huntingtin holiday,’ which may allow for clearance of disease-causing species that might take weeks or months to re-form. If so, then a single application of a drug to reduce expression of a target gene could ‘reset the disease clock,’ providing a benefit long after huntingtin suppression has ended.”

Beyond improving motor and cognitive function, researchers said the ASO treatment also blocked brain atrophy and increased lifespan in mouse models with a severe form of the disease. The therapy was equally effective whether one or both huntingtin genes were mutated, a positive indicator for human therapy.

Cleveland noted that the approach was particularly promising because antisense therapies have already been proven safe in clinical trials and are the focus of much drug development. Moreover, the findings may have broader implications, he said, for other “age-dependent neurodegenerative diseases that develop from exposure to a mutant protein product” and perhaps for nervous system cancers, such as glioblastomas.

Co-authors are first author Holly B. Kordasiewicz, Melissa M. McAlonis, Kimberly A. Pytel and Jonathan W. Artates, Ludwig Institute for Cancer Research and UC San Diego Department of Cellular and Molecular Medicine; Lisa M. Stanek, Seng H. Cheng and Lamya S. Shihabuddin, Genzyme Corporation; Edward V. Wancewicz, Curt Mazur, Gene Hung and C. Frank Bennett, Isis Pharmaceuticals; and Andreas Weiss, Novartis Institutes for BioMedical Research.

Funding for this research came, in part, from the CHDI Foundation.
