Dr. Michael Hayden and his colleagues at Child and Family Research Institute’s Centre for Molecular Medicine and Therapeutics (CMMT) in Vancouver, Canada recently discovered that, by preventing the cleavage or “cutting” of the mutant huntingtin protein responsible for Huntington disease (HD), the degenerative symptoms may be prevented from occurring in a mouse model. This may be the first time that a cure for HD in mice has been successfully achieved - but it is important to recognize that this “cure” was achieved by engineering a slightly different huntingtin protein. It was not achieved by delivering a drug.

Bottom-line: Many of the changes seen in HD patients may be erased in HD mice simply by engineering a change that prevents the protein from getting cleaved at a specific site. This study is important, because it confirms what was suspected by many researchers: that early in disease, cleavage of huntingtin plays a key role in making the disease protein toxic. In HD, this deadly cleavage is caused primarily by a specific protease called caspase-6 (the word caspase comes from cysteine-aspartic-acid-proteases.) Caspases are enzymes that are particularly well known for their role in mediating a certain kind of cell death known as apoptosis. Various caspases exist that cleave specific proteins in the cell when they are activated -- caspases are dormant most of the time. Through a cascade of protein cleavage, caspases serve to ‘execute’ the cell. While caspases may sound like very bad actors, they actually are necessary for normal development: caspase-mediated apoptosis helps to sculpt various tissues during development, including the brain. It prevents unchecked cell growth that can lead to tumors. Apoptosis also occurs in neurodegenerative disorders, like HD. Apoptosis is also triggered by stress in a cell, especially stress in the nucleus, and this is known to occur in HD and various other neurodegenerative disorders.

This research tells us more about the problems of toxic proteins produced from cleavage and gives us a new avenue for developing drugs. Hayden’s team will now try to test this prevention model in a mouse using drug inhibitors and then ultimately in humans.

CHDI, the nonprofit drug development organization for Huntington’s Disease, has been proactive about potential treatments for HD. Efforts are already underway to develop a safe, effective caspase 6 inhibitor. According to Dr. Robert Pacifici (Chief Scientific Officer at CHDI who spoke at HDSA in Milwaukee, 2006) they hope to have a caspase 6 inhibitor available for testing in mice by the end of the year. These compounds would need further development to make sure that they crossed the blood brain barrier (see article in newsletter about brain barrier) and are safe for long-term use in people.

What is RNAi and what are the hopes of RNAi treatments for HD?

RNAi is a naturally occurring biological process that takes place in all kinds of creatures, from plants to humans. It is a process by which cells can regulate the expression of specific genes at the RNA level. For the expression of some genes during development, regulation by RNAi occurs naturally. But scientists have now taken advantage of this machinery to introduce RNAi molecules into
cells to silence the expression of specific disease genes including the HD gene. Many genes code for proteins -- for example the HD gene codes for the protein huntingtin. In order for a cell to make huntingtin, the HD gene is transcribed into RNA - literally, a RNA copy is made of one strand of the DNA. This single-stranded RNA, called a messenger RNA or mRNA, leaves the nucleus and enters the cytoplasm of the cell. In the cytoplasm, the cell’s protein-producing machinery “reads” the mRNA and builds a protein based on the blueprint provided by the mRNA. In a nutshell, mRNA is the necessary intermediary or, messenger, that allows huntingtin and other proteins to foster. If mRNA is not made from the HD gene, or if the mRNA is rapidly destroyed, then huntingtin protein cannot be made. Because in HD and in many related neurological diseases, the disease protein is the bad actor, eliminating its production makes sense. By exploiting RNAi to destroy the mRNA -- essentially “shooting the messenger” -- scientists can prevent the production of a specific protein. Researchers at the University of Iowa led by Dr. Beverly Davidson applied this strategy to turn off the HD gene in HD mice (published in the journal Nature Medicine in 2004). The mice were not fully cured, but the disease was markedly slowed. And in the brain regions to which the RNAi was delivered, the HD protein was no longer expressed. RNAi is a hot topic right now with real promise for HD and other neurodegenerative disease. But there is still much more to be learned about its delivery, safety, sustain-

ability and specificity before we can move this forward with people. What is the best strategy to deliver the RNAi to the brain? What brain regions do we need to target in HD? Will long term, therapeutic RNAi expression in the brain somehow muck up the biological activity of naturally occurring RNAi molecule and, if so, will this harm the brain? And finally, in HD, can we turn down expression from both copies of the HD gene without causing harm or will we need to selectively turn down expression from the disease gene copy while preserving expression from the normal gene copy? Hopefully, answers to these questions will be forthcoming soon.

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What is the blood brain barrier and why is it important for HD research?

The blood-brain barrier (BBB) is a membrane that prevents the passage of toxic (or contaminated) substances in the blood from entering the brain and the central nervous system. It is a physical barrier between the local blood vessels and most parts of the central nervous system itself, and it stops many substances from traveling across it. The blood brain barrier protects the brain from chemicals in other parts of the body. A major challenge for treatment of most brain disorders, like HD, is overcoming the difficulty of delivering therapies to specific regions of the brain. In its role as protector, the blood-brain barrier acts to hinder the delivery of many potentially important therapies to the brain. Therapeutic molecules and genes that might otherwise be effective in diagnosis and therapy do not cross the BBB in adequate amounts.

Scientists at the University of Wisconsin are working at creating models of brain cells that can help clinicians deliver drugs where they are most needed. CHDI, a non profit organization that is specifically looking at treatments for HD, partnered with Edison Pharmaceuticals is also working at creating substances that can be tailored to the biochemical energy defect associated with HD and can penetrate the blood brain barrier.

Kmart offers 90 day medication program

Kmart Pharmacy has started a program where a patient can receive a 90 day supply of many generic medications for $15 with or without insurance. Any individual whom the pharmacist or prescriber determines would benefit from this program is eligible to participate. Any Kmart with a pharmacy has the program. Just ask the pharmacist about the 90 Day Generic Program. There is no application. Just visit a local Kmart, and the pharmacist will handle the request. There are about 20 Kmarts in the state of Iowa.
New Clinical Trial
Atomoxetine

The purpose of this study is to evaluate the effect of atomoxetine (also known as Strattera) compared to placebo (an inactive substance) on daily activities such focusing, thinking ability and muscle movements in participants with early HD. Participants must be between 18-60 years old and be diagnosed with Huntington’s disease.

Every participant will have the opportunity to take atomoxetine during this study. If you would like to participate, a screening visit will determine your eligibility. During the first four weeks you will be randomly assigned (like the flip of a coin) to receive either atomoxetine or a look-alike drug with no active ingredients (placebo). After four weeks, you will stop taking either the placebo or atomoxetine for two weeks, and you will begin taking the other.

The study will last for thirteen weeks, and you will complete five outpatient visits and three telephone visits. The visits will include motor examinations and thinking tests. Blood samples are taken to assess for general health only. The University of Iowa is the only site for this clinical trial. For more information, contact Bill Adams (319) 353-4411 at the University of Iowa.

RESPOND-HD

Looks at Issues of Discrimination

The University of Iowa received a grant award by the Department of Health and Human Services National Institutes of Health for the Respond HD study.

The information gathered in this study will allow us to examine the experiences of persons who have undergone genetic testing for the Huntington’s disease (HD) mutation. This study will seek answers to questions such as “How is knowledge used after genetic testing?” “What experiences occur following genetic testing?” and “Why might outcomes differ in persons undergoing genetic testing?”

Three groups at-risk for HD will be recruited and enrolled in this study: Predict-HD participants who received predictive testing and have the HD gene mutation, Predict-HD participants who received predictive testing and do not have the HD gene mutation, and PHAROS participants who are currently at-risk for HD and have not received predictive testing. Participants will be recruited from states that have differing discrimination laws for employment and insurance and from Canada.

For more information about this study, contact Elizabeth Penziner at (319) 353-4292 or Elizabethpenziner@uiowa.edu.

New Research Opportunity:
Cooperative Huntington’s Observational Research Trial- COHORT

COHORT is a multi-site, long-term observational study. Our goal is to collect information in order to learn more about HD (such as potential treatments, planning of future experimental drug studies, and work toward postponing the onset or slowing the progression of HD). The study will be open to both adults and children who have clinically diagnosed HD, and to adults who are part of HD families.

Participation in COHORT is voluntary, and visits will be scheduled annually for as long as individuals are able and choose to participate. At the initial visit (year one) a blood sample will be drawn for genetic testing of CAG repeat and other possible biomarkers. Medical and neurological evaluations will be performed at each yearly visit; these include standardized assessments of movement, thinking, memory, ability to perform everyday tasks and behavior. Participants will be asked to provide information about medical history and their current medications.

For more information regarding this study, please contact Anne Leserman (319) 353-4307 (anneleserman@uiowa.edu)

HD Support Groups:

DES MOINES
Valley View Village Conference
2571 Guthrie Ave
3rd Sunday at 1:30 pm
Kim Wesack
(515) 965-5469

OMAHA, Nebraska
Village Inn Restaurant
78th and Dodge
2nd Monday at 6:00 pm
Cathy McNeil
(402) 537-0739

IOWA CITY
University of Iowa Hospitals and Clinics
Della Ruppert Conference Room
6th floor, elevator H
4th Sunday at 1:00 pm
Anne Leserman
(319) 353-4307
What is respite care?

Caregivers face many challenges. Caregiving is a demanding task, and it is easy to neglect your own health and well-being when you are involved with your loved one’s needs. Caregivers need time off from their caregiving responsibilities to relieve stress and prevent burnout.

Respite care provides time off for family members who care for someone who is ill, injured or frail. It can take place in an adult day center, in the home of the person being cared for, or even in a residential setting such as an assisted living facility or nursing home. Although there are different approaches to respite care, all have the same basic objective: to provide caregivers with planned temporary, intermittent, substitute care, allowing for relief from the daily responsibilities of caring for the care recipient. Respite care is essential for all caregivers, whether they work in a caregiving facility or at home with family members or close friends.

Questions to ask about respite care programs

- How are care providers screened?
- What is the training and level of experience of the care providers?
- Will care providers need additional training to meet specific family needs?
- How, and by whom, are the care providers supervised?
- What procedures does the program have for emergencies?
- Are families limited to a certain number of hours of services?
- Does the program provide transportation?
- What is the cost of services? How is payment arranged?

Information from www.helpguide.org
Iowa resources to consider:
Iowa Compass http://www.medicine.uiowa.edu/iowacompas
http://www.healthcare.uiowa.edu/cdd/index.asp
http://www.iowafamilycaregiver.org/index.asp
http://www.irccc.com

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