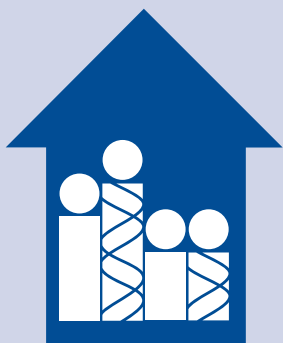


TOWARD A CURE

A R E S E A R C H U P D A T E



The HDSA Research Forum

By Marcy E. MacDonald, Ph.D.

The HDSA Research Forum convened bright and early Saturday morning June 6th in the Regency Ballroom of the Hyatt Regency Hotel in Phoenix Arizona. The audience was large and enthusiastic and was anxious to hear the latest in HD research from a stellar line-up of speakers.

To get things started, Louise Vetter warmed everyone up with a hearty welcome on behalf of the HDSA leadership, launching the morning with her well-aimed remarks on the importance of research to the HDSA mission of finding effective treatments for HD.

I was privileged to introduce our Keynote Speaker Mr. Charles Sabine, NBC News Correspondent. Charles took the podium and proceeded to captivate everyone with his **Personal Perspective** on HD research. Charles took us along with him on his own journey of HD discovery. His lively and poignant descriptions and photos of his talented father and brother, who both were affected with HD, were interwoven with dramatic video clips from some of his news reports from dangerous trouble spots around the world. Charles told us that when he learned that he too carries the HD gene mutation, he felt terror beyond anything that he had felt in a war

zone, for himself and for his young family. Thus he has decided to speak up about HD, urging activism – working to change the status quo in the private and the public sectors. He mentioned the workplace Genetic Information Nondiscrimination Act of 2008 (GINA), an important topic that Cheryl Erwin later addressed in a specific session, now available on the HDSA website. Health insurance and life insurance need tackling, and he suggested participation in observational studies and clinical trials.

Charles' talk was touching and funny and inspiring. It was the perfect introduction to the rest of the Research Forum, which highlighted the HDSA research programs and what HDSA scientists and researchers from around the world have learned about HD, in the quest for treatments.

Indeed, as the Chair of the Medical and Scientific Advisory Committee (MSAC), I spoke about **Discovery Research: Essential Clues for Designing Treatments**. My task was to illustrate how the HDSA research programs fuel the HD research cycle. HD research begins with studies of members of HD families, to generate detailed descriptions of the various subtle and overt features of HD, guiding efforts by scientists to then study the underlying disease process in humans and in mice and other laboratory organisms. These observations then provide measurements that are utilized to find factors that modulate the disease changes that are assessed in animal models and then, if they fulfill a set



Marcy MacDonald, Ph.D., Chair HDSA MSAC

of stringent criteria, some may be tested in clinical trials with humans, thereby completing one full turn of the research cycle. The HDSA research programs provide critical support at every stage; training new young scientists (several Fellowships per year), supporting experienced senior HD scientists (16 investigators from around the world) who work in teams to answer key discovery questions (the Coalition), then docking with industrial-scale research partnerships that are designed to test new potential treatments in clinical trials. Through its growing cadre of

Continued on page 12

In This Issue

- 2 Notes from the Lab
- 3 Coalition Looks to the Future
- 4 Stem Cell Research
- 8 Research Roundup
- 10 Gordon Conference

Notes from the Lab

By Marcy MacDonald, Ph.D.
*Chair, HDSA Medical and
Scientific Advisory Committee*

Welcome to a new issue of *Toward a Cure*. In June, HDSA welcomed HD family members to Phoenix for one of its biggest conventions ever. More than 725 people came together for three days of workshops, plenary sessions and sharing. As a researcher and member of the HDSA Coalition for the Cure, it is always amazing to be able to make the connection between the work I do in my lab and the hope that it brings to families struggling with this deadly disease. There can be no finer inspiration or impetus to our continuing to work as quickly as possible to find the answers to the HD puzzle.

In this issue, we share the highlights of a few sessions that sparked the imagination of the audience. Beginning with the captivating personal story of NBC news correspondent, **Charles Sabine**, to the excitement of new clinical studies that may yield a potential therapy, to the advent of stem cell research in HD – the *HDSA Research Forum* was the place to be on Saturday morning. You can read about the session beginning on page 1.

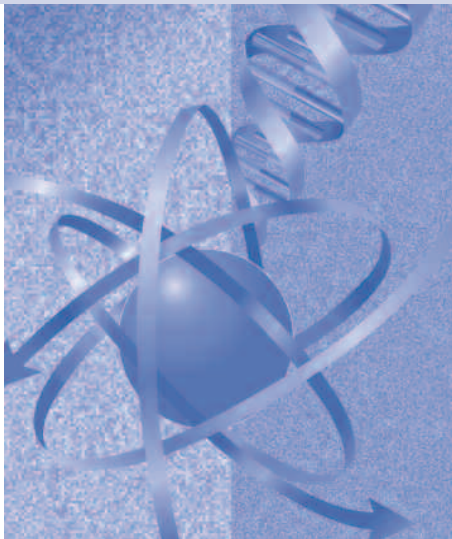
To help clarify how researchers are currently using stem cell technology in research, we offer both a primer on stem cells and an overview of research methods being employed at three different labs conducting HD research. We hope this article will answer some of the questions you may have about how this nascent approach is being used to understand the disease process.

As research advances to actual therapies, the need for people to participate in clinical studies will increase. At the convention, **John Caviness, M.D.**, from the Mayo Clinic in Scottsdale, conducted a workshop on the issue of safety in clinical trials. We hope that his article on page 6 will provide insight into what questions you should ask when considering a trial, concerns you should have and what safety measures are already in place before there is ever a call for volunteers.

Many of the presentations given by our esteemed speakers are posted on the HDSA national web site. To access them, go to the home page (www.hdsa.org), scroll down to “HDSA Events” and click on “HDSA National Convention.” We hope you find these presentations helpful.

In August, HDSA Coalition for the Cure investigators met in New York City to begin planning for future research projects. It is now time for the collaborative team-based Coalition to re-evaluate not only our progress but our questions. Look for a full report in the next issue of *Toward a Cure*.

In closing, the advances we have made in understanding this disease and in making rapid progress towards potential therapies would not have been possible without your support. The HDSA Coalition for the Cure began as a wish and became a reality because you believed in what we were doing. I ask you to continue to believe in what we do and make a donation today. Your gift, large or small, will fuel the fires of research and continue to make it possible for our dedicated HDSA investigators, like myself, to make a difference in the lives of those struggling with HD. *Thank you.*



TOWARD A CURE

Published twice yearly, as a public service, by the Huntington's Disease Society of America Inc.
505 Eighth Avenue, Suite 902
New York, NY 10018
(212) 242-1968 • www.hdsa.org

HDSA BOARD OF TRUSTEES

C. Walt Johnston, *Chairman of the Board*
Cheryl Kendrick, *Vice-Chair of the Board*
Jamie Greene, Esq., *Secretary*
Roger Vaughan, *Treasurer*

Donald Barr
Diane Carlson
Jang-Ho Cha, M.D., Ph.D., *Chair, CPEAC*
Gerry Francese, Esq.
Susan Huang
Steve Ireland
Barry Kahn
Marcy MacDonald, Ph.D., *Chair, MSAC*
Michael Roth, *Chair, Marketing*
Steve Seekins
Kimberly Silva
Leon Tibben, *Chair, NFC*
Dan Vandivort

Louise Vetter
Chief Executive Officer

Debra Lovecky
*Director of Education,
Programs and Services
Editor*

Laurie Straus, EllEss Design, Inc.
Layout & Design

The purpose of *Toward a Cure* is to provide information and opinion and to relay items of interest to individuals with Huntington's Disease and their families, healthcare professionals and interested friends and supporters.

The appearance of advertising, or the mention of commercial articles available for sale in articles published in this newsletter, is not an HDSA, Inc. guarantee or endorsement of the product or the claims made for the product by the manufacturer. Statements and opinions expressed in articles are not necessarily those of HDSA, Inc.

The Huntington's Disease Society of America (HDSA) is a national not-for-profit organization. The Society is dedicated to eradicating Huntington's Disease by promoting and supporting HD research; to helping families cope with the problems presented by HD; and to educating the public and healthcare professionals about Huntington's Disease.

HDSA is a member of the National Voluntary Health Agencies, the National Health Council, the National Organization of Rare Disorders, the International Huntington Association, the Alliance for Genetic Support Groups, and the Independent Sector.

The Huntington's Disease Society of America meets all nine standards of the National Charities Information Bureau.

 **Huntington's Disease Society of America**

HDSA Coalition for the Cure Looks to the Future

HDSA Coalition for the Cure investigators recently met in New York City to prepare plans to undertake the most compelling research advancements in its 13 year history.

The Coalition, the flagship research initiative of HDSA, consists of 16 of the leading HD scientists in the world working cooperatively in teams to advance basic research to define potential targets for therapies.

Founded in 1998, the HDSA Coalition for the Cure was created to attract senior HD investigators and channel their efforts towards solving the mysteries of Huntington's Disease. Four years ago these researchers formed teams to harness their talents collectively and avoid duplication of efforts while focusing on specific problems that must be resolved in order to move forward.

This latest meeting examined critical areas for HD research over the next three years. The teams are now planning the next major research questions, aimed at discovering new potential targets for developing therapeutics. Indeed, the unique structure of the Coalition, with its network of intra- and cross- team collaborations, permits rapid adjustments in research direction without major interruptions of the research efforts.

The Coalition will meet again in Vancouver, in conjunction with the World Congress on Huntington's Disease, to establish research goals – driven by the cooperative team efforts and high quality of the science.

Please visit the HDSA website and watch for future issues of *Toward a Cure* for updates on the scientific directions chosen by the HDSA Coalition for the Cure to advance future HD research. The Coalition scientists offer us the very best chance of success and they need and deserve our support. Please respond positively to requests for research funding that will be directed in its entirety to the HDSA Coalition for the Cure.



HDSA Coalition for the Cure Investigators

Gillian Bates, Ph.D.

Kings College, London, UK

M. Flint Beal, M.D., Ph.D.

Cornell University

David Borshelt, Ph.D.

University of Florida

Elena Cattaneo, Ph.D.

University of Milano, Italy

Jang-Ho Cha, M.D., Ph.D.

*Massachusetts General Hospital/
Harvard University*

Marian DiFiglia, Ph.D.

*Massachusetts General Hospital/
Harvard University*

Robert Friedlander, M.D.

Brigham and Women's Hospital

James F. Gusella, Ph.D.

*Massachusetts General Hospital/
Harvard University*

Michael Hayden, M.D., Ph.D.

University of British Columbia, Canada

Steven Hersch, M.D., Ph.D.

*Massachusetts General Hospital/
Harvard University*

Ron Kopito, Ph.D.

Stanford University

Marcy E. MacDonald, Ph.D.

*Massachusetts General Hospital/
Harvard University*

Richard Morimoto, Ph.D.

Northwestern University

Christopher Ross, M.D., Ph.D.

Johns Hopkins University

Leslie Thompson, Ph.D.

University of California, Irvine

Erich Wanker, Ph.D.

Max-Planck-Center, Germany

Stem Cells

and their Potential for Huntington's Disease

As stem cell research moves forward at a fast pace, the Huntington's Disease community has become an important part of the progress. HD patients are likely to benefit from the research in several ways.

Lines of stem cells with the HD gene are being used to model the disease. Cells with the HD gene are being compared to normal cells, beginning with the earliest stage of development, to gain new insights into early targets for treatments.

Harvard Stem Cell Institute researcher **George Q. Daley, MD, PhD**, and colleagues have produced a robust new collection of disease-specific stem cell lines, including one for Huntington's Disease. They used skin cells donated by a Huntington's Disease patient and turned them into stem cells by inserting genes that 'turn back the clock.'

"We wanted to produce a large number of disease models for ourselves, our collaborators, and the stem cell research community to accelerate research," Dr. Daley said. "The original embryonic stem cell lines are generic, and allow you to ask only basic questions. But these new lines are valuable tools for attacking the root causes of disease."

Last summer, Coalition researcher **Dr. Leslie Thompson** received a \$1.4 million grant to study the disease using stem cells. She is using embryonic stem cells to study the disease and test for treatments. She is also using induced pluripotent cells from HD patients with different CAG repeats and different symptoms to learn more about why the disease varies among patients. "We are thrilled that these grants were awarded," she said. "The cell lines will enable us to better understand how the disease starts and progresses and to test new drugs to stop it."

In addition to aiding in our understanding of the disease process, stem cell lines can be used in high throughput assays to screen potential treatments. CHDI Foundation has generated stem cells from HD mouse models and human gene carriers with the objective of developing neural endpoints to be used for target validation and secondary and tertiary screens for drug development and discovery.

Stem cells might be used in treating the disease. The potential for the future is great but there are still challenges to be overcome.

One possibility is to stimulate the brain's own production of stem cells. The adult brain maintains a pool of somatic stem cells that could be stimulated to proliferate in defined pathways. **Dr. Steven Goldman** and colleagues used a viral vector to introduce genes for factors BDNF and noggin into the brains of the R6/2 mice. New neurons were generated,

motor performance improved, and survival time increased. More research into issues of safety, effectiveness, and delivery will be necessary before this technique could be used in HD patients.

Another possibility is that stem cells could be introduced into the brain with the hope that they would replace or repair dead and dysfunctional cells. Stem cells might serve as a primary treatment or they might be used to restore brain cells lost in Huntington's Disease following a treatment or combination of treatments that halt progression. Challenges here include delivery and concerns about tumor production and immune response.

In April, **Dr. Jan Nolte** of the University of California, Davis, received a \$2.75 million translational grant from The California Institute for Regenerative Medicine. The goal of CIRM is to fund promising projects which will translate basic research into stem cells into a cure in the clinic. She plans to use mesenchymal stem cells into which short interfering RNA has been inserted. As the stem cells move through the affected areas of the brain, they will merge with and repair damaged brain cells and also reduce levels of the HD protein. Mesenchymal stem cells have not been associated with tumors and appear to be immunologically privileged. A Phase One safety and tolerability clinical trial is planned to start in about eighteen months.

The months and years ahead of basic, translational, and clinical trial research will be challenging, but the work holds great promise for the future.

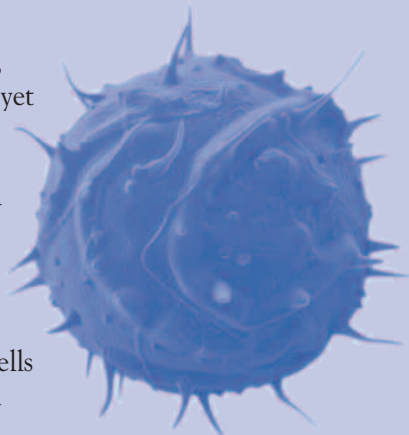
—By Marsha Miller, Ph.D.

The months and years ahead of basic, translational, and clinical trial research will be challenging, but the work holds great promise for the future.



Stem Cell Primer

Stem cells are undifferentiated cells, cells which have not yet developed into the distinct specialized cells of the body such as the neurons and glia of the brain or the red and white cells of the blood or the various types of cells in the skin. They can divide and replenish themselves indefinitely.



Embryonic stem cells are harvested from embryos in the blastocyte stage of development. They have the capacity to become any type of human cell; in other words, they are **pluripotent**. For human embryonic stem cells, researchers use embryos that were created for *in vitro* fertilization but were not needed.

Somatic or adult stem cells are tissue specific. They are undifferentiated but only have the capacity to develop into the cells needed in that tissue; they are multipotent. Adult stem cells are harvested from volunteers. For example, adult blood-forming stem cells have been harvested from the bone marrow of volunteers and transplanted to patients for five decades.

One type of adult stem cell appears to have special properties to repair damaged or dying cells.

Mesenchymal stem cells are multi-potential cells mainly found in the bone marrow that can develop into a variety of cell types. Recently, researchers have been able to ‘reprogram’ adult cells to become induced pluripotent stem cells. The new **induced pluripotent stem (iPS) cell** technique mostly involves the use of certain types of skin cells called fibroblasts but could theoretically use any cell type. The first technique used to accomplish this was the transduction of the cells with four genes inserted into viral vectors (a virus from which a part of the DNA has been removed so it can be used to deliver other genes).

The four genes reprogram the cells to become stem cells with the potential to become any cell in the body. These cells, or their derivatives, are not suitable for use in humans, for example for transplantation into the brain, because they are associated with the production of tumors, though scientists have begun to develop safer ways to produce iPS cells through non-viral chemical manipulation. IPS cells are extremely important for research because they provide the first system for discovering and modifying the earliest affects of the HD mutation in a variety of human cell types in cell culture.

HORIZON Phase III Clinical Trial of Dimebon is Enrolling

Pfizer and Medivation announced the initiation of a new Phase III clinical trial of Dimebon. The HORIZON trial, which will be an international effort, is designed to evaluate the potential benefits of the drug on cognition in people symptomatic with Huntington’s Disease.

“Based on the promising results of our Phase 2 trial of dimebon in Huntington Disease, we are pleased to advance dimebon into late-stage clinical development,” said **Lynn Seely, M.D.**, chief medical officer for Medivation. “Huntington Disease is a fatal genetic disease for which no medications are currently approved by the FDA to treat the cognitive impairment associated with the condition.”

Dimebon, which was originally developed as an antihistamine, has also been identified as a potential treatment for Alzheimer’s Disease. A Phase III trial for Alzheimer’s patients is already underway.

Study organizers hope to enroll 350 individuals to take part in a six-month trial. It will be a double blind, placebo-controlled trial, in which patients will receive either 20mg of Dimebon three times a day, or the placebo. There will be 50 participating sites in North America, Europe and Australia.

The Mini Mental State Examination (MMSE), which measures cognition and the Clinician’s Interview-Based Impression of Change, plus caregiver input (CIBIC-plus), which measures global function will be used for the primary evaluation of success of the therapy. The trial will include only patients who have cognitive impairment, as determined by an investigator, based upon their assessment and the participant’s MMSE score.

Dr. Karl Kieburtz of HSG is the principal investigator and **Dr. Bernhard Landwehrmeyer** of EHDN is the co-PI.

“This trial is exciting because it’s an international effort,” said Dr Kieburtz. “This is the first time that we have had global collaboration on a clinical trial for Huntington’s Disease.”

For information on the sites where you can enroll in HORIZON, please visit <http://www.huntington-study-group.org/ClinicalResearch/ClinicalTrialsObservationalStudiesInProgress/HORIZON/tabid/108/Default.aspx> or call 800-487-7671.

This is the first time that we have had global collaboration on a clinical trial for Huntington’s Disease

Safety

in HD Clinical Trials

By John N. Caviness, M.D.

Why talk about safety in clinical HD trials?

Nothing could be more important than the successful execution of HD clinical trials. It is only through such trials that new treatments for HD will become reality. Molecular research in HD has produced more exciting possibilities than ever for new treatments. These treatments must be tested before they become available to the HD community. Clinical trials must be conducted with a “safety first” philosophy or they can not be done.

In any clinical HD treatment trial, there will be risk. However, it is extremely important that the HD community realize the extent to which clinical HD treatment trials are designed to be as safe as possible. Participation in HD studies should be encouraged. However, we all must be keenly aware of what is involved in a given HD study. Clinical trials are designed not only to evaluate treatment effectiveness but also to evaluate its safety. This goal is accomplished in a variety of ways.

Important Tools for Increasing Safety

Education and communication are the two most important tools used to promote safety in clinical trials. The key for both of these tools is being active, not passive.

Education Tips:

When a person is interested in a study, they should ask to read a copy of the **study consent form** before meeting with the clinical investigator or study coordinator. Study personnel are more than happy to do this. The consent form contains much information about the study, and by federal law, it has to use terms that non-scientists can

understand. It contains the purpose of the study, the treatment being studied, procedures, time commitment, potential benefits, and possible safety risks of the study. This is usually a tremendous amount of information to understand and think about. Rather than trying to digest this information in a few minutes at the first appointment with the study team, it is much better to have more time to think about various aspects of the study. It also allows time to use the information to consult and discuss with family members and others.

Everyone involved in a clinical HD treatment trial should do their own research. We have more resources than ever to educate ourselves. Other people in the HD community, support groups, associations, internet resources, and personal physicians and healthcare professionals can be used to gather information about the pros and cons of a research study. All treatments that are tested in human beings must have some preliminary evidence of both safety and effectiveness. The internet search engines are commonly used by everyone to research and look for information on a particular topic. Of course, the mere presence of information on a possible HD treatment on the internet does not mean that it is true. Rather, the information

gathered should be discussed with the study team at the initial study visit, or a subsequent time, if an individual decides to participate in the clinical trial.

The investigator should always be asked to summarize and highlight the study, its objectives, procedures, risks, and benefits to the potential research participant and their accompanying persons. This is an opportunity to get an idea of how the local site research team feels about the study. If the individual decides to participate, then at subsequent appointments the research team can be asked, “Is there any new information about the study?”

Communication Tips:

The study coordinator/investigator should be contacted whenever a safety concern arises. It is important that research participants know when and how to notify their local research study team. In a given study, there may be pre-planned times when the participant and research team exchange information. Certain types of instances that prompt communication are discussed below.

Any doctor that the research participant sees during the course of the study should be informed about the “study drug” and given the opportunity to contact the research team.





Monitoring Individuals for Safety

Study participants undergo a variety of procedures to monitor safety. The initial study visit, often called the “screening visit,” includes collecting information to determine whether it is safe for the study participant to be in the study. Such procedures might include asking questions, physical exam, EKG, blood tests, urine tests, pregnancy test, among others. If the results of these procedures are not within safety guidelines, subsequent participation in the study may not be safe. For all participants, similar procedures are carried out throughout the study to monitor safety. If an abnormality is found, the study drug may have to be discontinued as per the rules of the study.

Adverse events or experiences need to be reported to the local study team by the study participant, *whether or not related to the study drug*. Such adverse events include major changes in HD symptoms and signs. The study team should give guidelines for reporting such events, *but when in doubt, the participant should contact the study team to discuss how he/she is feeling*. There is a special type of adverse event known as a **serious adverse event**. Serious adverse events

include but are not limited to a life-threatening event, hospitalization, significant cause of disability, birth defect, and death. These events should be reported to the study team as soon as possible.

Monitoring the Overall Study for Safety

Multiple mechanisms exist to monitor safety of all study participants as a group. The sponsor, who funds the study, implements methods to evaluate safety during the study. If a group of academic investigators is organizing the study (e.g. the Huntington Study Group), then the group will also have ways to review safety during the study.

The institution or facility where the study is performed will have an institutional review board (IRB). The IRB oversees the local operation of the study on behalf of the institution or clinic where the study is performed. The study sponsor or investigator group may provide for an independent data safety monitoring board (DSMB). Results of the DSMB review are communicated to investigators, study sponsor, and the IRBs involved in the study.

Summary

Clinical trials are critically important to evaluating potential treatments for HD. Such studies are designed to provide evidence of treatment effect. However, studying safety of the proposed treatment is equally important. Safety during the study is closely monitored for the sake of protecting those who are so courageous as to be involved in HD research. They are owed nothing less. Multiple methods are used to monitor safety. In this way, studies can be made as safe as possible. By understanding safety issues in clinical HD treatment trials, there can be more confidence about entering an HD clinical treatment trial or knowing that a loved one’s safety will be a top priority in such a study.

By John N. Caviness, Professor of Neurology, Mayo Clinic College of Medicine

HDTrials.org

To register so you can be contacted about clinical trials and research studies being conducted in your area, go to HDTrials.org. Enter your email address, or if you don't want to use your personal email, follow the instructions to set up a separate email account strictly for HDTrials.org. When a researcher or clinical trial sponsor selects your area as a site, you'll be contacted with information about the study and who to contact. It is up to you to decide if the study or clinical trial is right for you. Visit HDTrials.org today. Consider being a part of the solution to the HD puzzle.



Research Roundup

Evaluation of Potential Treatments

Drugs and supplements continue to move through the HD research pipeline.

There are now four compounds in clinical trials: CoQ10, creatine, Dimebon, and ACR-16. CoQ10 and creatine are both antioxidants which also act to boost cellular energy.

Dimebon appears to strengthen mitochondria, the cell's energy factories, which are not managed properly in Huntington's Disease. ACR-16 is a new class of drug which stabilizes the neurotransmitter dopamine, raising levels that are too low and lowering levels which are too high.

In September, with support from the European HD Network (EHDN) and the Huntington Society of Canada (HSC), a double blind placebo controlled study of the efficacy of bupropion (Zyban) for the treatment of apathy in HD patients will begin. This drug is already approved by the FDA in the U.S. for a variety of other conditions. There is currently no known treatment for the symptom of apathy in Huntington's Disease.

A new potential treatment has been added to the pipeline. Phytopharm, a pharmaceutical firm located in the UK, has entered into an agreement with CHDI Foundation to evaluate the effectiveness of its orally active, neurotrophic factor inducer, Cogane, in an HD preclinical R6/2 mouse model. Cogane elevates levels of brain-derived neurotrophic factor (BDNF) which is reduced in the brains of HD patients. The results of R6/2 mouse model-testing will be completed and announced in the first half of 2010. Cogane is currently in Phase I trials for Parkinson's Disease in the UK.

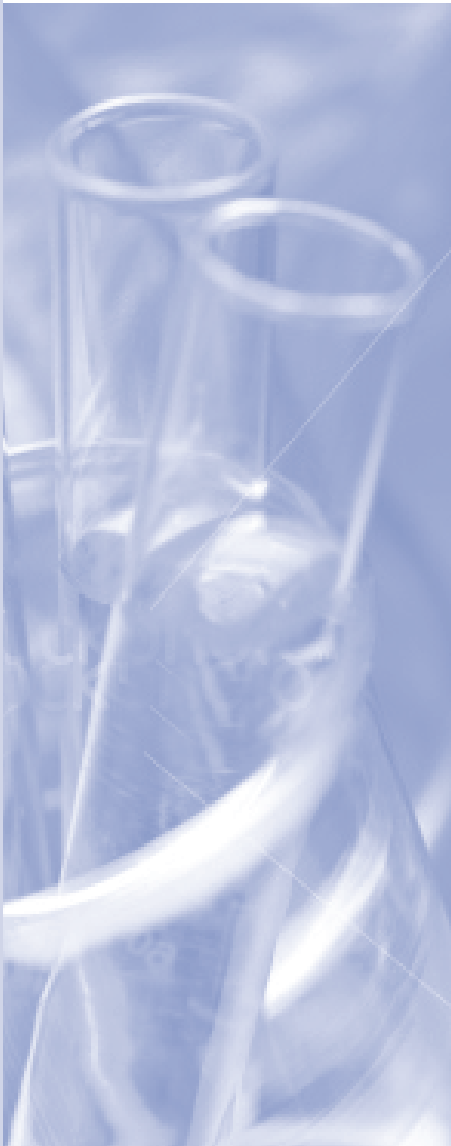
Exciting progress continues to be made in gene silencing. Many researchers believe that treatments aimed at decreasing the amount of the harmful mutant huntingtin protein by shutting down (silencing) the gene's expression, would ultimately be the most effective treatment, but there are a number of significant challenges to be overcome and this approach is in its infancy. One of these is delivery. Since short interfering RNA doesn't cross the blood brain barrier, the method of delivery in animal models has been

intrusive, requiring injections directly into the brain using stereotaxic surgery. This method would be too intrusive for treating human beings and the delivery would be too localized to be effective. **Dr. Beverly Davidson** and colleagues have attached siRNA to a peptide derived from the rabies virus glycoprotein which is known to cross the barrier into the brain. They were able to achieve a 50 percent knockdown of the target gene. Repeated administration did not induce inflammation nor did it create antiviral antibodies, suggesting that this procedure is likely to be safe when it is further developed. Another question that needs to be answered is how much huntingtin can be decreased without harming cells, which need it to function normally. Indeed, a third challenge is to ensure that the normal huntingtin protein continues to be produced while the HD protein is silenced. Work done by teams led by HDSA Coalition for the Cure researcher **Dr. Robert Friedlander** and by **Dr. Neal Aronin** has shown that it is possible to achieve allele specific silencing by developing short interfering RNA that distinguishes between the normal and the expanded HD gene based on a DNA sequence change found elsewhere on the mutated version of the gene in some HD individuals.

Preclinical research in HD experimental organism models suggests a variety of new treatment possibilities. New research by Coalition for the Cure scientist **Dr. M. Flint Beal** has shown that CoQ10 and creatine have additive effects in the HD model mice. Coalition researcher **Dr. Michael Hayden** has found that the Alzheimer's drug, memantine is neuroprotective in a mouse model of HD. Memantine is currently in clinical trials with

Preclinical research in HD experimental organism models suggests a variety of new treatment possibilities.

Continued on page 11





Ways to Give

HDSA is an organization that strives to make every dollar count. Your generosity has allowed us to develop programs that positively impact the lives of people with HD. With your continued support we will expand these programs to help to make a difference in the lives of people with HD.

Your donations help us fulfill the three parts of our mission to improve the lives of people with HD and their families:

■ **To find effective treatments and ultimately a cure for HD by funding:**

HDSA Coalition for the Cure investigators who focus on basic research to identify the bio-mechanisms that cause HD.

HDSA Grants and Fellows program that complements work being conducted by the HDSA Coalition for the Cure.

■ **To help people with HD and their families by funding:**

HDSA Centers of Excellence that provide people with HD and their families with quality medical care and social services as well as serving as focal points for clinical trials and genetic testing programs.

HDSA Chapters, Affiliates and Social Workers who work with HDSA Centers of Excellence to provide access and information about community-based services and support.

HDSA Support Groups that provide emotional support as well as serve as outlets for resources and referrals.

■ **To educate the public and healthcare professionals about HD by providing:**

Informational publications for people with HD and their families.

Professional publications for the healthcare community.

Regional and national conferences and conventions for HD families and medical professionals.

National website (www.hdsa.org) and helpline (800-345-HDSA) that provide information to the worldwide HD community.

There are many ways for you to make your contribution to HDSA.

Please visit www.hdsa.org and click on “To Make a Donation to HDSA click here!” This will take you to a secure page where you can make a direct donation to HDSA. Or, you can print out the form and mail it to: HDSA, 505 Eighth Avenue, Suite 902, New York, NY 10018, or fax it to 212 216-9004.

You may choose to establish a **Family Fund** to honor your family or remember a loved one. Join with friends and relatives, and pool your resources, to make your dollars work harder than you could individually.

Other options include the **HDSA Heritage Club**: create a planned giving opportunity; **HDSA Tribute Gift**: honor a friend or relative; or an **HDSA Memorial Gift**: honor the memory of a loved one. Your employer may be part of the **HDSA Matching Gifts Program**, which doubles your donation. If your employer is not listed on our website, we can enroll your company or organization. It's another way for you to help HDSA, now, and in the future.

In addition to these cash gifts you can help HDSA through a donation of:

Appreciated Stocks and/or Mutual Funds – earn a charitable tax deduction for the full fair market value of the gift while you lower your capital gains taxes.

Life Insurance – donating a life insurance policy will earn you an income tax deduction equal to the lesser of the cash value of the policy or total premiums paid.

Real Estate – a gift of a property that is fully paid off will allow you to remove that asset from your taxable estate. You can then deduct the fair market value of your gift while avoiding all capital gains taxes on the property. Transfer the deed of your home or farm to HDSA now and retain the right to use the property for your lifetime and that of your spouse.

For more information on donating any of these financial instruments, please contact the HDSA National Office, 800 345-HDSA (4372).

Visit our website regularly and browse the **HDSA Marketplace**. Purchasing our Care2Cure Bracelets, Awareness Necklaces, holiday cards, amaryllis plants and other items makes a difference – and helps us build awareness at the same time.

**Now more than ever, we need your gift.
Please make your donation today.**

Gordon Conference

Unites Researchers Working on HD and Related Disorders

With support from HDSA, the fourth Gordon Research Conference on “CAG Triplet Repeat Disorders” was held from May 31 to June 5 at Waterville Valley, New Hampshire. Gordon Research Conferences (GRCs) are recognized as high quality scientific conferences.

The structure of the Gordon Research Conference is unique. Each day, there are scientific sessions in the morning and again after dinner. After lunch, scientists are expected to spend the time in a casual unstructured setting – playing soccer, golfing, or perhaps participating in a mountain hike. In this fashion, world-renown scientists might be on the same Ultimate Frisbee team as a beginning graduate student. Prior to dinner, spirited poster sessions provide scientists with an opportunity to present their latest data. This time-tested formula has proven to be wildly successful, and over 370 GRCs are held on a wide range of topics, including Atomic Physics, Chemical Oceanography, Vascular Cell Biology, and Molecular Approaches for Tropical Diseases.

The first “CAG Triplet Repeat Disorders” GRC took place at Mount Holyoke College in 2001. Subsequent “CAG Triplet Repeat Disorders” conferences have been held at Il

Ciocco, Italy (2003), Mount Holyoke College (2005), and Aussois, France (2007). This particular GRC has a tradition of alternating between a European and a US site, reflecting the worldwide distribution of scientists researching these disorders. The molecular defect leading to HD is an expansion of a cytosine-adenine-

guanine (CAG) triplet repeat in the gene that encodes the protein huntingtin. There are several other neurological disorders including several of the spinocerebellar ataxia (SCA) disorders, Kennedy’s disease (also known as spinobulbarmuscular atrophy, SBMA), and dentatorubropallidoluysian atrophy (DRPLA) that share the same molecular defect. Therefore HD researchers pay attention to research advances in these other related disorders.

HDSA was well represented at this year’s “CAG Triplet Repeat Disorders” GRC. **Jang-Ho Cha, MD PhD**, from Massachusetts General Hospital, an HDSA Coalition for the Cure Investigator and Chair of the HDSA Center Programs and Education

Advisory Committee, chaired the conference. **Laura Ranum, PhD** from the University of Minnesota, served as Vice-Chair while **Harry Orr, PhD** from the University of Minnesota and Chair of the HDSA Coalition for the Cure Review Committee, was the Conference keynote speaker, discussing his groundbreaking research in spinocerebellar ataxia type 1 (SCA1). Coalition for the Cure members **Marian DiFiglia, PhD** and **Gillian Bates, PhD** were two of just 20 speakers, while Coalition members **Leslie Thompson, PhD, Chris Ross, MD, PhD**, and **Gill Bates** served on the Program Committee, and **Jim Gusella, PhD** was one of the Structured Discussion leaders.

This particular GRC has quickly come to be regarded as one of the premier meetings addressing research advances in Huntington’s Disease. Over 130 persons attended. The Gordon Research Conference has a strict ‘off the record’ policy which does not allow anyone to report the content of the presentations; this strict policy

serves to allow the free exchange of the most up-to-date scientific advances, and contributes greatly to the quality of the scientific exchange.

Support for this conference was provided by HDSA, the National Institutes of Health, CHDI,

Hereditary Disease Foundation, National Ataxia Foundation, the Kennedy Disease Association, and Lundbeck Pharmaceuticals. Funding was used to support the registration and travel of speakers, as well as allowing junior researchers (graduate students and postdoctoral fellows) to attend at no cost.



This particular GRC has quickly come to be regarded as one of the premier meetings addressing research advances in Huntington’s Disease.

An exciting addition to this year's Gordon Research Conference was the Gordon-Kenan Graduate Research Seminar (GRS), a two day pre-meeting specifically for graduate students and postdoctoral fellows, chaired by Mary Heng, PhD, of the University of Michigan. The aim of this event was to provide a forum for young scientists to discuss and present their innovative, unpublished findings in a supportive environment, to spur stimulating discussions led by recognized leaders in

triplet repeat disorders, and to foster the growth of new ideas and form new interdisciplinary collaborations for future research. Jang-Ho Cha presented a lecture on "How to Give a Good Talk," and Margaret Sutherland from the National Institutes of Neurological Disorders and Stroke, a part of NIH, gave a talk on getting grants.

Participants from all over the world rated the GRC a great success. After spending a week discussing the latest exciting ideas in HD and related

disorders research, scientists left Waterville Valley revitalized and enthusiastic to tackle new experiments. In addition, a new generation of young scientists was ushered into the exciting world of CAG Triplet Repeat research. The assembled participants unanimously voted to submit an application to hold another GRC in 2011, and we look forward to seeing what new advances will be reported then.

— By Jang-Ho Cha, M.D., Ph.D.

Research Round up (cont'd from page 8)

HD patients to see if it improves symptoms. **Dr. Gary Lynch** and colleagues found that a drug called an ampakine up-regulated BDNF improved memory deficits in the HD knock-in mouse model. Brain derived neurotrophic factor (BDNF) is down-regulated in the brains of HD patients and in mouse models of the disease. BDNF protects neurons and facilitates the growth of new ones. It also plays an important role in long term memory. BDNF signaling is part of a system of synaptic changes that encode long term memories. It promotes theta burst stimulation which in turn induces actin polymerization which stabilizes long term potentiation. Long term potentiation involves a change in the electrical properties of neurons and is a necessary component of memory.

Researchers at the University of Illinois at Chicago College of Medicine have suggested a way in which axonal transport is impaired in neurons in HD experimental models. Using mouse, squid, and cell models of HD, **Dr. Scott Brady** and **Dr. Gerardo Morfini** and colleagues found that the HD protein activates an enzyme called JNK (for cJun N-terminal kinase) which causes the impairment. Finding a way to inhibit JNK activation would be a promising therapeutic strategy.

Researchers at the University of Southern California led by **Dr. Kelvin Davies** discovered that the RCAN1-11 protein is reduced by 70 percent in the brains of HD patients after death as compared to controls who died of other causes. The dysregulation of gene transcription is a known pathology in Huntington's Disease and the expression of many genes is affected, but Dr. Davies and colleagues suggest that more

Many researchers believe that treatments aimed at decreasing the amount of the harmful mutant huntingtin protein by shutting down (silencing) the gene's expression, would ultimately be the most effective treatment but there are a number of significant challenges to be overcome and this approach is in its infancy.

research into whether restoring the expression of this particular protein would be therapeutic is warranted.

Researchers at Johns Hopkins led by **Dr. Solomon Snyder** have discovered that a protein called rhes binds to the HD protein and causes toxicity. Rhes is a protein found mostly in the striatum where brain damage is most extensive in Huntington's Disease. Working with mouse striatal cell lines, the team found that survival time was the same for wild type (normal) or HD (knock in) cells as long as rhes was absent. When rhes was overexpressed, survival time decreased by 60 percent in the HD cell, but not in the normal one. Though this is a mild difference, the authors suggest, from these experimental model studies, that locking the binding of rhes and the HD protein could be a therapeutic target.

Visit the research section of the HDSA website for the latest research news: www.hdsa.org/research/news

—Marsha L. Miller, Ph.D.

To obtain the latest information on clinical trials go to the HDSA website using the link:

www.hdsa.org/research/clinical-trials/ongoing-clinical-trials.html.

Another good way to keep abreast of upcoming trials is to sign up for confidential email notices at www.hdtrials.org

The HDSA Research Forum *(cont'd from page 1)*

researchers, HDSA continues to influence every aspect of the HD research cycle and each of the dozens of new treatment pipelines that are being pursued.

Following these general remarks, I had the pleasure of introducing the audience to three outstanding HD investigators, each of whom delivered an excellent talk that addressed a specific topic from the HD research cycle.

Dr. Jane Paulsen (University of Iowa) 'wowed' us with her remarks on Observational Research: **What Happens and When in HD**. Jane told us about the PREDICT-HD study, which employs a variety of measurements to document the pattern

and timing of neurobiological and neurobehavioral changes in people who have not yet been diagnosed with HD but who carry the HD gene mutation. Summarizing the data in a series of lively graphs, Jane showed us how signs of the HD disease process can be measured several decades before the more overt clinical symptoms of HD become manifest. Jane then told us why this new, more precise description of HD is important – the knowledge that HD is a life-long disease process, together with the tools to measure specific subtle changes (for example brain imaging and cognitive and motor tests), both point to key features of the disease process in the brain and now open up new avenues to the design of clinical trials to test potential HD treatments earlier in the disease process.

Dr. Joseph Giuliano (CHDI Foundation, Inc.) continued this theme with a beautifully illustrated and comprehensive update on **Clinical Research: Testing Potential Treatments**. Joe



Jane Paulsen, Ph.D.,
University of Iowa

emphasized the growing need for increased participation in clinical trials, as more than two thousand HD patients are already engaged in eight ongoing trials that in some cases continue beyond the year 2011. The ongoing trials are HART (ACR16), Pre-CREST and CREST-E (creatine), 2CARE and PREQUEL (Co-enzyme Q10), HORIZON

(Dimebon), CIT-HD (citalopram), and Memantine. Joe urged the community to seriously consider efforts to seek to improve the regulatory aspects of trials, which can cause delays in enrollment, as well as efforts to improve (and make more efficient) the access of HD patients to registry studies (for example COHORT) and clinical trials, with an emphasis on education and

outreach for HD patients and families. Current trials evaluate drugs that have been around for awhile, so

Joe summarized the current 'pipeline' to identify molecules from new HD treatment areas emerging from 42 different projects; Energy homeostasis, Histone deacetylases, Huntingtin processing, Modulation of huntingtin levels, Inflammation, Neurotransmission, Phosphodiesterases, Protein Folding, Transcriptional

dyregulation and Trophic factors. Joe then spotlighted four 'target' areas that are the furthest along the new treatment pipeline – histone deacetylase 4 modulators, phosphodiesterase 4 modulators, antisense oligonucleotides to modulate huntingtin levels and the concerted efforts to find biomarkers for energy defects in HD. Joe's presentation ended with an apt

quote from the author Anne Lamont 'You wait and watch and work: you don't give up'.

Following the break, the audience was treated to a stellar presentation by Dr. Leslie Thompson (University of California Irvine) who shared her expertise in **Stem Cell Research and Its Implications for HD**.

Leslie showed images of human stem cells and induced pluripotent stem cells growing in a dish. Leslie illustrated how these cells are being made from HD individuals and how, once in hand, they can be induced to differentiate into different and distinct end-stage cells, such as brain cells, or muscle cell, in a petri dish.

The consequences of the HD mutation have been studied traditionally in a laboratory organism (such as a mouse). Leslie showed us how, with the advent of human HD stem cells for HD research (not treatment), researchers can, for the first time, study the consequences of the HD mutation in different human cell types in great detail. Leslie,

along with other HDSA researchers, is at the forefront of this cutting edge methodology. As Leslie said, this research promises, for the first time, to reveal new details of the earliest response of human brain cells to the HD mutation, while offering an unprecedented opportunity to identify modulators of these early responses in living human brain cells in the culture

dish. Exciting stuff indeed.

The major goal of the Research Forum is to inform the HDSA community of the fruits of its research program. I hope that the audience at the National Convention left the Forum with a sense of progress and excitement, as we strive together toward a deeper understanding of the HD disease process and new effective HD treatments.



Charles Sabine,
NBC News Correspondent