

# Northwest HD Chapter Symposium

## Update and Research News

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July 2003

First Edition

### Research News

Those of you who returned our recent questionnaire stated that there was great need and desire for more information about research and potential drug treatments. This is a first effort in that direction. I need your input back to me if this is helpful (or not).

The first three articles will summarize the lectures presented at the "Seattle Drug Development Symposium" hosted at the Fred Hutchinson Cancer Center in May 2003.

The two articles following gives some background information about different stages of Huntington's research, and how it moves into drug development and finally into clinical trials.

In knowledge is power. Power to win the battle against Huntington's. Read on.

### MRI Imaging in HD

Dr. Elizabeth Aylward Prof. of Radiology UW Medical School  
*summarized by LaVonne Veatch Goodman*

Dr. Elizabeth Aylward from the University of Washington Medical School spoke to us about "MRI Imaging in Huntington's Disease." Dr. Aylward has been a researcher in HD imaging for many years and is a member of the Huntington's Study Group, a collaborative group of many researchers across the country. The Northwest Huntington's community is fortunate to have her here.

She has been and remains actively involved in the study of how MRI brain scans can be useful in tracking brain changes over time in individuals with HD. She studies MRI brain scans on both presymptomatic HD gene carriers and those already symptomatic with the disease. She and her collaborators have shown fairly predictable decrease in volumes of specific brain areas in both of these patient populations.

These studies are critically important because if a pattern can be well defined, this technology can be used to study drug effects more quickly than our standard clinical trials. It will also give the optimal time to start drugs in those still asymptomatic or before disease symptoms.

MRI brain scans give good pictures of the basal ganglia structures called the caudate and putamen. These structures taken together are called the striatum. The striatum is the part of brain most damaged by Huntington's. Dr. Aylward and others have shown that over time these structures get smaller and lose volume.

Dr. Aylward has shown that in the person already with Huntington's symptoms that there is a 5.5%/year decrease in caudate volume, and 3.5%/year decrease in putamen. Statisticians estimate that if a drug is 50% effective in reducing this atrophy, in the range of 60 people would need to be studied over a 2 year period to be able to tell if the drug worked. Less effective drugs would need more people and/or longer study times.

Dr. Aylward has further shown that in the person who has the Huntington's gene, but has not developed symptoms yet, there is a decrease in caudate volume by about 2.5%/year, putamen by 4.5%/year. The researchers begin detecting this effect about 12 years before symptom development.

In another study (preliminary data, as yet unpublished), Dr. Aylward has been able to find the approximate volume of basal ganglia that is present as a person passes into symptom development. Or stating it another way, basal ganglia volume measurements by MRI could be used to predict approximate time of onset of the disorder (within a 2 year time frame). These results are based on small numbers of patients, and she stated it was too early to generalize these results to the entire HD population.

She told us about the ongoing PREDICT study, which is taking place at 21 centers across the United States, that hopes to enroll 500 known gene-positive subjects. These volunteers will undergo MRI and clinical testing and will be followed over a 4 year time period. MRI brain scans and symptoms at clinical onset will be studied. The initial encounter takes a whole day, (which is reimbursed) the subsequent encounters only 1-2 hours.

She also told us about PHAROS, which is a study that does clinical testing of individuals at risk for Huntington's, both gene positive and negative. There is no MRI scanning in PHAROS. This study is being performed to assess the earliest signs

and symptoms that occur in a large number of Huntington's subjects.

She ended her talk with the plea that more people are needed for these studies.

## **Moving New Experimental Therapeutics for HD — From Bench to Bedside**

Blair R. Leavitt M.D., C.M.  
*summarized by LaVonne Veatch Goodman*

Dr. Blair Leavitt from Vancouver, British Columbia, gave a talk entitled "Moving New Experimental Therapeutics for Huntington's Disease — From Bench to Bedside." Dr. Leavitt is a neurologist and a scientist at the Centre for Molecular Medicine and Therapeutics at the University of British Columbia, and is the Director of the Canadian Genetic Disease Network Transgenic Core Facility.

He explained that to have effective testing of treatments for Huntington's, it is necessary to have:

- (1) appropriate animal models of HD, that are as true as possible to the disease in humans
- (2) methods of getting treatments into brain whether this is small molecule drug, gene therapy, or stem cell therapy
- (3) reliable and repeatable outcome measures to see if a treatment is working.

Dr. Leavitt works with Huntington's disease (HD) mouse models that have the entire human HD gene expressed appropriately in the laboratory mouse. This mouse model was developed in the laboratory of Dr. Michael Hayden (where Dr. Leavitt did his fellowship), and this group has been able to make various model mice that have the human HD gene with 18, 46, 72, or 128 CAG repeats. The gene is contained in a yeast artificial chromosome (or YAC) that

allows it to be grown in cultured yeast cells (the same yeast that is used in bread). This YAC containing the HD gene is then injected into the fertilized embryo of a mouse. These genetically engineered mice are "transgenic" for the human HD gene and those mice with the expanded CAG genes will eventually develop neurological symptoms, similar to that which occurs in people with Huntington's disease. Those mice with more repeats develop these neurological changes earlier, just as happens in people.

Dr. Leavitt does most of his experiments on a transgenic mouse model in trials that last until the mouse is 12 months old, but these mice begin to develop well recognized and reproducible symptoms as early as 3 months. The change in motor coordination ability is tested in automated fashion by timing how long the mouse can walk on a rotating rod before falling. Other behavior changes are measured, as well as the amount of brain damage, as measured by measuring the size of specific brain regions affected in HD or by counting the numbers of brain cells lost in these regions. The mice also develop neuronal inclusions (aggregates), but this occurs very late in the course of the illness. All of these test measurements are done by automated machinery whenever possible, to increase the speed at which these trials can be performed.

In this fashion, a mouse trial of a specific new drug can be completed in about 6 months. With the present capacity of Dr. Leavitt's lab, there can be about six to eight separate studies (with six different drugs) going on at the same time in this very efficient "mouse factory."

Dr. Leavitt's lab can put the study drugs into food or water, or they can be injected it into the mouse's bloodstream, or directly into the brain. He described the specialized

"mouse microsurgical suite" where mice are anesthetized, then given treatments directly into specific brain regions using tiny needles. This is a technique that can be used to administer gene therapy treatments.

Dr. Leavitt's lab has been up and running about a year. They have been working with Dr. Hayden's Group and a drug company to look at the effects of drugs called "caspase inhibitors." This work is currently ongoing. They (like several other labs) have shown that exercise may be beneficial in slowing disease progression, and have data to suggest that it can prevent brain changes in the YAC mouse model.

They have EPA (fish oil) studies in process, and many others not directly identified. They are also planning studies using a variety of techniques for delivering therapeutic brain growth factors.

### **Dr. Leavitt then reviewed some of the ongoing human clinical trials in HD.**

Trials which are currently underway (or about to start) in HD include Riluzole, minocycline, tetrabenazine, the observational trials PREDICT-HD and PHAROS, and Ethyl-EPA. While he did not present the results from the first phase of the Ethyl-EPA (LAX-101) trial as a part of his talk, he was asked to comment on the previously reported results of this trial by a member of the audience.

While the results of this trial were somewhat complicated by the small number of people in the trial and because a large number of people were eliminated from some of the analyses because they did not follow the treatment protocol or they dropped out of the trial early, those people that completed the trial appeared to have some benefit. Another larger human clinical trial is

planned to better determine whether this agent is beneficial. He suggested caution for people with HD using EPA outside of research trials (such as various forms of fish oils from health food stores or off the internet), because it is not presently a regulated pharmaceutical and may not be pure or may have harmful contaminants such as mercury or other heavy metals.

## Exploring Chemical Space for an HD Cure

James Olson M.D., PhD.  
*summarized by LaVonne Veatch Goodman*

Dr. James Olson from the Fred Hutchinson Cancer Center, and Children's Hospital, Seattle gave a talk entitled "Exploring Chemical Space for an HD Cure." This occurred as part of the May 24 2003 "Symposium on Drug Development in Huntington's Disease" hosted by the Northwest Chapter of HDSA with hosting site the Fred Hutchinson Cancer Research Center.

Dr. Olson is a pediatric oncologist, who takes care of children with brain tumors. He told us how the treatment of children with malignant cancer over the last 30 years has gone from less than 10% survival to just over 75% survival. This happened because of incremental improvements with drugs each having small benefits of 5 and 10%, with improvements building on past small benefits. He told how 90% of children with brain tumors are enrolled in clinical drug trials. This is a cooperative effort with researchers, physicians, and patients, and patient families that together have brought this success story.

Using childhood cancer response as comparison, he pointed out that we may need to design our HD clinical trials to have sufficient power to

detect relatively small improvements. This may require more patients enrolled in studies and improved measures for whether a drug is working. He encouraged greater participation from the patient population as drug trials begin in earnest. He believes that with this same cooperative effort between researchers, physicians, patients, and patient families, success will come to Huntington's treatment as well.

Dr. Olson's laboratory now focuses on developing new therapies for Huntington's disease and pediatric brain tumors. His presentation focused on how he and collaborators used information from a powerful technology called microarrays to guide pre-clinical drug testing for HD. He then discussed how these efforts are evolving into a more advanced drug discovery program for HD.

### Microarray Studies

Microarray technology allows for testing of thousands of genes at a time against a sample to be tested. Using this instrument, and computer-assisted result recording, the researcher can find out what genes are being affected in various disease states at various times. Using this method, Dr. Olson and collaborators were able to identify a gene group that was one of the earliest changes that happens in Huntington's disease at the molecular level. This technique, along with work done in several other labs, revealed that compounds called HDAC inhibitors and drugs that reduce inflammation in the brain might be of value for HD.

Dr. Olson's laboratory has shown that these gene changes happen not just in brain, but in other cells including muscle and probably skin cells. This may make testing of drug results in people much easier because improvement in muscle is easier to detect than improvement in brain.

Dr. Olson commented on the long history of extraordinary cooperation between research groups in the Huntington's community. He complimented HDSA (Huntington's Disease Society of America) and HDF (Hereditary Disease Foundation) and HSG (Huntington's Study Group). He was instrumental in creating the Hereditary Disease Array Group to follow in the example of research data sharing. In fact, the data is openly available to all researchers through a public data site.

Dr. Olson's group continues to study HDAC inhibitor drugs cooperating with sites that study the same drugs in other test systems. These include yeast cells, nerve cell cultures, flies, and worm models of HD. Dr. Olson's group also does many mouse studies using several different mouse models. There is capacity in his center for studying over 400 mice at a time.

### FK 506

Dr. Olson's microarray studies also suggested that immune system responses were affected in early Huntington's gene changes. This led to his testing FK506. This is an experimental drug that is an immune regulator used in transplant therapy. It works by preventing the immune response that would reject the transplant, (bone marrow or kidney), etc. Dr. Olson showed that this drug is also beneficial in the HD mouse model by significantly delaying onset of neurological symptoms in the mouse. There is also evidence that this drug is neuroprotective (data not presented). Dr. Olson and colleagues are working with a drug company to test related drugs in Huntington's mouse models.

### Protoporphyrin IX

This is an agent which has been shown to work well at preventing aggregates in cellular assays, in the

worm model, but unfortunately (at least so far) not in the mouse. This drug, like the HDAC inhibitors, is being studied for cancer therapy as well. Dr. Olson is collaborating with another company locally to advance and study this compound for HD use as well.

### **Future Plans**

A collaborative group has proposed a drug-discovery/research project which will proceed over 5 years with a start date (if it is given the go-ahead by NIH) of December 2003. This will be a comprehensive project for Huntington's disease Drug Discovery that incorporates resources similar to those found in large pharmaceutical companies!

This project will include the screening of over 350,000 compounds in various screening assays in eleven research labs world-wide. Collaborations are planned with two companies that have extensive experience with drug discovery and development. These companies will bring large libraries of real and virtual chemicals to be studied. Medicinal chemists will modify and improve on agents that are promising. Selected treatment candidates will then be put through vigorous retesting in several model systems in 5 different research laboratories before proceeding to the mouse. After promising mouse studies, drugs would then go into clinical or human trials.

The Fred Hutchinson Center, where Dr. Olson works, is now focusing a major effort on improving clinical human trials. They are supporting superb statistics scientists to help design the kind of trials that would work best in diseases like cancer or Huntington's disease.

Dr. Olson ended his remarks by stressing the need for patient and family participation in clinical trials to make for the earliest success possible.

## **Background Information for Clinical Research in HD**

Extensive laboratory research and "preclinical" work must occur before testing of a drug or treatment for people with Huntington's disease. For Huntington's, this research included (1) the discovery of the gene in 1993, followed by the (2) development of single cell models of Huntington's disease which involved the placement of the Huntington gene into single cell systems like yeast (the same yeast that is used in bread making), all the way to specialized nerve cells. Scientists also put the gene into whole organism models including the fly, the worm, and the mouse. The mouse model (there are about 20 different ones) is the closest to the disease in humans.

Scientists use these various model systems to study disease mechanism, or how the mutant (or bad) huntingtin protein damages the cell. Through extensive study, they have shown that this mutant protein affects the cell at not one, but several different points in the biologic systems of the cell. They then try to find a treatment that would fit the biologic system they have identified: or in the science lingo, they target a drug to an active site. This type of testing is called "preclinical," the term used for all the work that goes into getting a drug or treatment from the research stage to testing in people.

Our scientists now have designed testing that uses yeast cells, nerve cells, flies, etc. that can screen hundreds of potential drugs for activity in slowing down or preventing the Huntington's disease process at one or more sites. When a drug candidate is found in these screens, chemists try to make it into a medicine that will have a better chance of working in people. For instance, for a

drug to work in Huntington's, chemists must make sure it can be gotten from the blood stream into brain cells.

The final step before testing a drug in people is to test it in mouse models of Huntington's. It is very important that any drugs that look like they work in mice be "confirmed." This means repeating the mouse study to make sure the experiment really worked.

### **What Does FDA Approved Mean and Why Is This Important?**

It is important to recognize the difference between testing drugs for use in Huntington's disease that are already FDA approved and those that are still "experimental" or have not been FDA approved. FDA approved means that extensive testing has already been done, and that the Federal Drug Administration has given approval for its use. FDA approved means that a medical doctor can write a prescription for it now. This means that an already FDA approved drug could be used in people FIVE TO TEN YEARS EARLIER than a drug that is still experimental.

Even though a drug may already be FDA approved, it is still very important to test it for use in Huntington's people. This is because we don't know that what works in a mouse with the HD gene will work in a person. Even if it does work, without human testing we won't know the best dose of drug to use, and insurance companies are not obligated to pay for it.

An experimental drug is a drug that has never been tested in people before, and therefore must go through a more intensive and time consuming process for federal approval. This process takes on the average another 5-10 years.

## How Are Drugs Tested in People? What Are Clinical Trials?

Clinical trials are the process for testing drugs in people. This process can be divided into three phases.

**PHASE ONE:** Phase one studies test for safety. Already FDA approved drugs have gone through much if not all of this phase already and can often be combined with phase two. This saves a lot of time. For an experimental or non FDA approved drug this usually takes 20-100 healthy volunteers to make sure the drug causes no bad side effects. This phase studies how the drug affects different parts of the body. It also finds out what side effects occur if the dosage is increased. This phase is usually measured in months of time.

**PHASE TWO:** Phase two tests for best dosage. It can also give preliminary efficacy results and give early (but not conclusive) information about whether a drug will work. This phase of testing needs more people, in the range of several hundred people who have the disease. This phase is measured in months of time, and for a slow disease like Huntington's, it may take years of time to be sure of best dosage.

**PHASE THREE:** After a phase 2 studies suggest effectiveness in a small number of people, and best dosage is recommended, it goes to larger scale testing. Phase 3 tests include several hundred to several thousand patients. In this phase, longer and more thorough testing of the drug's effectiveness is done. The full range of benefits or adverse side effects is studied. This is by far the most expensive phase.

After a successful phase three study: (1) if the drug is already FDA approved, the drug can be prescribed by any doctor. (2) If the drug is still experimental, a request for FDA review and approval must be accomplished before that drug can be

prescribed. This adds another 5-10 years before a doctor can prescribe it.

### Clinical Trial Types

The most common type of drug trial is the "double blind placebo controlled" one. This involves both the participant (you) and the investigator (the doctor) not knowing whether you as participant in the trial receive active drug or inactive (placebo control) pill. In the real trial, the pills will look alike. Results from people taking active drug will be compared to those who took inactive "placebo" pills.

This type of study usually gives the best scientific results, but requires large numbers (hundreds to thousands) of people. This kind of study works well in "common diseases" with large populations like diabetes or heart disease. It works less well in diseases that do not have large numbers of people (like Huntington's). By its design, it also requires that some fraction of people participating in the trial get no active drug treatment. The clinical study of Coenzyme Q in people used this design, but didn't have enough people enrolled to know for sure whether it worked or not. Results can take years of time in a slow disease like HD.

### Small Clinical Trial Design

Scientists sometimes need to use other types of clinical trial design for studies in diseases that do not have large numbers of patients. One such model is commonly used in cancer studies (particularly the more rare kinds). In this type of clinical trial, each person is given a drug or drug combination. In one type of study, it would be similar to how a doctor uses drugs to treat a person with high blood pressure. In each patient with hypertension, the drug or drugs finally settled on for best treatment occur only after trying one or more

till the best drug or combination of drugs are found. The best combination for an individual patient isn't known at the beginning.

Of course, drug response measurement in hypertension is accomplished in weeks of time. In Huntington's drug response measurement is much more difficult and will take months, perhaps even years of time. But the process would be similar.

This type of study would likely not get results any faster than the placebo controlled ones. However, the advantage of this type of study would be that each person participating would receive active study drug or drugs. If any of these drugs are successful, then the patient has the advantage of being treated during the trial. This type of study would also allow the early introduction of a new drug to be tested as they became available. In addition, multiple drugs could be tested at the same time.

## Clinical Trials in the Northwest for HD

There is news of clinical drug trials in the Northwest! First, Dr. Penny Hogarth from OHSU is reported to be in final stages of her Huntington's study on Kava Kava.

Also very exciting is another study soon to begin in Oregon. Dr. Hogarth will be starting a clinical trial to test another drug that is already FDA approved for another disease. This study will primarily get information on the best dose of the drug to use in Huntington's people. This dosing information is very important. And if this drug works, people will be treated at the same time!

This drug is already FDA approved for use in another rare disease. Scientists believe it might be helpful in Huntington's. This drug belongs to a class of drugs that interfere with inflammation. There is

evidence that this drug is also helpful in the mouse model. And, because it is already FDA approved, if successful in the study, it would be immediately available to all people with Huntington's!

***Heartfelt Thanks to Dr. Hogarth from the Huntington's Community in the Northwest***

We also have the good news that our Northwest researchers are in the early planning stages of human drug trials for those drugs already FDA approved that have shown benefit in mice. The first step is to do the statistical work that predicts how many people would need to be studied to determine if these drugs are beneficial. We are calling this the "Treatment Now Initiative." An anonymous donor has given \$100,000 to jump-start this effort.

Like Dr. Hogarth's study on the anti-inflammatory drug mentioned above, all people participating would get an active test drug. While this type of study is experimental, if any of the candidate drugs work, people will also be treated at the same time. That is why we are calling it the "Treatment Now Initiative." Like Dr. Hogarth's study, finding the "right" dose is essential, and will be a vital part of this study.

***Heartfelt Thanks to Northwest Doctors and Researchers***

**We Need People to Be Ready for Clinical Trials**

The good news is that we have several already FDA approved drugs that are at the stage for clinical trials. Now that research has brought us potential drugs, WE NEED THE PEOPLE. A Seattle-based Huntington's researcher, Dr. Jim Olson, is a medical doctor for children with brain cancer. He has told us that over 90% of children with brain cancer nationwide are in

clinical trials so they can learn if experimental medicines work. That is how all these children get drugs, and then get better drugs efficiently.

The Huntington's patient community needs to have 90% participation too. If we don't come forward to be counted in clinical trials, we'll never know whether these drugs work. Researchers can't do this step for us.

Of course it is easier to get brain cancer children enrolled in studies, because almost all of these children get medical care at academic research centers where drugs and clinical trials are offered. It is vastly different in Huntington's. Most of the patient community is not known to the researcher, and vice versa.

**We Need Your Help Now**

A very important and time consuming part of clinical trials in Huntington's is finding enough patients. Our disease is rare, so we need almost everyone to be successful. We can start this part right now.

We need to identify each and every family affected by Huntington's. And, we need as many as possible of those identified to volunteer for studies.

**How to Help**

You can help immensely by identifying yourself or a family member. In this way, you can be contacted about the upcoming studies and receive information about them. If you know of a Northwest family that is not on our mailing list, please help convince them to join this effort. We need everyone to step forward.

Support groups need to get the message out to every member. Help do your part and return this contact information to our local chapter.

Return this card to: **Huntington's Disease Society of America  
Northwest Chapter  
PO Box 33345  
Seattle, WA 98133**

Name: \_\_\_\_\_

Address: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Contact telephone: \_\_\_\_\_