February 2008 #1

HD NEWS euro-hdnews.info

THE NEWSLETTER OF THE EUROPEAN HUNTINGTON'S DISEASE NETWORK · PDF VERSION

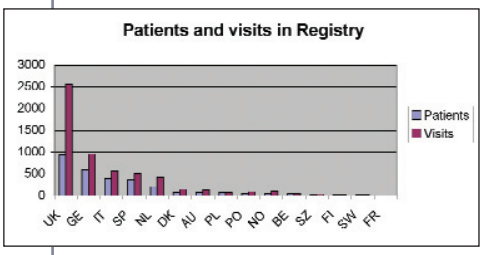
2008 welcomes the EuroHDNewsletter

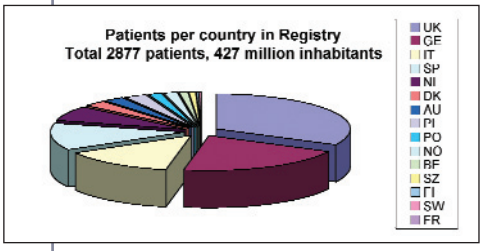
The European Huntington's Disease Network (EHDN) will publish the EuroHD-Newsletter aimed at communicating the activities of the Network, progress in HD research and development of treatments for HD to affected families, the general public, health care professionals and the scientific community. The Newsletter will be quarterly and the first issue will appear on the EHDN Website (http://www.euro-hd.net/html/network/news) in February 2008.

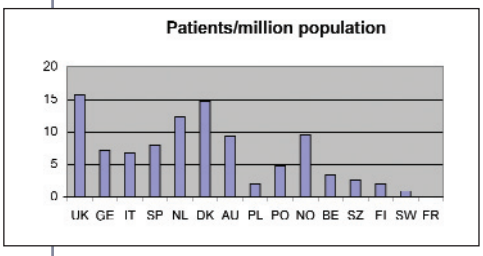
The Newsletter was borne out of discussions amongst members of the Executive Committee and was finally approved in Madrid in November 2007. The appointment of Dr. Diana Raffelsbauer, a freelance medical journalist (PharmaWrite, Germany), has been a pivotal event in launching the EHDN newsletter.

We hope that EHDN members find the Newsletter a useful vehicle for communication and dissemination of ideas to help improve the course of HD and hopefully find its cure.

The status of "REGISTRY"







"Registry" is the core study of the EHDN. It comprises a collection of clinical data and biosamples aimed to improve HD research and to provide valuable resources to find the cure or at least to develop treatments which substantially modify the course of the disease.

In 2007 "Registry" has continued to grow. To date, there are approximately 3000 patients enrolled from across Europe, with clinical data obtained from over 6000 visits. In addition, biosamples have been obtained from a significant proportion of these patients. Registry now represents one of the most successful and valuable resources that can be used to facilitate and speed up HD research on a global scale.

Studies of different clinical phenotypes, modifying genetic and environmental risk factors, biomarkers related to the course of HD, and many other aspects of the disease can be investigated in a way that was not previously possible.

All of the EHDN member countries are actively contributing to the Registry project, but there has been a particularly outstanding contribution from the following countries: the United Kingdom, Denmark, The Netherlands, Austria and Norway. We hope that in the futue all countries will continue their effort towards achieving our goal to enrol 10,000 patients into Registry by 2010.

AU: Austria, BE: Belgium, DK: Denmark, FI: Finland, FR: France, GE: Germany, IT: Italy, NL: The Netherlands, NO: Norway, PL: Poland, PO: Portugal, SP: Spain, SW: Sweden, SZ: Switzerland, UK: United Kingdom

By EHDN

Working Groups

THE WORKING GROUPS (WG) OF THE EHDN ARE VITAL TO THE ACTIVITIES AND SUCCESS OF THE NETWORK. BY DEFINITION, A WORKING GROUP IS AN INTERDISCIPLINARY COLLABORATION OF RESEARCHERS WORKING ON NEW RESEARCH ACTIVITIES THAT WOULD BE DIFFICULT TO DEVELOP UNDER TRADITIONAL FUNDING MECHANISMS (E.G. GOVERNMENT AGENCIES). THE LIFESPAN OF A WG CAN LAST ANYWHERE BETWEEN A FEW MONTHS AND SEVERAL YEARS. SUCH GROUPS HAVE THE TENDENCY TO DEVELOP A QUASI-PERMANENT EXISTENCE ONCE THE ASSIGNED TASK IS ACCOMPLISHED; HENCE THE NEED TO DISBAND (OR PHASE OUT) THE WG ONCE IT HAS PROVIDED SOLUTIONS TO THE ISSUES FOR WHICH IT WAS INITIALLY CONVENED. SUCH GOALS TO BE ACHIEVED MAY INCLUDE CREATION OF AN INFORMATIONAL DOCUMENT, CREATION OF A STANDARD, OR RESOLUTION OF PROBLEMS RELATED TO A SYSTEM OR NETWORK.

The WGs may assemble experts (and future experts) on a topic together for intensive work. It is not an avenue for briefing novices about the subject matter. Occasionally, a group might admit a person with little experience and a lot of enthusiasm. However, such participants should be present as observers and in the minority. Working groups are also referred to as task groups or technical advisory groups. (Wikipedia)

EHDN members are welcome to propose ideas for new working groups. There are 16 Working Groups currently active in EHDN, and two more in the planning stage. The EHDN Working Groups and their objectives are:

1 **Behavioural Phenotype:** to improve the quality of the generally-accepted behavioural or psychological assessment scales of the Unified Huntington's Disease Rating Scale (UHDRS) and to develop, test and validate new tools for objective quantitative outcome measures in longitudinal studies and interventional trials.

2 **Biological Modifiers:** to improve the drug and marker discovery process in HD, integrating data on biological and genetic modifiers using a network systems approach to identify and validate therapeutic targets.

3 **Biomarkers:** to identify biomarkers that can be used to track disease progression, detect disease-related changes, and monitor treatments that may delay onset of HD, especially in presymptomatic individuals.

4 **Brainbanking:** to collect and set quality standards for collection of post-mortem tissues of consenting HD patients for research purposes using novel molecular biological technologies in order to correlate the neuropathological findings with well-characterized clinical phenotypes.

5 **Cognitive Phenotype:** to design a core battery of cognitive assessments that is efficient, useful for research but also for patients and families, repeatable, as short as possible, and that can be used across all countries and languages.

6 **Genetic Tests/ Counselling:** to be a multidisciplinary group with clinical and lab geneticists, neurologists, psychologists, psychiatrists and persons of the EHDA.

7 **Genetic Modifiers:** to set up a European-wide study to investigate the genetic basis of phenotypic variables in HD that are not explained by CAG repeat length in the HD gene.

8 **Health Economics:** to assess the economic impact of HD in order to heighten awareness of the impact for policy makers, health service agencies, and research funding bodies.

9 **Imaging:** to explore the usefulness of imaging techniques, specifically MRI and PET, also known as 'dry' biomarkers, as non-invasive tools to track progression of disease in symptomatic and presymptomatic HD mutation carriers.

10 **Juvenile HD:** to conduct a more detailed and exten-

sive Natural History Study and Qualitative Analysis for publication in order to provide improved services for juvenile HD families.

11 **Motor Phenotype:** to improve the clinical assessments performed by HD motor raters by producing a training video of the UHDRS-Total Motor Score (TMS); to improve sensitivity of the UHDRS-TMS to assess disease progression; and to develop, test and validate novel quantitative motor assessment tools.

12 **Neuroprotective Research:** to provide recommendations for the improvement of clinical trials.

13 **Quality of Life:** to conduct a systematic data collection and evaluation of the well-being of HD patients and caregivers in order to improve the quality of existing outcome measurements.

14 **Standard of Care:** to document practice, and the different approaches around Europe to the management of HD with a view to developing evidence based guidelines for best practice.

15 **Surgical Therapy:** to assess potential surgical approaches for treating HD such as deep brain stimulation (DBS), siRNA, gene therapy and neural transplantation.

16 **Symptomatic Research:** to improve the symptomatic treatment of HD patients and to establish treatments for HD with studies that fulfill the criteria of fact-based medicine.

The Functional Assessment WG and the Physiotherapy WG are in the planning stages.

For more information on EHDN Working Groups, please visit:
www.euro-hd.net/html/network/groups

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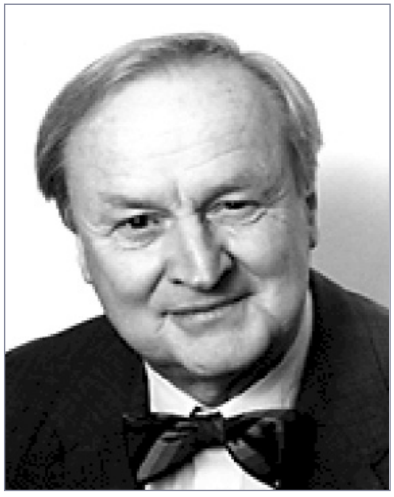
By Christine Schwarz and introduction by Roger Barker

New drug trial in HD for 2008



The second major European drug trial in HD is soon to commence which involves a compound called ACR16 developed by NeuroSearch – a company set up to develop ideas from the Nobel laureate Arvid Carlsson, who discovered that dopamine is a transmitter in the adult brain. ACR16 stabilises dopamine systems in the brain so it could help both the movement disorder of HD as well as some of the other cognitive and affective aspects of this disorder. To date this drug has only been tried in a small group of patients with HD but the results looked very encouraging, and so we are looking forward to seeing what happens in this larger trial. This trial will target patients with mild-moderate HD and then follow them over 26 weeks using a number of different measures,and will compare the effects of the drug against placebo in a double blind fashion, so that neither the doctor nor the patient knows whether they are taking the actual drug. It is only by using such approaches that the true effects of the drug can be ascertained.

In the next few months a new clinical trial in patients with Huntington´s disease (HD) will take place in Europe. The compound to be tested is ACR16 and the clinical indication is treatment of dyskinesias. Dyskinesias, mostly chorea and dystonia, are an important feature of HD. Although today we recognize that other movement disorders as well as cognitive and behavioural abnormalities play an important part in disability of patients with HD there are still patients in whom their deficit, at least during a certain period of their evolution, is largely related to the severity of their dyskinesia.

Dyskinesias are treated with a number of compounds, mostly neuroleptics and dopamine depleting agents. These agents reduce effectively the severity of dyskinesia but often produce severe side effects. Neuroleptics produce parkinsonism and dopamine depleting agents cause, in addition, hypotension and depression.

ACR16 (Arvid Carlsson Research 16) is a new compound synthesized and produced by Prof. Carlsson and his colleagues. Prof. Carlsson has dedicated a good part of his very fruitful life to the pharmacology of the dopamine system. He discovered that dopamine is a neurotransmitter by itself and not merely a precursor of norepinephrine in brain. He also found that the parkinsonism produced by reserpine in experimental animals was related to the depletion of dopamine and was reversed by L-DOPA. He discovered the mechanism of action of neuroleptics and antidepressants and he made many other important contributions to neuro-psycho-pharmacology. For that work he has received many important international awards including the Nobel Prize in Physiology and Medicine in the year 2000.

Prof. Carlsson has kindly agreed to answer to the questions of Christine Schwarz and to explain to the readers of Euro-HD Newsletter the properties of ACR16 and the putative benefits of this compound for HD patients .

Christine Schwarz – **Prof. Carlsson, thank you for agreeing to talk about ACR16 with the members of the Euro-HD Network. Could you explain for us what ACR16 is?**

Professor Carlsson – The development of ACR16 was based on several decades of research in our group in the Department of Pharmacology, University of Göteborg, Sweden. We had discovered that dopamine receptors are much more heterogeneous than had been assumed by molecular biologists. For example, one and the same subtype of dopamine receptors, the dopamine D2 receptor, in spite of being derived from a single gene, can behave very differently in different locations. There are subpopulations of D2 receptors that are actually mutual functional antagonists, and they respond with very different sensitivity to dopamine as well as to exogenous compounds acting either as stimulants or antagonists on the receptor. In drug development it is necessary to take this heterogeneity into account, and thus the generally used in-vitro screening is inade-

By Christine Schwarz and introduction by Roger Barker

quate. For the screening of molecules with optimal pharmacological profiles it is necessary to place much more weight than usual on intact in-vivo systems, using a combination of sophisticated biochemical and behavioural methodologies. ACR16 has a profile that could not be predicted from in-vitro data used so far. It operates on the dopamine system as a stabilizer, that is, it does not change the baseline activity of the system so much but can antagonize both under- and overstimulation of the system.

– In which way is ACR16 different to the classical dopamine agonists or antagonists and to the other compounds actually used for the treatment of chorea? How do you believe this compound may be superior to other compounds used for the treatment of movement disorders?

– The drugs available so far are overt dopamine antagonists, which means that it is hard to avoid understimulation of certain parts of the dopamine system. ACR16 will counteract overstimulation, for example chorea, but it will spare the dopamine system from understimulation, which would impair both motor and mental functions.

– Do you think that ACR16 may be the precursor of a new kind of pharmacological compounds which may stabilise neurotransmission in other systems? In other words, is it possible to find compounds which act in a more complex way in glutamate or serotonin neurotransmission rather than acting merely as receptor agonists or antagonists and that this new class of compounds may be useful in other diseases of the nervous system?

– Yes, as so often before the pharmacology of the dopamine system will probably guide the way for a new strategy where stabilisation rather than straightforward agonism or antagonism will be applied, leading to imbalances and subsequent long-term dysfunctions.

– ACR16 has been used in preliminary trials in some patients with HD. What are the first results?

– They are very promising, with indications of improvement not only of chorea but also of mental symptoms such as depressed mood and cognitive defects.

– The main interest of ACR16 is related to the treatment of motor disorders. But other additional problems in patients with HD are related to behavioural abnormalities. We do not know precisely what molecular mechanisms cause these symptoms but among other possibilities it has been proposed that some of them, for instance, apathy, may be related to abnormal dopamine neurotransmission in the mesolimbic cortical dopamine system. What effects, if any, do you think ACR16 may have in behavioural symptoms, such as apathy?

– Huntington's disease is characterized by degenerative changes not only in the movement-controlling but also in the limbic parts of the basal ganglia which regulate mental functions. ACR16 acts on both these portions. Therefore, from a theoretical point of view, one would predict that ACR16 should improve both motor and mental functions, and this seems indeed to be the case.

– Professor Carlsson, ACR16 is supposed to be a drug for the symptomatic treatment of HD. At times it is difficult to differentiate between purely symptomatic and neuroprotective or disease modifying treatments. For instance, L-DOPA is considered a purely symptomatic treatment of Parkinson´s disease (PD), but before the L-DOPA era the risk of death of patients with PD was 2.2 greater than that of aged matched healthy individuals. Now the risk of death in patients with PD is similar to that of normal subjects. But, other than quality of life or indirect effects, do you believe there are pharmacological data to support that ACR16 or any related compounds may have disease modifying effects in HD?

– It is important to de-emphasize the distinction between symptomatic and neuroprotective treatment. Imbalances in the brain may well lead to cell damage due, for example, to excitotoxicity, and such a mechanism could well play a role in a lot of neurodegenerative disorders. Thus it is not unreasonable to assume that ACR16, by restoring destructive imbalances, could actually have neuroprotective properties, implying that early onset of treatment could have a beneficial effect on the entire course of this serious degenerative disease.

– Well, thank you very much for your willingness to illustrate to the readers of Euro-HD NewsLetter. Is there any thing else that you would like to add?

– I have great expectations on this study. It may not only alleviate the suffering of numerous patients with Huntington's disease. In addition it could well lead to a more optimistic attitude to neurodegenerative disorders in general, just like what happened with the introduction of L-DOPA in the treatment of Parkinson's disease.

By Diana Raffelsbauer

4th Annual Plenary Meeting of the **European Huntington's Disease Network**

The 4th Annual Plenary Meeting of the European Huntington's Disease Network (EHDN), held in conjunction with the 3rd World Congress on Huntington's Disease (HD), convened in Dresden (Germany) on September 7th and 8th, 2007. The event attracted more than 500 scientists, clinicians, members of lay organisations and relatives of HD patients from all over Europe. Outstanding researchers introduced different hot topics, which were further deepened in working group sessions. New projects were presented. A report on the activities of the EHDN in the last year with an outlook for 2008 was provided. There is a complete report on the Meeting, which you can download from the following link: http://www.euro-hd.net/html/network/events/ehdn2007/ The next plenary meeting will be held in conjunction with the 12th bi-annual meeting of the European Huntington Association (EHA) in Lisbon (Portugal) from September 5th to 8th, 2008.

The plenary sessions were well-balanced between subjects of interest for caregivers and for scientists. The presentations on weight loss in HD, apathy and depression, self-medication, and standard of care covered relevant aspects in daily life of HD patients, whereas the topics on RNA therapeutics, assessment of motor symptoms, juvenile HD and biomarkers were more tailored to scientists' interests.

● **Sheila Simpson (NHS Grampian, Aberdeen, UK) and Maria Björkqvist (University of Lund, Sweden)** discussed weight loss in HD based on studies conducted with 8 mid to late stage HD patients focusing on diet, calorie requirement and energy expenditure, which showed that all patients had a calorie intake below the recommended amount. Simpson reported data from Audrey McGregor, a dietician from Aberdeen, who has postulated that "patients with carers who were able to devote much time and effort towards the nutritional needs of their patient better managed to meet the nutritional goals".

● **Gillian Bates (University of London, UK)** gave an overview of antisense oligonucleotide and RNA interference therapies as two different genetic approaches aiming at the treatment of HD. Antisense oligonucleotide therapeutics has been shown effective in animal models for the treatment of neurodegenerative diseases whose pathogenesis is driven by the accumulation of neurotoxic mutant proteins (e.g. amyotrophic lateral sclerosis). In HD many antisense oligonucleotides have been found to inhibit mouse and human huntingtin (htt) expression. Previous work in the field of RNA interference showed that short hairpin RNA molecules directed against mutant htt reduced gene expression in cell culture and in HD mouse brain. Importantly, HD gene silencing improved behavioural and neuropathological abnormalities associated with HD. Despite these preliminary positive results in animal models, there are many remaining challenges that need to be resolved concerning the efficacy, safety and tolerability of RNA therapeutics as treatments for HD in humans.

● **David Craufurd (University of Manchester, UK)** reported on behavioural symptoms of HD with focus on apathy and depression. HD patients often perceive mood disturbances as more distressing than motor and cognitive impairments. They also exert a greater impact on carers and the viability of community care. Craufurd presented data from a study he conducted in 134 HD patients using the Problem Behaviors Assessment for HD. The most common symptoms were loss of energy and initiative, poor perseverance, impaired judgment, poor self-care and emotional blunting (88-66% of patients). Affective symptoms such as depression and anxiety occurred in approx. 30-40% of the patients studied. The behavioural symptoms reported can be divided into 3 categories: apathy, depression and irritability. Antidepressants are generally effective in improving low mood and irritability, but not apathy.

● **Bernhard Landwehrmeyer (University of Ulm, Germany)** pre-

By Diana Raffelsbauer

sented the topic "Self-medication" discussing the motivation of people for using medicinal products on their own initiative and the risks it bears. "People accept more responsibility for their health and inform themselves to make better decisions", he said. There are non-prescription medicines of good quality which are safe and effective. On the other hand, self-medication may be a sign of a failing relationship between health care professionals and patients or may just reflect the lack of efficient treatment options. The use of non-prescription medicines is common among people at risk for HD and in virtually all early stage HD patients. Nonetheless, the impact of self-medication on the course of HD is unknown due to the lack of information. These data could be collected through the studies of the EHDN.

● **Ralf Reilmann (University of Münster, Germany)** discussed clinical tools for motor assessment in HD focusing on the Unified Huntington's Disease Rating Scale - Total Motor Score (UHDRS-TMS), a rating system developed to provide a uniform assessment of the motor symptoms in HD. Reilmann has been working on methods to decrease inter- and intra-rater variability and improve the reliability of the test. In cooperation with the Motor Phenotype Working Group, he recorded a UHDRS-TMS teaching video with detailed instructions on how to perform and rate the exam. The goal is to improve clinical motor rating and hence enable a more objective and sensitive clinical motor assessment in the setting of treatment trials. A programme for motor training and certification, the UHDRS-TMS Rater Certification Project, is being developed within the EHDN.

● **Oliver Quarrell (Sheffield Children's Hospital, UK)** summarised the activities of the Juvenile HD Working Group. The Natural History Study is aimed at the development of assessment tools to diagnose and monitor the course of juvenile HD (JHD) more accurately. To meet this purpose, the UHDRS has been adapted for JHD patients. A Quality of Life Study of JHD affected families, which was previously conducted in the United Kingdom, is now being extended to other European countries. Other projects include the Diary Study and the Drug Survey, aimed at the collection of data concerning the symptomatic course of JHD in response to pharmacological therapies. One of the priorities of the Working Group is the organisation of information on JHD currently available. For instance, an international meeting was held in 2006 which will form the basis of a book about JHD.

● **Sheila Simpson** presented interim results of a project developed by the Standard of Care Working Group aiming at the creation of a guideline based on best practice which describes a standard of care for HD patients that can be used internationally. In many countries there are no designated clinics for HD patients, and within some countries, the care provided varies widely. The data collected from 28 HD specialists in 9 European countries clearly showed that the majority did not follow published guidelines and that clinical diagnostic methods were also not uniform. Simpson is working on a model called "Managed Care Network", which comprises multidisciplinary specialised services for HD patients. In the future the Working Group will focus on the publication of the guideline on the EHDN website and in a peer reviewed journal, the collection of data from new centres, the audit of current practice and the further development of the proposed Managed Care Network.

● **Sarah Tabrizi (University College London Hospitals, UK)** presented the "Challenges in establishing biomarkers for HD", highlighting why the identification of biomarkers that measure disease progression accurately is so important for the efficacy assessment of disease-modifying therapies. A major goal of clinical HD research is to improve early diagnosis and presymptomatic detection of neuronal dysfunction, with the hope that a better understanding of the early events in disease progression may allow delaying symptom onset. There are multiple pathways which can be triggered for therapeutic design. Indeed, most novel drugs have been targeted to early events in the molecular pathogenesis of HD. Different approaches are ongoing to identify neuropathological, biochemical and genetic biomarkers for HD. The methods used include transcriptomics, proteomics, peptidomics and metabonomics analysis of biofluids and tissues, imaging techniques (brain scans) and clinical markers. Several small cross-sectional biomarker studies have been already conducted involving pre-manifest gene carriers and HD patients in different stages. Importantly, the biomarker research has sparked a renewed interest in the "peripheral" pathogenesis of HD. Tabrizi is leading the EHDN Project TRACK-HD, a multinational observational biomarker study of pre-manifest and early stage HD patients aimed at evaluating the sensitivity of individual and combined clinical and biological outcome measures for tracking progression of HD with a view to validating these measures for use in future therapeutic trials.

By Diana Raffelsbauer based on report by Lisa Bain

3rd World Congress on Huntington's Disease

The 3rd World Congress on Huntington's Disease (HD), held in Dresden, Germany, from September 8th to 11th, 2007, was a joint event of the World Federation of Neurology (WFN) Research Group on Huntington's Disease and the International Huntington Association (IHA). Under the motto "Joining forces for HD", the Congress offered more than 500 scientists, clinicians, representatives of lay organisations and members of HD affected families from all continents the opportunity to share results, ideas and experiences. **Elizabeth McCusker (WFN, Sydney, Australia), Christiane Lohkamp (IHA, Stuttgart, Germany)** and **Bernhard Landwehrmeyer (EHDN, Ulm, Germany)** opened the Congress, which was organised in joint plenary sessions on topics of general interest and more specialised parallel sessions targeted to either scientists, clinicians or lay people. There is a complete report on the Meeting, which you can download from the following link: http://www.worldcongress hd.net/html/2007/ The next World Congress on Huntington's Disease will take place in Vancouver, Canada, from September 12th to 15th, 2009.

● The Congress began with a review and preview of research in HD. Looking back, **Alice Wexler (University of California, Los Angeles, USA)** described the village of East Hampton, Long Island, New York, USA, where George Huntington lived and worked as a physician. In the late 19th century, the families who lived there, descendents of an HD affected woman named Phebe Hedges, helped identifying the pattern of inheritance of HD. Likewise, in 2007, progress in HD research continues to be made through a community-wide effort with affected people, family members, scientists, and clinicians working together.

● **Helga von Wilucki (Deutsche Huntingtonhilfe, Hannover, Germany)** recalled the foundation of the IHA in 1979, the lay organisation aimed at providing support for HD affected families. Today the IHA comprises 47 member countries. Through a collaborative relationship with the research community, HD affected families have doubtless played an important role in advancing research and shaping the clinical management of the disease. This collaboration ultimately evoked the bi-annual World Congress on HD.

● Tribute was made to **Milton Wexler**, one key figure in HD history, in recognition of his work searching for a cure for HD. Wexler died on March 16th, 2007, at the age of 98, leaving behind a legacy of breaking down divisions between families and scientists. Together with his daughters Alice and Nancy, Wexler founded the Hereditary Disease Foundation (HDF) in 1968 after his ex-wife and their mother, Leonore, developed HD. One decade later, **Nancy Wexler (HDF, New York, USA)** started a project to study the largest HD family in the world in Lake Maracaibo, Venezuela, which led to the identification of the HD gene in 1993. These families now consist of more than 18,000 people, and research is still ongoing to provide further details on the molecular mechanisms of pathogenesis of HD, such as genetic modifiers of age at onset, progression rate and symptoms.

● Looking forward, **James Gusella (Massachusetts General Hospital, Boston, USA)** provided a geneticist's perspective of future HD research. "It starts and ends with patients and families", he said. The predictive genetic test enables researchers and clinicians to intervene at a pre-symptomatic stage, aiming at preventing the disease development or delaying the symptom onset. Drugs can be targeted at any stage of the disease process. Whereas clinical trials have so far targeted the symptomatic phase, most novel drugs in the pipeline focus on neuronal dysfunction and cell death. But yet there is still much to learn about HD, and "ultimately the gold standard is what is happening in people", said Gusella.

● The next three sessions were devoted to the basic biology

By Diana Raffelsbauer based on report by Lisa Bain

of HD. **Leslie Thompson (University of California, Irvine, USA)** presented an overview of the biological mechanisms that lead "from a faulty gene to a bad disease". The HD gene mutation affects many cellular processes, such as energy production, neurotransmission, gene transcription, protein modification, trafficking, cleavage and degradation. The complexity of these mechanisms makes the search for treatments more difficult, but at the same time provides multiple targets for therapeutic design. Several in vitro systems and animal models have been developed to study these changes, such as different cell lines, yeast, *Drosophila* (fruit fly), *Caenorhabditis elegans* (a roundworm), mouse and rat models. For instance, studies in mice have helped scientists understand the effects on behaviour, cognition and survival, and assess the efficacy and safety of compounds in pre-clinical trials.

- **Ron Wetzel (University of Pittsburgh, USA)** has been studying the biophysical properties of the Huntingtin protein, particularly its ability to misfold and form aggregates. Proteins normally tend to aggregate into lower energy states following certain biophysical rules. Clarifying these rules as well as the causes of misfolding may lead to a better understanding of how the mutant protein disrupts normal cellular processes. Aggregates might lead to neuronal dysfunction and death through a number of possible mechanisms, each of them suggesting potential therapeutic strategies. This includes inhibiting protein degradation which generates toxic species, stimulating the formation of non-toxic species, promoting removal or breakdown of the aggregates, or blocking the downstream effects of the cytotoxic mechanism that is activated by aggregates.

- Recent data from human imaging studies and HD mouse models have demonstrated the importance of changes in the cerebral cortex and corticostriatal pathways in the course of HD. Using a neurophysiological approach, **Michael Levine (University of California, Los Angeles, USA)** showed that, in HD mice, there is a loss of excitatory input to the striatum coupled with an increase in inhibition, while the opposite effects occur in the cortex. Further experiments conducted by Levine using mice that do not express the mutant Huntingtin protein only in the cortex showed that striatal neurones could recover their normal activity, suggesting that the search for therapeutic targets should go beyond the striatum.

- One of the main focuses of the Congress was on how clinical studies and trials can help elucidate the pathogenesis of HD and establish new treatment options with a view to improving quality of life of HD patients. In this context, the identification of biomarkers that detect disease onset and progression accurately is essential for the efficacy assessment of new drugs in clinical trials. The PREDICT-HD Study was designed to identify these early markers of HD. **Jane Paulsen (University of Iowa, USA)**, principal investigator of PREDICT-HD, said that the study design came in part from families coming to her with ideas about subtle signs that might indicate disease onset. The Project achieved its goals: A high number of pre-manifest HD gene carriers (almost 1000 participants) was enrolled, the sample size needed for pre-symptomatic HD clinical trials was reduced by up to 40%, markers of disease progression were identified, the formula of age of onset based on the CAG repeat length was validated, a wide database of MRI scans, biological samples and clinical assessments was established.

- **Julie Stout (Monash University, Melbourne, Australia)**, another investigator involved in the PREDICT-HD Study, described the HD Toolkit Project, which applies the principles of evidence-based medicine to identify suitable assessment strategies. Based on a literature review, Stout rated assessment tools from different categories according to their sensitivity in detecting decline in pre-symptomatic HD subjects over 2-4 years. The aim is to build a cognitive battery that will achieve the maximum sensitivity with the fewest tests, thus improving the design of clinical trials and reducing the sample size.

- **Diana Rosas (Massachusetts General Hospital, Charlestown, USA)** reported on how MRI imaging studies may help in neuroprotective treatment trials for HD, as they may explain the neurological

By Diana Raffelsbauer based on report by Lisa Bain

basis of the clinical abnormalities seen in HD. Atrophy occurs not only in the striatum, but also in other parts of the brain, including the cortex, white matter and subcortical structures. At the time of diagnosis, more than 50% of the striatum is lost. At the time of death the brain weight is reduced by more than 30%. A better understanding of the changes that happen in the brain during the course of the disease may help explain why clinical symptoms continue to progress. Rosas' studies on the cortex of pre-manifest HD subjects have shown the most extensive thinning in the motor, sensorimotor and occipital areas of the cortex, with preservation of the frontal cortices. “We need to understand the 'where' in order to understand the 'how', 'why', and 'when'”, said Rosas.

● **Robert Pacifici (CHDI Inc., Los Angeles, USA)** provided an update of the work that CHDI Inc., a non-profit organisation and successor of the Cure Huntington's Disease Initiative, is doing in the field of drug discovery and development. CHDI pursues multiple parallel approaches which result in a widespread drug pipeline including several new targets in addition to the classic ones (e.g. Huntingtin protein, caspase-6, transglutaminase and BDNF). However, “targets must be both biologically validated and chemically tractable, or 'drugable'”, he said.

● **Ira Shoulson (University of Rochester, USA)** reported on the recently completed, ongoing and upcoming interventional trials conducted by the Huntington Study Group (HSG), and **Bernhard Landwehrmeyer (University of Ulm, Germany)** summarised those trials conducted by the EHDN. Concluded studies encompass PHEND-HD (Phenylbutyrate), TREND-HD (Ethyl-EPA), DIMOND-A (Dimebon, phase I-II), TETRA-HD (Tetrabenazine) and EHDI (Riluzole). DOMINO (Minocycline) and DIMOND-B (Dimebon, phase III) are in progress. Upcoming studies are 2-CARE (Coenzyme Q10), CREST-E (Creatine), PREQUEL (CoQ and Ubiquinone in pre-manifest HD) and ACR-16 (a dopaminergic stabiliser).

Most of these studies are symptomatic treatments trials conducted in manifest HD subjects. However, there are now efforts to begin conducting neuroprotective trials in pre-manifest subjects. In addition, four observational studies are ongoing: PHAROS (subjects at risk for HD), PREDICT-HD (pre-manifest gene carriers) and COHORT and REGISTRY (manifest, pre-manifest and at-risk subjects, and family members not at risk). Intensive research in drug development has increased the number of compounds undergoing clinical trials from 12 in 2004 to 18 in 2007.

● **Monica Busse (Cardiff University, UK)** discussed the use of physical therapy (PT) as a means of improving movement and function in HD patients. The base of scientific evidence is still limited to confirm the benefits of PT in HD. At the HD clinic in Cardiff, Busse is evaluating PT assessment tools which could be used as robust outcome measures, as well as examining the content of physiotherapy according to the stage of the patient's condition and the level of impairment. The aim of her work is to provide concrete evidence to support the use of PT and to design clinical trials to assess its effectiveness.

● A day-care rehabilitation programme for HD patients was presented by **Herwig W. Lange (RZD, Dinslaken, Germany)** which comprises occupational therapy, physiotherapy, speech and swallowing therapy, neuropsychological interventions, medication and social work. A small study involving 17 HD patients failed to show a significant benefit, although a tendency towards improving motor, cognitive and behavioural symptoms was detected.

On Sept. 10th and 11th, the presentations were divided into scientific, clinical and IHA sessions. The scientific sessions comprised the topics pathogenesis and pathophysiology of HD, inflammatory and metabolic alterations in HD, cell replacement in HD, experimental models and HD therapies in experimental models. The clinical sessions covered understanding the clinical features of HD, biomarkers in HD, genetic testing, predicting onset and phenotype and guidance for care, recent and upcoming clinical studies and trials in HD, and HD related disorders. The IHA sessions were devoted to the topics of people with HD, support systems for HD families in member countries, rehabilitation in HD, quality of life and challenge of genetic information in HD.

By Diana Raffelsbauer

Meeting of the International Huntington Association

THE MEETING OF THE IHA WITHIN THE SCOPE OF THE 3RD WORLD CONGRESS ON HUNTINGTON'S DISEASE WAS HELD IN DRESDEN, GERMANY, ON SEPTEMBER 10TH AND 11TH, 2007. DIFFERENT ASPECTS OF HD WERE PRESENTED BY OUTSTANDING HD SPECIALISTS AND LAY ORGANISATION REPRESENTATIVES. THE TOPICS, WHICH WERE DIVIDED IN 6 SESSIONS, INCLUDED SUPPORT SYSTEMS FOR HD FAMILIES, QUALITY OF LIFE OF HD PATIENTS AND THEIR PARTNERS, AND CHALLENGES OF GENETIC INFORMATION IN HD. YOU CAN DOWNLOAD THE COMPLETE REPORT FROM THE FOLLOWING LINK: http://www.worldcongress-hd.net/html/2007/

● **James Pollard (Tewksbury Hospital, Tewksbury, USA)** described the main cognitive symptoms of HD and their impact on daily life. HD patients typically show the following cognitive patterns: slower thinking, recognition is easier than recall, topic changes are difficult, difficulty organising and planning, and “can't wait”. These features result in three conditions: narrow focus on what is coming next, apathy and irritability. A better understanding of these impairments may help family members and caregivers to accommodate the changes caused by HD, to more efficiently interact with affected people and to explain the disease to others in a new way. These accommodations may avoid confusion, anger and apathy, help in daily activities and maintain a warm relationship throughout the course of the disease.

● **Lucienne van der Meer (Leiden University Medical Center, Leiden, the Netherlands)** presented data from a study that she conducted with 77 early to middle stage HD patients. The study assessed how HD affects quality of life, how patients and their partners perceive HD, and how they cope with the problems they encounter in daily life. According to this study, the largest impacts of HD are seen in the parameters of work, alertness, home management, recreation, communication, psychosocial aspects and emotions. HD patients believe that they have many severe symptoms, that they will be ill for a long time, that HD influences their whole life and that there is nothing that can be done. These subjective illness perceptions affect quality of life, as they decrease vitality, physical and mental health.

● **Karen Keenan and Catherine Martin (Scottish Huntington's Association, Aberdeen, UK)** reported on their work at the National Youth Service focusing on young people's view of growing up in a family with HD. Some of these children have been caring for their affected parents and are therefore particularly at risk for physical and/or emotional harm. The problems they face include issues around caring activities, coping strategies, communication, family relationships, understandings of inheritance, risk perceptions, attitudes to genetic testing and having children. HD affects parenting capacity and children often experience multiple losses. The burden of risk and possible lack of information may lead to prolonged anxiety. Young people may also experience stigma and taboo associated with HD, all of which can lead to some children being considerably isolated.

● **Paola Zinzi and Stefano Maceroni (Home Care Nova Salus, Trasacco, Italy)** conducted a pilot project with the aim of providing a quantitative assessment of the effect of rehabilitation therapy on HD patients. The programme comprised physical, respiratory, speech, cognitive and occupational therapies. At the end of each 3-week treatment, HD patients showed a significant improvement in specific tests for physical performance, gait and balance. In tests of depression, cognition and daily living functionality, patients maintained the initial level and did not deteriorate beyond the baseline scores over a 2-year-period. In qualitative questionnaires, improvements

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were reported in motor control, speech, balance, swallowing and gait. Positive effects were also observed in mood state, family and social relationships. These results provide evidence that rehabilitation is an effective tool to improve both physical and psychosocial symptoms of HD.

● **Don Lamont (Huntington Society of Canada/HSC, Kitchener, Canada)** presented the Canadian Model as an example of how lay associations can serve people with HD. Due to the geographic and demographic features of Canada with a population density of 3.2 people/km2, this model is unique. The core service network consists of 10 HSC family resource centres in larger communities, as well as 12 individual and family service workers in areas with lower populations. Since its foundation in 1973, the HSC has been committed to supporting individuals and families affected by HD. The HSC strives to maximise the quality of life of people living with HD by delivering services, enabling others to understand the disease by offering educational programs and furthering HD research. Independent of HSC, there are 8 multidisciplinary HD clinics and 6 Huntington Study Group sites in Canada, with whom HSC staff collaborates.

● **Michael Orth (University Medical Center Hamburg-Eppendorf, Germany)** reported on the HD Clinic in Hamburg, where a multidisciplinary team of specialists treat and advise patients and their families. The aims of the Clinic are predictive genetic counselling and testing, management of neurological and psychiatric symptoms, social support including legal matters, therapeutic clinical trials and research. To provide HD patients with a continuum of care services, the Clinic works closely with other health care professionals, including psychologists, speech and language therapists, physiotherapists, social workers and HD lay organisations. One of the cooperation partners is the Northern German HD Support Network, which was represented by **Gabriele Ritter** (**DHH Nord, Grossenbrode, Germany**). The Network brings together HD affected families, self-help groups and professionals of different institutions and care facilities to a well functioning supportive system.

● **Aileen Ho and Mevhibe Hocaoglu (University of Reading, UK)** summarised interim results of the Huntington's Disease Quality of Life Project, developed in cooperation with the Quality of Life Working Group of the EHDN. The features of HD are unique, raising the need for an HD-specific assessment tool which is valid, reliable and sensitive. Hence, a questionnaire is being developed which addresses the specific ways in which patients' ability to live their lives has been affected by HD reflected through the subjective experience of the patients. The Project is divided in three stages: Stage 1 is aimed at the generation and selection of questionnaire items by interviewing HD patients and their carers. In Stage 2 suitable items will be derived to conceive a prototype instrument. Stage 3 will evaluate the psychometric properties of the instrument. The Project is currently in Stage 1. Based on a review of the literature, semi-structured interview questions were developed which reflect different aspects of health-related quality of life (physical, functional, cognitive, emotional, social, legal and financial). Preliminary findings have revealed the major impairments that HD patients encounter in the course of the disease.

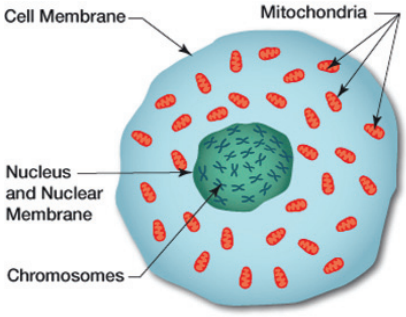
● **Claudia Downing (University of Cambridge, UK)** presented the challenges that arise for those aware of their or their partner's risk for HD when considering becoming and being parents at a time when genetic testing and new reproductive techniques (in vitro fertilisation and preimplantation genetic diagnosis) have become available. Challenges comprise identifying the risks, undergoing the procedures, justifying rejecting the new options, deciding whether to have children, living with uncertainty or clarifying it, and parenting with the knowledge of a gene positive status, which also includes the uncertainty about the at-risk parent's ability to sustain a parenting role. Those parents with a positive predictive test result face issues such as living with uncertainty about when they will develop the symptoms and planning how best to use this time to meet the responsibilities towards their dependent children. Planning for the future includes making appropriate care and housing arrangements, finding ways of “being there” for children's milestones, ensuring that the other parent is aware of the implications for the children and passing on values as well as genes.

● *Kosinski et al., Movement Disorders, Vol. 22, No. 11, 2007*
By Justo García de Yébenes and Diana Raffelsbauer

Myopathy as a **first symptom of Huntington's disease** in a marathon runner

In this very interesting publication, Kosinski and colleagues describe the case of a 37-year-old man at risk for Huntington's disease. As a semi-professional marathon runner, he had been running since he was 20 years old for at least 6 miles a day. From 1997 on he developed severe muscle weakness and pain which persisted after rest. In 1998 he was examined at the Hospital of the University of Würzburg, Germany, where he was found to have mild myopathy (a muscle disease resulting in weakness, cramps and pain in the muscles), slightly increased levels of creatine kinase (an enzyme involved in energy supply for muscles) and an expanded trinucleotide repeat in the huntington gene of 43 CAG repeats.

His running performance progressively declined and in 2004 he was evaluated at the University Hospital RWTH in Aachen, Germany. At that time, he showed obvious symptoms of early stage HD: mild chorea, slow eye movements and mild bradykinesia (a slowing of movements), with a motor score of 8 in the Unified Huntington's Disease Rating Scales. Again, he had mild myopathy and his creatine kinase was increased. No huntingtin aggregates (a hallmark of HD) were observed in muscle cells. However, his muscle biopsy showed an accumulation of mitochondria (the 'powerhouses' of the cell), which were dramatically enlarged. The activity of a certain mitochondrial enzyme called complex IV cytochrome c oxidase was severely reduced. This enzyme is involved in the production of energy for the cells. Moreover, the level of citrate synthase, a marker enzyme for intact mitochondria, was clearly increased. These results suggest that the energy supply to the muscle cells was below the required level.



The key message of this case report is the finding that intense physical exercise may trigger mitochondrial myopathy in early stage of HD

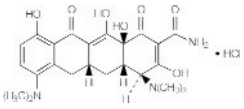
The key message of this case report is the finding that intense physical exercise may trigger mitochondrial myopathy in early stage of HD. Mitochondrial dysfunctions have been previously reported in muscle and brain tissues of HD patients, most notably in those with very large CAG repeat expansions. Mitochondrial respiratory deficits have been also found in muscles of HD transgenic mice. However, mitochondrial myopathy as a first symptom of HD was never recognised before.

Since the Huntingtin protein is expressed in all cells of the body, we do not know why HD affects preferentially the brain. Medium spiny neurones of the striatum (a brain structure responsible for movement control), the most severely affected in HD, show one of the highest metabolic rates of the brain. It has been hypothesised for a long time that this feature makes them so susceptible in HD.

The data presented by Kosinski and colleagues may provide new evidence on the role of the mitochondrial energy-providing system in triggering cell death in HD. This may disclose new biomarkers for clinical trials and may help to design therapeutic strategies based in novel approaches, such as lowering the metabolic rates of the most vulnerable neuronal systems.

● *Gordon et al., The Lancet Neurology, Vol. 6, No. 12, December 2007*
By Diana Raffelsbauer

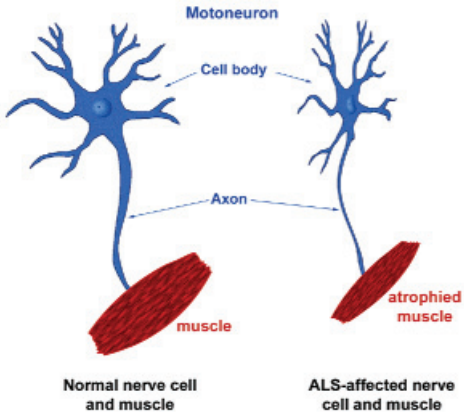
Efficacy of minocycline in patients with amyotrophic lateral sclerosis: a phase III randomised trial



Amyotrophic lateral sclerosis (ALS) is a neurological disorder caused by degeneration of motor neurones, the nerve cells that control voluntary movements. The disease affects both the upper and lower motor neurones, which degenerate and die, ceasing to send signals to muscle cells. The result is muscle weakness and atrophy throughout the body. ALS leads to death on average within 3 years of symptom onset. Different strands of investigation are ongoing aimed at slowing disease progression.

Neuronal loss in ALS is mediated by inflammation and programmed cell death. Inhibition of these processes is therefore a promising therapeutic strategy. Minocycline, an antibiotic of the tetracycline group, was shown to reduce the activity of enzymes that promote inflammation and cell death. In mice, for instance, it decreases the loss of motor neurones, slows disease progression and prolongs survival.

Several studies are ongoing to assess the putative neuroprotective effect of minocycline in humans. This article reports the results of a clinical trial aimed to test the efficacy of minocycline for treating ALS. The study was designed as a multicentre, placebo-controlled phase III trial involving 412 patients, who received either placebo or minocycline in increasing doses of up to 400 mg/day for 9 months. The primary outcome measure was determined using the revised ALS functional rating scale (ALSFRS-R assesses the level of functional impairment in performing daily tasks). Secondary outcome measures were forced vital capacity (FVC measures the total amount of air that you can blow out after full inspiration), manual muscle testing (MMT assesses muscle strength), quality of life, safety and survival.



In this study, minocycline failed to provide any benefit for ALS patients, since the ALSFRS-R score worsened even faster in the minocycline group than in the placebo group. Patients on minocycline also recorded faster, though statistically non-significant declines in FVC and MMT scores. Quality of life did not differ between the treatment groups. Safety assessments yielded a similar frequency of serious adverse events in both groups. In contrast, non-serious gastrointestinal and neurological adverse events were more common in the minocycline group. Most alarming, the minocycline group showed a higher mortality rate than the placebo group. Taken together, these data provide evidence for a harmful effect of minocycline on ALS patients, which was not predicted in laboratory and animal studies. This finding may have implications for trials in patients with other neurodegenerative diseases.

A few pilot studies were performed in small groups of HD patients aimed to assess the safety and tolerability of minocycline in this patient group. Minocycline was well tolerated and no serious adverse events were reported. Importantly, the drug was shown to be effective in stabilising motor and neuropsychological functions in one study. Nonetheless, the small study populations do not permit an extrapolation of these results.

Taking into account the negative findings obtained from some animal studies and especially the harmful effects reported from the ALS clinical trial, caution should be exercised regarding the use of minocycline for treating HD as long as its efficacy and safety have not been undoubtedly established in long-term placebo-controlled trials.

● *Cho et al., The Journal of Clinical Investigation, Vol. 117, No. 10, October 2007*
By Diana Raffelsbauer

Induction of **neostriatal neurogenesis slows disease progression** in a transgenic murine model of Huntington disease

The mutant Huntingtin protein exerts a neurotoxic effect which causes degeneration of certain neurones (nerve cells). The most severely affected are the medium spiny neurones (MSNs) of the striatum. The result is a dramatic atrophy of the striatum, which is one of the hallmarks of HD. Hence, one possible therapeutic approach would be to induce regeneration of the striatum starting from stem cells, a process called 'neostriatal neurogenesis'.

In adult humans, neural stem cells can be induced to differentiate and survive as neurones by a protein called brain-derived neurotrophic factor (BDNF). However, most cells generated either die or differentiate as glia (non-neuronal cells that provide support for neurones). The authors of this interesting publication raised the question whether it could be possible to enhance neuronal production by suppressing differentiation into glial cells. One candidate drug was identified as Noggin.

Noggin suppressed the genesis of glial cells, thus expanding the pool of stem cells responsive to neuronal induction by BDNF. In normal adult rats, the overexpression of Noggin and BDNF yielded a substantial increase in the number of neurones in the striatum, most of them MSNs. The newly generated MSNs expressed proteins which are typical for GABA (an inhibitory neurotransmitter) producing neurones, a characteristic feature of MSNs. Moreover, the BDNF-induced neurones extended axons to their usual target, the globus pallidus. The globus pallidus is a structure of the brain involved in the regulation of movements at a subconscious level. It is divided into external and internal globus pallidus. Equal numbers of both types of neurones were detected: the ones with projections to the external globus pallidus and the ones to the internal globus pallidus. This is important because both pathways are essential for initiating and controlling voluntary movements and preventing involuntary movements.

One possible therapeutic approach would be to induce regeneration of the striatum starting from stem cells, a process called 'neostriatal neurogenesis'

When tested in HD transgenic mice expressing the mutant Huntington gene with 145 CAG repeats, this strategy yielded similar results as those observed in healthy rats. Importantly, treatment with BDNF and Noggin relieved, at least partially, the HD phenotype in the mouse model. Treated mice showed a delay in worsening of movement symptoms with a substantial improvement of physical performance and motor activity relative to untreated control mice. Moreover, they survived significantly longer than did untreated mice. BDNF treatment alone, which provides neurotrophic support but only a limited induction of neuronal cell generation, failed to confer any benefit. The improvements on physical performance and survival induced by BDNF and Noggin could be blocked by Ara-C (an inhibitor of cell division). These findings provide evidence that the benefits of the treatment were due to the generation of new neurones (neurogenesis), rather than to any neuroprotective effect exerted by BDNF alone. The results presented by Cho and colleagues suggest a putative disease-modifying therapy to replace neuronal cell death in the striatum of HD patients.

2008 Calendar

JANUARY

Jan 17-19 . . . . . .4th Human and Medical Genetics, Lille, France
http://www.assises-genetique.org/

Jan 25-27 . . . . . .International Brain Conference at UCF, Orlando, USA

FEBRUARY

Feb 4-7 . . . . . .3rd Annual CHDI, Inc. HD Therapeutics Conference, Palm Springs, USA
www.chdi-inc.org

APRIL

Apr 12-19 . . . . . .American Academy of Neurology (AAN), Chicago, USA
http://www.aan.com/go/am

Apr 23-26 . . . . . .Spanish Society of Neurology (SEN), Las Palmas de Gran Canaria, Spain
http://www.neurolaspalmas2008.es/

MAY

May 31 - Jun 3 . . . .European Society of Human Genetics, Barcelona, Spain
http://www.eshg.org/eshg2008

JUNE

Jun 7-11 . . . . . .European Neurological Society (ENS), Nice, France
http://www.akm.ch/ens2008/

Jun 22-26 . . . . . .Movement Disorder Society (MDS), Chicago, USA
International Congress of PD and Movement Disorders
http://www.movementdisorders.org/congress/congress08/

Jun 27-Jul 1 . . . . . .International Special Neurochemistry (ISN) Conference, Beijing, China
International Meeting for Brain Energy Metabolism “Neurodegeneration and Regeneration”
http://www.isnbeijing2008.org/

Jun 28 . . . . . .Austrian Huntington Association Congress, Graz, Austria
http://www.huntington.at

JULY

Jul 12-16 . . . . . .Forum of European Neuroscience (FENS), Geneva, Switzerland
http://fens2008.neurosciences.asso.fr/

AUGUST

Aug 8-11 . . . . . .HDF Conference (CAGn) Cambridge, MA, USA
http://www.hdfoundation.org

Aug 23-26 . . . . . .European Federation of Neurological Societies (EFNS), Madrid, Spain
http://www.kenes.com/efns/

Aug 30-Sep 3 . . . . .European College of Neuropsychopharmacology (ECNP), Barcelona, Spain
http://www.ecnp.eu/emc.asp?pageId=963

SEPTEMBER

Sep 5-8 . . . . . .5th Annual Plenary Meeting of the European Huntington’s Disease Network (EHDN), in conjunction with the 12th bi-annual meeting of the European Huntington Association (EHA), Lisbon, Portugal.
http://www.euro-hd.net/html/network/events

Sep 21-24 . . . . . .American Neurological Association (ANA), Salt Lake City, USA
http://www.aneuroa.org/index.php?submenu=AnnualMeeting&src=gendocs&link=FutureMeetings

OCTOBER

Oct 3-5 . . . . . .Deutsche Huntington Hilfe e.V. (DHH), Annual Conference, Duderstadt, Germany
http://www.huntington-hilfe.de

NOVEMBER

Nov 11-15 . . . . . .American Society of Human Genetics (ASHG), Philadelphia, PA, USA
http://www.ashg.org/genetics/ashg/menu-annmeet.shtml

Nov 12-14 . . . . . .HSG Education and Training Program and Annual Meeting, Tradewins Island Resort, St. Pete Beach, Florida, USA

Nov 15 . . . . . .HD Clinical Research Symposium, St. Pete Beach, Florida, USA

Nov 15-19 . . . . . .Society for Neuroscience, Washington, DC, USA
http://www.sfn.org/index.cfm?pagename=annualMeeting_futureandpast&section=annualMeeting

Please send us your comments and suggestions: newsletter@euro-hd.net