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EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Ethan Signer in Palm Springs 2016

HD Therapeutics 2016: huntingtin back in the spotlight

Michael Orth, Central Coordination

The 11th Annual HD Therapeutics Conference saw a renewed focus on huntingtin as a key player in HD pathogenesis. The researchers who gathered in Palm Springs, USA, from 22 to 25 February presented a raft of insights into what the still mysterious protein looks like, and what it does.

Delegates paid hommage to the common sense of Ethan Signer, who recently stood down as scientific advisor to CHDI. He has long reminded that organisation, along with others interested in HD, that the disease is caused by a known mutation that gives rise to a mutated protein, hence that protein must matter. The first safety and tolerability trial in man of a huntingtin-lowering therapy, IONIS-HTT$_{Rx}$ (*http://clinicaltrials.gov*) is the realisation of that rationale. However, huntingtin interacts with other important biological entities in bewilderingly complex ways, so revisiting the basics of HD pathogenesis may help provide a clearer picture of how best to tackle the disease.

Several speakers presented new findings as to what is happening in HD pathogenesis at the genetic level. Steve Horvath (University of California, Los Angeles) showed data from studies of post-mortem human brain tissue, suggesting that in HD, the internal or epigenetic clocks of certain brain areas may run faster than in healthy controls. Cells in those areas may therefore age faster. One mechanism underlying this effect could

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relate to the instability of the CAG expansion in the gene that encodes huntingtin. As a result of that instability, said Vanessa Wheeler (Massachusetts General Hospital (MGH)), it is possible that the CAG repeat number is higher in those brain regions than in other tissues such as blood.

Huntingtin is known to be a large protein, but we know little about its actual structure. Ralf Langen (University of Southern California) presented new insights into how the protein misfolds, while Hilal Lashuel (École Polytechnique Fédérale de Lausanne) and Ihn Sik Seong (MGH) described their use of sophisticated methods to visualise the protein in 3D. Huntingtin, it turns out, bears a surprising resemblance to a potato—and it may be just as versatile. Ali Brivanlou (Rockefeller University) showed stunning data indicating that human embyonic stem cells that harbour the HD mutation do not organise themselves into the same patterns as control cells during development.

Some of the therapeutic approaches that lower huntingtin make use of genome editing tools. Feng Zhang (Massachusetts Institute of Technology) gave an overview of a new and exciting genome editing technique known as CRISPR-Cas, which is essentially a pair of impressively precise genetic scissors invented by bacteria. Using CRISPR-Cas, he said, researchers will potentially be able to explore the relationship between a gene or genes and a phenotype. It may even be useful in therapy, one day.

With or without a thorough understanding of the underlying causes of HD, there is a school of thought that holds that ridding cells of potentially toxic mutant huntingtin is likely to be good for their health. David Rubinsztein (Cambridge University) and Eric Reits (University of Amsterdam) described how two waste disposal systems in cells—autophagy and the ubiquitin proteasome pathway—could be harnessed to that end.

Novel technologies present exciting new opportunities. It remains essential, however, to ask the right questions and to apply the most appropriate measures. This is particularly true in the clinic, said Doug Langbehn (University of Iowa), where the choice of measure, and critical appraisal of the quality of different measures, really counts. In his keynote lecture, Marcus Munafò (Bristol University) emphasised the need to ground research based on new technologies in solid methodology and analysis. Only then will findings become reproducible, so that real effects can be identified and, eventually, translated into better treatments for those affected by HD.

The scientific presentations from the conference can be found here. A video postcard that outlines some of the major themes for HD families is available here.

EHDN committee elections

Voting for two important EHDN committees opens on 1 August: the EHDN's Executive Committee (EC) and Scientific and Bioethics Advisory Committee (SBAC) are both looking to recruit new members. Those elected will serve on their respective committees for four years, at which point they will rotate off. EC members may seek re-election for a second term.

The EC's role is self-explanatory. The role of the SBAC is to facilitate HD research in Europe by advising the EC and the network's membership more generally on scientific and bioethical matters. This advisory role includes, but is not limited to, making recommendations with regard to seed fund and data mining applications.

There are currently five vacant seats on each committee. David Craufurd, Ralf Reilmann, Joaquim Ferreira, Sarah Tabrizi and Bernhard Landwehrmeyer rotate off the EC this year. Chris Frost, Jennifer Thompson and Patrick Weydt stand down from the SBAC this year, while Flaviano Giorgini and Hugh Rickards will do so next year; all five need replacing.

The complete list of candidates is available here, along with their personal statements. Once voting opens, members will be able to vote via the same link. Each regular member of the EHDN has five votes per committee. Voting will remain open until 16 September—the first day of the EHDN2016 plenary meeting—and the results will be announced the following day, 17 September, at the EHDN business meeting.

The EHDN encourages its members to vote in these important elections.

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Dina De Sousa

Patient representative joins the SBAC

Dina De Sousa has joined the SBAC as a patient representative. In March 2013, this newsletter featured an article about Edinburgh-based Dina and her husband Paul's quest to contribute to the search for therapies for HD. Dina, who tested positive for the HD mutation in 2008, is still asymptomatic. A scientist herself, she works as a research assistant in an epigenetics lab, and her way of coping with her status is to understand as much as she can about the disease. "More information makes me feel more in control," she says.

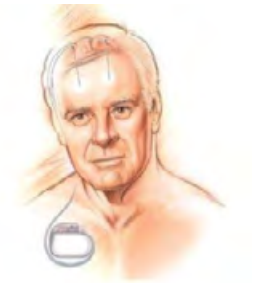
She told this newsletter: "Ever since finding out about the EHDN and going to my first plenary—in Prague in 2010—I have been amazed at what the network accomplishes for this rare disease. Going to the meetings gives me a sense of hope. For a few years that was the full extent of my involvement, but recently I have decided that there is more I can do as an HD advocate. There is a lot of great science going on into HD, but I know that most scientists have a limited understanding of the complexity of the disease as it plays out day to day, and many have little or no contact with patients. I am excited to be getting involved, and to be bringing a patient's perspective to the SBAC."

Update: Clinical trials

Jenny Townhill and Tim McLean, Central Coordination

In this edition we shine a light on an investigator-initiated trial of deep brain stimulation (DBS) for HD that is sponsored by the University of Düsseldorf in Germany, and that the EHDN endorsed in 2013.

HD-DBS, as the trial is called, springs from accumulating evidence that DBS is an effective treatment for the symptoms of movement disorders other than HD. Only a few case reports exist of DBS as applied to HD, however, so between 2009 and 2012, Jan Vesper of the University of Düsseldorf conducted a pilot study which showed that DBS of the globus pallidum significantly alleviated chorea in HD, and improved the Unified Huntington's Disease Rating Scale-Total Motor Score (UHDRS-TMS). The goal of the current trial, which is led by Vesper and his co-principal investigator Alfons Schnitzler of the same institution, is to reproduce those findings in a larger group of patients (50), and to demonstrate the short- and long-term safety and efficacy of pallidal DBS in HD.



Deep brain stimulation (DBS) of the globus pallidus: implantation of electrodes and stimulator.

Specifically, HD-DBS will investigate the potential impact of DBS on quality of life (QOL) and motor symptoms. The primary endpoint is the difference in UHDRS-TMS scores at baseline and 12 weeks following surgery to implant the electrodes. UHDRS scores and potential side effects will be reviewed for up to a year post-operatively. Motor score assessment, quantitative motor measurements, cognitive and psychiatric evaluations and QOL questionnaires will be conducted or applied at 12 weeks and six months post-surgery.

HD-DBS is currently recruiting at six sites in Germany and is in set-up at Lübeck in Germany, Berne in Switzerland, Innsbruck in Austria and Amiens/Lille in France. To be eligible for the trial patients must be over 18, be able to give their own consent, and have significant chorea despite receiving the best available medical treatment.

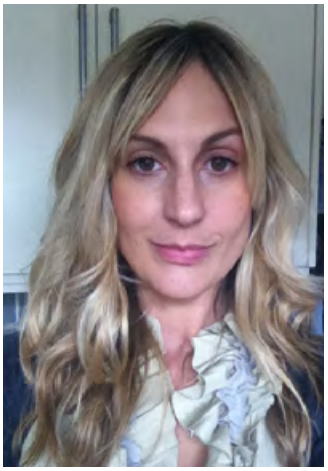


Photo: ARTIFOX, Gabriele Stautner

If you are a clinician and have patients who might be eligible to participate in the trial, please contact EHDN LanCo Pauline Kleger: pauline.kleger@euro-hd.net

Amaryllis: This trial of a PDE10 inhibitor sponsored by Pfizer stopped recruiting in the spring of this year, having reached its target number of patients. The last patient is due to complete treatment this coming autumn, and results are expected before the end of the year. The study continues in the form of a 12-month, open-label extension in which all patients receive the drug.

Pride-HD: This phase 2 dose-finding and safety study of pridopidine sponsored by Teva Pharmaceuticals continues, with patients moving across from the core study to the open-label extension trial, **Open Pride**. Database cleaning is underway in preparation for analysis of the final Pride-HD data, with results due to be presented at the EHDN2016 plenary in September.

LEGATO-HD: Following a protocol amendment to remove the highest dose condition and to increase safety monitoring, recruitment to this Teva-sponsored, phase 2 safety and efficacy trial of laquinimod continues and is likely to do so into 2017.

IONIS: Recruitment is proceeding according to plan to this phase 1/2a trial of the antisense drug IONIS HTT_{Rx}.

For more information about these clinical trials, please visit: http://clinicaltrials.gov

Preparations for the HD Clinical Trial Site Registration scheme are ongoing ahead of its projected launch in the autumn.

Update: Enroll-HD

Selene Capodarca, Global Project Manager, Enroll-HD

On 8 April, Enroll-HD recruited its 10,000th participant. This important milestone was reached in less than four years from the recruitment of the study's first participant, and was achieved thanks to the hard work of site personnel, EHDN and CHDI staff, the dedicated IT team and above all, the study's participants.

As of 30 May 2016, a total of 10,678 participants had been enrolled at 136 sites in 14 countries. Europe continues to contribute strongly to the study and is now the highest recruiting region, having provided 5,760 participants. The George Huntington Institute, Münster, Germany is the study's top recruiting site, having enrolled 454 participants to date.

The recruitment rate is expected to increase as more sites transition from Registry to Enroll-HD, and new sites are activated. Eventually, 135 European sites in 17 countries are expected to join the study—120 that were involved in Registry, and 15 new sites. More than half of these have already been activated and are now recruiting.

Poland, Denmark and the UK have already completed the transition from Registry to Enroll-HD. Germany and the Netherlands are expected to complete transition by the third quarter of 2016, while transition will continue into the first quarter of 2017 for Italian and Spanish sites. Switzerland, Austria and Belgium are expected to enter transition before the end of 2016, and France, the Czech Republic and Portugal are expected to activate their first sites in the first quarter of 2017. Ethical review board submission for the remaining countries (Sweden, Norway and Russia) is planned for the last quarter of 2016, in preparation for transition of the first sites in those countries.

The second Enroll-HD periodic dataset was made public in December 2015. Data from 4,146 participants were included in the release and are now available to researchers through the Enroll-HD website. A third data release is planned for December 2016 and will include Registry data. Since the first data release in February 2015, a growing number of researchers around the world have applied for access to the data. As of 30 May 2016, 83 such requests had been submitted, of which 69 were approved by CHDI. 54 ongoing research projects, covering a wide variety of topics, are using data from Enroll-HD. Descriptions of them can be found here.

Two platform studies—that is, studies that make use of the Enroll-HD network and database, or "platform"—are ongoing (see EHDN newsletter March 2016). One of these, HDClarity, is expected to enroll its first participant this summer. The HDClarity database, which is integrated into the Enroll-HD electronic data capture database, is now live.

Roundup: funding news

Fionnuala Margreiter, Grant Manager

News

The 8th European Conference on Rare Diseases & Orphan Products (ECRD 2016) took place in Edinburgh in May. The event was well-attended and EHDN was represented by Tim McLean, Clinical Operations Manager, who was accompanied by patient advocate Dina De Sousa (see page 3). Both took part in a panel discussion on "patient engagement throughout the life cycles of medicines", in which the immense value to HD research of patient participation in the observational studies Registry and Enroll-HD was highlighted, as was that of patients' early involvement in the review of study protocols and patient-facing documents through patient and public involvement (PPI) groups. Industry representatives pointed out, however, that they are often not able to follow the recommendations of PPI groups due to regulatory inflexibility. They called for regulators to engage more with patients too, to help solve this problem.

EHDN was involved in drafting an application for the setting up of a new European Reference Network (ERN) on rare neurological diseases. The idea behind these networks is to bring together Europe's top specialists to tackle complex or rare medical conditions that require highly specialised healthcare and a concentration of knowledge and resources. If the application is successful, the project is likely to get underway in January 2017.

Follow me on Twitter **@EHDN_GRANTM** for the latest news on EU funding and events and policy developments in the domain of rare diseases.

Funding opportunities

Having trouble getting a project funded? If you have a high-quality, well-developed project idea, consider applying for an Individual Fellowship from the EU's Horizon 2020 programme, before the deadline of 14 September 2016. These are offered to the most promising researchers of any nationality, to support employment in the academic or non-academic sectors, in EU member states or associated countries. Application should be made jointly by the researcher and the potential employer.

Need funding to travel to an international neuroscience conference? The International Brain Research Organization is offering International Travel Grants of up to €1,500 to neuroscientists worldwide (except in the US and Canada). The aim is to foster neuroscience research, especially in less well-funded countries. The next deadline is likely to be 1 September 2016.
For other examples of ongoing funding opportunities, please consult previous editions of this newsletter.

IMPORTANT: support available to EHDN researchers!

To discuss your project idea, find out about funding calls, request assistance with your application or scope out opportunities for collaboration, please contact Fionnuala Margreiter: fionnuala.margreiter@euro-hd.net

Albert Stroh (left) and Axel Methner

Lesley Jones

Maria Björkqvist

Three new seed grants awarded

Long before neurons start to die in HD, the way they communicate with each other is perturbed. In a project that the EHDN approved for seed funding in 2014, Axel Methner and Albert Stroh of the University of Mainz in Germany are using state-of-the-art techniques—two-photon microscopy and optogenetics—to explore those network perturbations at the level of microcircuits in an HD mouse model, with a view to devising potential future therapies that work by correcting them.

In a second project approved for seed funding in 2015, Lesley Jones, Thomas Massey and Anne Rosser of Cardiff University, in collaboration with Stephen Jackson of the University of Cambridge in the UK, are investigating how cellular machinery for repairing DNA may contribute to the expansion of the CAG repeat in the *HTT* gene, potentially giving rise to HD. Their research could lead to the development of drugs that prevent that expansion.

Last but not least, seed funding goes to a project led by Maria Björkqvist of the University of Lund in Sweden, to explore the hormone ghrelin as a potential therapy for the peripheral pathology associated with HD—notably weight loss, altered metabolism and muscle atrophy—in an HD mouse model.

Seed funds are intended to support pilot studies that will eventually kickstart larger projects. The next deadline for applications is 1 November 2016. More information about the programme and how to apply can be found here.

Ignacio Muñoz-Sanjuan and Claudia Perandones during a visit to deliver food to HD families in the Maracaibo region of Venezuela.

Duty calls

Laura Spinney

Does the scientific community have a moral responsibility to help people who were crucial to its research, once that research bears fruit? In a *Nature* article published on 10 March 2016, CHDI's Vice President of Translational Biology, Ignacio Muñoz-Sanjuan, argued that it does.

Without the contribution of families in the Maracaibo region of Venezuela, where the prevalence of HD is very high, the genetic mutation that causes HD would not have been identified—or at least not so soon. Yet those families, who have been the subject of intensive research for decades and many of whom are very poor, have seen few benefits from that research. "I have seen people shunned and neglected by their relatives, sitting alone in darkened rooms, devoid of medical or social support," wrote Muñoz-Sanjuan.

He was inspired to write the article after the launch of the first clinical trial of a potential disease-modifying therapy for HD, IONIS-HTT$_{Rx}$. As he told this newsletter, "I wanted to contrast the advances being made in the field of therapeutic development for HD, with the poverty, discrimination and neglect that many people affected by HD continue to experience."

In 2012, after visiting the Maracaibo region, Muñoz-Sanjuan and Claudia Perandones, a clinical geneticist at the National Administration of Laboratories and Institutes of Health in Argentina, founded Factor H, a non-profit project that helps Latin American families affected by HD. They realised that many of the obstacles these families face could be solved with a little help from outside. In Venezuela, for example, people who take the test for the HD mutation are forced to travel to the capital, Caracas, to obtain the results, but many cannot afford to do so—and Colombians find themselves in a similar predicament. Through its fundraising activities and links with local patient organisations, Factor H provides families with clothing, food and toys. It has also organised educational meetings for families and is financing the production of audiovisual guides that inform patients and their relatives about the care available to them.

To donate to Factor H's campaign to sponsor children living in HD families in Colombia, click here.

Photo: Juliana Bronzova

Juliana at Arches National Park, Moab, Utah in 2015

Words into action

Profile of Juliana Bronzova

Juliana Bronzova wears several hats within the EHDN, but her overarching aim as a key member of its Central Coordination team is to drive implementation of the network's scientific strategy.

Tell us about your career before you came to EHDN.

I am a physician, and for many years I worked as a genetic counsellor in Bulgaria, where I come from. Later I moved to Rotterdam where I became involved in clinical epidemiology, particularly in the design of clinical trials, and in 1998 I went to work for the pharmaceutical company Solvay in the Netherlands. That was a great experience, because it allowed me to bring my clinical skills and knowledge of genetics to the development of new interventions for neurological diseases. It was challenging, because it required me to think in new ways. As a physician, you worry about the one patient who is standing in front of you; in clinical development, you worry about all the patients with that disease, and the safety and wellbeing of those taking part in your trials. You also have the excitement and novelty of research. From Solvay I came to EHDN—that was in 2012.

How did you make that jump?

By 2010 Abbott had bought Solvay's pharmaceuticals division. It was a time of change, of mergers and acquisitions, and I began to think about moving in a new direction myself. I was tempted to leave the corporate world and go into the non-profit sector—and I was drawn in particular to the idea of a research organisation whose interest was rare diseases. My thinking was that such organisations may not have the money of Big Pharma, but they still have something valuable to contribute in terms of ideas and populations.

At a conference in 2011 I got chatting with Joaquim Ferreira, EHDN's then scientific director. That was the first time I heard about the network, and when I did some more research into it, I realised that it was exactly what I was looking for.

What was it about EHDN that attracted you in particular?

First and foremost, the community it represented. It was so united. That is something really rare, even in the world of rare diseases! Then its strategy. The idea was to build a bridge between patients and scientists on the one side, and potential trial sponsors on the other, to facilitate clinical trials in a way that made efficient use of resources and produced meaningful outcomes. The foundations of that bridge were already in place, and it was obvious to me that the network had immense potential. When I saw the numbers involved in the observational study REGISTRY, I thought, "Wow"!

> *"No other disease community that I knew of was so motivated or so mobilised, certainly not at a global level."*

What is your exact role?

My role evolved as I saw where and how I could contribute. Currently, I oversee implementation of the scientific strategy. There are two main aspects to that.

Photo: ARTIFOX, Gabriele Stautner

Juliana and Fionnuala Margreiter at work

Photos: ARTIFOX, Gabriele Stautner

At the EHDN Plenary Meeting, Barcelona 2014

With colleagues, I coordinate bottom-up activities in the form of the working groups, which play an important role in feeding new scientific ideas to the network. From the top-down direction, I'm involved in the Clinical Trials Task Force (CTTF).

How does the CTTF implement EHDN strategy?

The CTTF currently has three mutually reinforcing goals: to improve the ability of clinical sites to perform trials, to build consensus in matters of importance to clinical development such as methodology, and to advise trial sponsors. I coordinate the task force's advisory activities. The EHDN has always offered the possibility of trial endorsement, which is when sponsors come with their final study protocol, and if the network endorses it, they obtain access to the EHDN's operational support for that trial. Since its creation in 2012, however, the CTTF has expanded that role: it encourages the sponsor to come much earlier in the process of protocol development, so that we can help them optimise it.

Tell us about some of your other activities within the network.

I am involved in some of the EHDN's exciting scientific projects—developing physical exercise as a therapeutic intervention for HD, for example. I work with the grant manager, Fionnuala Margreiter, to set up research collaborations, seek out funding opportunities, and position the EHDN within the larger EU project that is the European Reference Network for rare neurological disorders. I am involved in an initiative to empower patients and bring more of them into research, and I also work on the One

Study Team project whose goal is to integrate and align EHDN and CHDI resources with respect to clinical trials.

What do you want to see the network achieve in the next year?

As clinical trials near completion, I want to see outcomes that are informative—that give yes/no answers and teach us something. Some are close now—PEARL-HD, a CHDI-supported PET imaging study, has just been completed and the data are now being analysed, for example. From the network point of view, I want to see more projects and ideas flowing in, so that the knowledge pipeline can be accelerated, because the clock is ticking for patients. For that to happen we must have a clear direction. The scientific strategy is currently being updated, and the next version will be unveiled at the plenary meeting in September.

Photo: Juliana Bronzova

Juliana with her dog in Yundola, Bulgaria

And looking further ahead?

There is always room for improvement, and one thing we are not yet good at is marketing ourselves. Last year we presented the EHDN at the World Orphan Drug Congress and people from other disease communities were amazed by how well-organised we were. They envied us and wanted to learn from us. We can and do help those who come seeking our advice—it's our policy—but perhaps we could do even more in that direction. The new-look website, due to be launched at the plenary, will help with that. Finally, I'd like to see the HD community come together even more than it already has. It was the community that drew me to EHDN in the first place, but now it has to unite at the global level. European, Chinese and Latin American networks are already beginning to work together, so it will happen, and when it does the community's potential to have a meaningful impact on the disease will be even greater.

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Dates for your diary

Save the dates for

- EHDN2016 plenary and European Huntington Association meeting, The Hague, The Netherlands, 16-18 September 2016. Register here until 31 July.
- The Lancet Neurology Conference: Preclinical neurodegenerative disease: towards prevention and early diagnosis, London, UK, 19-21 October 2016
- World Orphan Drug Congress, Brussels, Belgium, 15-17 November 2016