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EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Photo: Laura Spinney

Cristina Sampaio

Photo: Gabriele Stautner, artifox

Juliana Bronzova

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Second mandate for the Clinical Trials Task Force

Cristina Sampaio, Chair, Clinical Trials Task Force, and Juliana Bronzova, Central Coordination

The Clinical Trials Task Force (CTTF) this year takes up its second mandate with a modified role. While continuing to act as the network's nominated advisory body for consultation on trial protocols and developing the HD clinical trials site certification process, it will now also coordinate with the leadership of the Enroll-HD platform to ensure the optimal execution of such trials going forward, as well as working towards obtaining international consensus on HD trials methodology.

The CTTF was appointed by the Executive Committee (EC) of the EHDN in 2012, to act as an interface between the network and its partners in the area of clinical trials. Those partners are mainly pharma, biotech and device companies, but also academic consortia with an interest in the clinical development of HD therapeutics. One of the CTTF's key functions is to evaluate trial protocols submitted to the EHDN for its endorsement, independently of, but in parallel with, the elected Scientific and Bioethics Advisory Committee. Both bodies provide the EC with

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Laura Spinney, Editor (Paris, France)
Gabriele Stautner Artifox Communication Design (Ulm, Germany).

The CTTF minus Juliana Bronzova, who took the picture (see here for members' names)

reports and recommendations to endorse the protocol or not, and the EC takes these into consideration in making its decision. Only endorsed protocols gain access to the network's logistical resources—resources that have proved critical to the success of clinical trials.

The CTTF also plays an important role in facilitating and improving clinical development plans for HD therapeutics. One way it does so is by offering coaching in the development of trial protocols. Through collaboration between the party proposing the protocol and CTTF experts, a draft protocol is refined until it attains a satisfactory level of conceptual clarity. Through such collaboration, those proposing the trial also learn how the EHDN can support them in terms of feasibility assessment, site selection and recruitment, as well as by providing more specialised cultural and linguistic support at sites.

The CTTF's second mandate alters and enlarges its remit significantly. The establishment of the Enroll-HD platform has meant that trials can now be supported at a global level. Enroll-HD is now fully operational in much of Europe, the US, Australia and New Zealand, as well as in parts of South America, and it is this platform that now provides the logistical infrastructure for clinical research in HD. The CTTF must therefore take a global perspective and coordinate its activity with that of Enroll-HD, while retaining the EC's trust in it as its principal advisor in the area of trial protocols.

In this second mandate, which will run until 2018, the CTTF will therefore develop activities in three main areas: facilitating clinical trials in the HD therapeutic space; developing a "certification on readiness to participate in HD clinical trials" process for sites; and organising a series of workshops and consensus conferences in collaboration with regulatory partners, with the goal of publishing international recommendations on the development of therapeutics for HD. ■

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IMPORTANT:

New calls for seed fund applications in 2016 announced

There will be two calls for the seed funds in 2016:
1 March and 1 November

What we learned in Cardiff

Noit Inbar and Angela Nuzzi

As beneficiaries of EHDN's Fellowship Exchange Programme, we feel proud to take the knowledge we have gained at Cardiff University's HD Centre in Wales, back to our own institutions: the Tel Aviv Sourasky Medical Center in Israel, and the University of Bari in Italy, respectively. We would like to thank our hosts in Cardiff, Anne Rosser and Monica Busse, who were always willing to share ideas, methods and data, and who made it possible for us to observe different aspects of research into, and treatment of, HD.

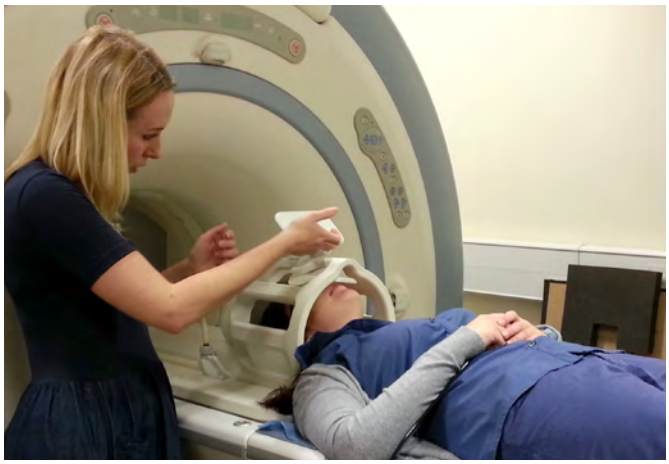
From left to right: Noit Inbar, Monica Busse, Angela Nuzzi

During our six weeks in Cardiff, we observed clinical trials, assisted with the functional, cognitive and behavioural assessments of patients, attended multidisciplinary preclinical meetings, and sat in on meetings with healthcare professionals and researchers.

The HD clinic in Cardiff is one of the top 10 enrolling sites for the Enroll-HD observational study in 2015, so we were able to observe that study process from the first presentation and obtaining of patient consent, through the gathering and discussion of data, to the long-term follow-up. We personally tried out the exercise DVD and physical activity workbook that are being tested in ENGAGE-HD, a multicentre, randomised trial of home-delivered physical activity in HD, and found them to be well-designed and user-friendly. And we learned about the effects of acute exercise on neural response in HD, which is being investigated by psychologist Jessica Steventon.

We especially enjoyed the in-depth discussions we had with members of the team, and the freedom we felt to raise questions, knowing that a network of open-minded and curious scientists and clinicians would help us to formulate answers. With physiotherapist Una Jones, for example, we tried to understand better the respiratory function of people with HD, in order to quantify their risk of aspiration. With orthodontist Hashmat Popat, we became familiar with the 3dMDface system—impressive technology for imaging and quantifying facial movements. Katy Hamana taught us much about patients' and caregivers' views on exercise, while with Susanne Clinch and Emma Yhnell we learned about cell-based treatments for HD.

Throughout the fellowship, we felt we were observing a well-organised clinic, where professionalism, multidisciplinary expertise, devoted teamwork and compassion came together. For that we have to thank Anne Rosser, Duncan McLaughlan and research nurse Rebecca Cousins, whom we joined every Wednesday at the HD clinic, and Monica Busse, who challenged us to think and rethink, to turn the impossible into exciting research projects, and to build the foundations of future collaborations. ■



Psychologist Jessica Steventon and, in the scanner, guinea pig Angela Nuzzi

New trials with old drugs—why not for HD?

Roger Barker, Cambridge Neuroscience, UK

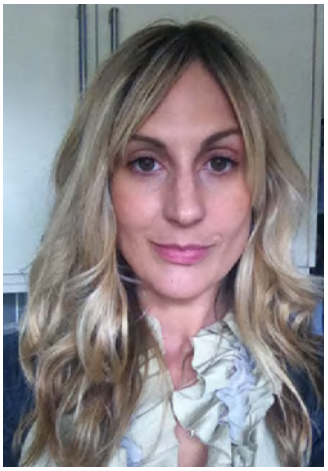
In recent years there has been a great deal of interest in so-called "linked trials"—that is, trials of drugs that are already in clinical use for one indication to see whether they may be of value in other, unrelated conditions. This is the strategy that my group adopted in completing a small trial with the anti-hypertensive drug rilmenidine, in patients with mild HD. The results are under analysis.

We undertook the feasibility and tolerability trial because of results obtained by David Rubinsztein and his team at the Cambridge Institute for Medical Research, showing that rilmenidine upregulates autophagy in animal models of HD, and thereby increases the efficiency with which mutant huntingtin is cleared from the diseased nervous system.

The concept of linked trials is not new, but recently it has been taken up by many labs seeking to screen their favourite disease assay, not only against established libraries of compounds held by pharmaceutical companies, but also against drugs already approved by the US Food and Drug Administration. Such an approach has many advantages. For example, the dose to be used and the side effect profile are known, which simplifies trial design and means that the drugs can go to trial quickly. The reduced safety profiling requirements also mean that non-specialist centres can be included in multicentre studies, which in turn means that large numbers of patients can be enrolled quickly.

There are also disadvantages. The dose used for the drug's primary indication may not be the optimal dose for attenuating the effects of mutant huntingtin, and if the latter is the higher of the two the trial will be subject to the same requirements that apply to an experimental drug—and hence no faster. Or the drug may act peripherally for its primary indication, without crossing the blood-brain barrier, and have no effect in the central nervous system. The side effect profile may be acceptable in relation to the primary indication, but not in patients with chronic neurodegenerative conditions and relatively few symptoms. Finally, some argue that the approach is unlikely to succeed in general, because if the drugs concerned had a significant clinical effect in the conditions for which they are being proposed, it would already have been reported.

Despite these drawbacks, the approach has been adopted enthusiastically by leading funding organisations in the field of Parkinson's disease (PD), such as the Cure Parkinson's Trust in the UK. As a result of the trust's success with the anti-diabetes drug exenatide, a GLP-1 agonist, it has now entered into partnership with the Van Andel Institute in Grand Rapids, Michigan, to take more trials to clinic. The original open-label trial of exenatide has been extended into a double-blind trial with the support of the Michael J Fox Foundation. New trials are being planned for anti-diabetes drugs deferipone and simvastatin, as well as for other GLP-1 agonists. In our view, linked trials represent an exciting new area of therapeutics. ■



Update: clinical trials

Jenny Townhill and Tim McLean,
Central Coordination

Significant clinical trial activity continues to take place across Europe, North America and Australia.

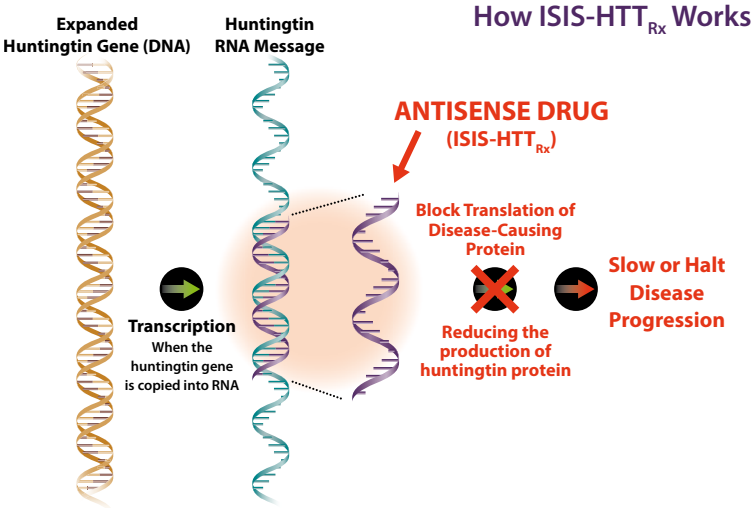
Pride-HD, the phase 2 dose-finding and safety study of pridopidine sponsored by Teva Pharmaceuticals, completed recruitment in June with 408 patients randomised. Current efforts are focused on ensuring that data queries are resolved in preparation for database lock and final data analysis in 2016.

Meanwhile, an open-label extension trial, **Open Pride**, is in the process of start-up. In an open-label study, all participants receive the study drug and there is no placebo group. All those who completed Pride–HD are eligible to participate in Open Pride, and the first patients have recently been enrolled. Open Pride is currently approved to run for 12 months, although this may change in the light of the analysis of additional safety data.

LEGATO-HD, a phase 2 safety and efficacy study of laquinimod, also sponsored by Teva, is enrolling participants from the Czech Republic, the UK, Portugal, Spain, the Netherlands, Germany, Italy, the US, Canada and Russia. Recruitment is expected to reach its target of 400 patients some time in 2016.

The Pfizer **Amaryllis** trial of a PDE10 inhibitor continues to recruit participants from Germany, Poland, the UK, Canada and the US, with a target of 260. A 12-month, open-label extension study is underway.

Isis Pharmaceuticals has initiated a phase 1/2a trial of an antisense drug, **ISIS-HTT$_{Rx}$**—the first therapy to enter clinical development that is designed to address the genetic cause of HD directly, by targeting huntingtin RNA and so reducing the production of the huntingtin protein. It is administered via lumbar puncture (intrathecal injection) and travels to the brain via the cerebrospinal fluid. Inside the brain, it binds to and destroys huntingtin messenger RNA (mRNA), resulting in decreased production of huntingtin protein. Preclinical research in animal models of HD has demonstrated that lowering huntingtin mRNA and protein levels with an antisense drug slowed disease progression, increased survival and resulted in improvements in physical symptoms that were sustained for several months.



Six sites have been activated for the University of Düsseldorf's **deep brain stimulation** trial to date, and three participants have been randomised.

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

Recruitment has now closed in two trials of exercise- and physical activity-based interventions being conducted by the Cardiff HD Physiotherapy Group, **ExeRT-HD** and **ENGAGE-HD**. The results of ExeRT-HD, which were presented at the October 2015 meeting of the Huntington Study Group in Tampa, Florida, show that performing the intervention three times a week for 12 weeks was safe and feasible, and resulted in significant improvements in cardiovascular fitness and motor function. The next step will be to conduct larger trials to explore further the potential clinical and neuroprotective benefits of exercise in HD. The results of ENGAGE-HD are expected in the first half in 2016.

For more information about ENGAGE-HD and ExeRT-HD, please visit: www.activehd.co.uk

New site certification scheme is launched

The HD Clinical Trial Site Certification scheme, an initiative of the Clinical Trials Task Force, is expected to enter a phased launch early in 2016. Its main aim is to provide sites with a transparent, clearly defined route to registering their interest and capacity to participate in HD clinical trials. Certified sites may be included in listings put forward for feasibility assessment in relation to trials that have been endorsed by the EHDN. An important requirement for site certification will be full completion and/or update of the Global Site Investigator Database (GSID), as well as of a simple online application. The scheme will be open to all European HD centres to begin with. More details about it and how to apply will be circulated ahead of the launch.

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Kathryn Bowles

Robert Lahue

Martina Zügel-Velders

Three new seed grants awarded

Kathryn Bowles, a postdoc in integrative neuroscience at the Icahn School of Medicine at Mount Sinai Hospital in New York, USA (but until recently at Cardiff University), has been awarded a seed grant for a study of the role of Smad-dependent TGFβ signalling in transcriptional dysregulation in early-stage models of HD.
Robert Lahue, a molecular geneticist at the National University of Ireland, Galway, has received a grant to probe the dual therapeutic benefits of isotype-selective HDAC inhibition in HD, while Martina Zügel-Velders, a postdoc in exercise physiology at the University of Ulm in Germany, has been awarded a grant for a feasibility study designed to establish fine needle skeletal muscle biopsy as a tool to monitor metabolic capacity at rest and during physical exercise in HD clinical trials.

Seed funds are intended to support pilot studies that will eventually kickstart larger projects. More information about the programme and how to apply can be found here.

Update: Enroll-HD

Olivia Handley, Global Project Manager, Enroll-HD

The first two platform study proposals have been approved by the Enroll-HD scientific planning committee. The first, HDClarity, involves the collection of cerebrospinal fluid at multiple sites, to facilitate therapeutic development. The second, very different, compares and evaluates the impact of choosing—or not—to have predictive testing for HD.

Platform studies make use of the Enroll-HD network and database—the "platform"—and facilitating them represents one of Enroll-HD's key aims. Since its launch in 2012, Enroll-HD has collected observational data on more than 7,000 participants. Its data repository contains prospective and systematically collected clinical research data (demography, clinical features, family history, genetic characteristics), as well as biological specimens (blood).

A proposal for a platform study comprises a description of its aims, hypotheses, background and methods, as well as operational considerations. The Enroll-HD scientific planning committee—whose 12 members have expertise in basic science, genetics and clinical research—reviews its scientific aspects, while the Enroll-HD operations committee assesses its feasibility in terms of impact on participants and sites, and integration into the Enroll-HD electronic data capture system. Between two and four further platform studies are expected to be submitted for review in the near future.

For further information, please contact EnrollHD@quintiles.com or visit www.enroll-hd.org

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James and the Giant Gene

Emma Yhnell of Cardiff University's Brain Repair Group has won first prize in the written category of the 2015 annual science communication competition run by the *The Biochemist*, the magazine of the UK's Biochemical Society. Her story, entitled "James and the Giant Gene", took HD as its theme and was published in the August edition of the magazine. You can read it in full here.

Roundup: funding news

Fionnuala Margreiter, Grant Manager

News

- **Your grant manager now has a Twitter account! Follow me @EHDN_GRANTM for the latest news on EU funding and events and policy developments in the domain of rare diseases.**

- In stage 2 of Horizon 2020's rare diseases funding call, one project scored over the threshold for consideration but not highly enough to be funded, while another scored very highly and is on the reserve list. The draft programme for Horizon 2020 (personalised medicine) in 2016-2017 is available and the final version will soon be released. Please contact me for details.

Funding opportunities

- The European Molecular Biology Organization (EMBO) awards long-term fellowships for up to two years to support postdoctoral research visits to laboratories all over the world. The next deadline for applications is **12 February 2016**. Other funding opportunities are also available (see EMBO website for details).

- The international, Bratislava-based Visegrad Fund offers small (less than €6,000) and standard (more than €6,001) grants to support a common workshop/seminar or a project. There are four annual deadlines for applications for small grants, and two for applications for standard grants.

- The Human Frontier Science Program provides research grants for teams of scientists from different countries who wish to combine their preferably multidisciplinary expertise to address questions in the life sciences that cannot be answered by individual laboratories. The next call is expected to be announced in December with a deadline in **March 2016**.

- The Rosetrees Trust in the UK supports research into all aspects of biomedical science. It provides small grants of, typically, between £5,000 and £20,000 per year for up to three years, and is mainly though not exclusively targeted at research being conducted in the UK. Applications are accepted any time; the review committee meets every two months.

- Up to CHF30,000 is available to Swiss researchers who want to organise a 2-5 day international exploratory workshop in Switzerland, with colleagues working in their field abroad. The next deadline for applications is **2 March 2016**.

- The Thyssen Foundation supports German researchers pursuing projects on molecular causes in the development of illnesses. The next deadline is **15 February 2016**.

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

North America holds its first HD youth camp

Chandler Swope, Director of Youth Services—Mid-Atlantic Region, Huntington's Disease Youth Organization

The first HD youth camp in North America was held in Newburg, Maryland between 24 and 27 August of this year. 41 young people from the United States and Canada participated in what we hope was an inaugural event.

The Huntington's Disease Youth Organization (HDYO) took the lead in organising the camp with the aim of providing support, education and fun for young people affected by HD. The participants were able to attend educational sessions and request one-on-one support, as well as enjoying recreational time. Educational topics included grief and loss, healthy living, testing, communication, relationships, support, caregiving and research, but all the sessions were linked by the theme of living positively and finding hope.

For most of the young people who attended the camp, it provided their first opportunity to meet others from HD families. That connection made all other differences fade into the background, and they supported each other with compassion and hope. They left on a high note, and many have since expressed their gratitude for the experience, which was made possible thanks to generous funding from Teva Pharmaceuticals, support from the Huntington's Disease Society of America, and private donations.

As one participant put it, "This camp has made me more comfortable with myself and the world I live in." ■

HDYO
HUNTINGTON'S DISEASE YOUTH ORGANIZATION

Matt Ellison and his wife Marianna in Iceland in 2015

Mind the gap

Profile of HDYO founder Matt Ellison

Since it was launched in 2012, the Huntington's Disease Youth Organization (HDYO) has grown exponentially. Matt Ellison, Project Coordinator, explains how it came to be such a success.

What is your personal link with HD?

My Dad had HD. He was diagnosed at the age of 40, when I was seven. I was told about HD straight away, but I didn't really understand. By the time I was 13 my Dad's symptoms were obvious, and I was having a really hard time accepting that he wasn't a normal father. We didn't talk much about HD in the family, and I didn't want to either—I was in a state of denial. I was struggling to cope with everything that was going on at school and at home.

What happened?

I left school at 13, started home schooling and became a carer for my Dad. I don't recommend dropping out of school, but in my case it gave me the space I needed to work things out—I became less angry. By 16 or 17 I had come to terms with his disease, but then my Mum started to be overwhelmed by the burden of caring for him. I didn't want him to go into a home, so I cut back my hours at work—I was a lifeguard at a local swimming pool—and devoted more time to him. When I was 19 I tested positive myself. My Dad died two years later, in 2009, and it was then—when I'd come to terms with my own result—that I started getting involved with the HD community.

Where did that lead you?

I joined forums and attended conferences, and I soon realised that there was very little support available for young people. I started thinking about that gap and how to fill it. I developed a good relationship with the Huntington's Disease Association for England and Wales. A key moment for me came in 2009 when I won a scholarship to go to the World Congress on HD in Vancouver. That was when I met young people from other countries and realised that they had experienced the same support gap.

Was support all that was missing, for young people?

No. There was also an issue around education. If you're a young person trying to find information about HD, there's a lot of serious, grim and very scientific stuff on the internet. It can terrify people, and to me it didn't seem right that this was all there was. That's when I had the idea of creating an international organisation that would provide those two things: education and support for young people.

How did you go about it?

I built up a small volunteer team, all young people, and in 2011 I left my job to devote myself to the project full-time. That meant creating content for the website, translating it into different languages, and fund-raising. In 2011 I ran 11 marathons! Our combined efforts brought in enough money to get us started, and we launched in February 2012. After that we got the support of a number of HD associations, and that enabled us to grow. We've grown pretty quickly, in fact. In the first month we had around 20,000 page views, and we were ecstatic about that. Now we get twice that in a day.

You're a youth organisation, social media is obviously an important tool for you.

We have 8,500 social media followers. Over half the young people who attended our North American summer camp last month came to us via social media.

What does HDYO consist of today?

170 volunteers, most of whom are young people from HD families all over the world. We answer contacts and requests for support in 10 languages from, so far this year, 61 countries. Our project funding still comes

from the HD associations, but we now also get grant funding for two full-time staff, one of whom is the project coordinator—me. The time came when I was working 60-70 hours a week and I couldn't sustain the workload on a volunteer basis. The other staff role is our North American youth worker, Chandler Swope, who is based in Washington DC.

Are you hopeful that a cure will be found in your lifetime?

I'm 27 and I've tested positive, so I watch progress closely, but I never rely on it to cope. I've accepted to some extent that HD could take my life, but I also see what's happening now as very exciting. In 10 or 20 years' time we could actually have effective treatments—if not in time for me, then in time for younger generations.

> *"A lot of young people don't realise how much money is being pumped into HD research, or that clinical trials are even going on—and yet that knowledge can change perspectives."*

Matt and Marianna's wedding day, May 2014

As an organisation, we're about feeding them the *right* kind of information, so we have researchers come and talk to them at the youth camps. I take part in research too, and I encourage young people to do the same. For me, realistic optimism is the way forward. ■

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wikipedia/commons/e/e4/Arthurs_seat_edinburgh.jpg

Dates for your diary

Save the dates for

- 11th Annual HD Therapeutics Conference, Palm Springs, USA, 22-25 February 2016
- 3rd International Congress on Research of Rare and Orphan Diseases—RE(ACT), Barcelona, Spain, 9-12 March 2016
- 8th European Conference on Rare Diseases & Orphan Products—ECRD, Edinburgh, UK, 26-28 May 2016
- 10th Federation of European Neuroscience Societies (FENS) Forum of Neuroscience, Copenhagen, Denmark, 2-6 July 2016
- 9th EHDN plenary meeting, The Hague, The Netherlands, 16-18 September 2016. Online registration will open in March 2016.