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EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Have an idea for a project that could be funded by an EHDN seed fund?

The next deadline for applications is 1 July 2015. Find out more on page 2.

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www.euro-hd.net

The next 10 years

Jean-Marc Burgunder, Chair, Executive Committee

In 10 years, EHDN has turned itself into an indispensable player in European HD research. With its observational study Registry, it created a platform of expertise, data and biological materials that scientists all over Europe could draw on to fuel their research. Registry's successor, Enroll-HD, will expand that reach beyond Europe to a large part of the world. EHDN must now reposition itself to place Enroll-HD at the core of its mission, to support that study as far as possible and bring to it strong and enthusiastic European participation.

In the immediate future, the network's priorities will be to improve its readiness for clinical trials in Europe in terms of logistics and training, and to make sure that those seeking to use the Enroll-HD platform get optimal performance out of it. In return, we hope to harness those users' experiences, to feed them back into the platform and so refine and improve it. The European Huntington's Disease Association (EHA) will be an invaluable

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partner in this, because no progress is possible without the participation of HD patients, families and carers. The EHA's role complements ours, as it promotes understanding of HD and HD research among those affected by the disease, inspiring them to get involved.

EHDN has grown from nothing in a decade, and its structure must evolve to reflect that. The Executive Committee must now assume a more strategic and less operational role, looking to the future and pursuing a clear vision. That vision will be laid out in the next scientific strategic plan, the roadmap that we are currently preparing and that will guide us over the next four years. As the network continues to grow, we will continue to seek out new opportunities for collaboration with potential partners including the Huntington Study Group, the Chinese HD Network, patient advocacy organisations and the pharmaceutical industry.

We thank our members, partners and sponsors for the support they have given us over the last 10 years—particularly CHDI, without which nothing would have been possible—and we look forward to working with them in the next ten.

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Update: Seed funds awarded

Michael Orth,
Central Coordination

HD is caused by a mutation in the Huntingtin gene (*HTT*) which in turn leads to changes in the huntingtin protein that are thought to be important for how the disease develops. Translating genes into proteins involves a number of steps allowing variability to creep in, probably in response to the cell's needs.

This may also be true for mutated genes, a possibility that will be explored in people who carry the HD mutation by **Alis Hughes** of Cardiff University, with the support of a seed fund.

Even in the normal range, the number of CAG repeats in the *HTT* gene can vary, leading to variation in the huntingtin protein that nevertheless does not cause HD.

Ahmad Aziz of Leiden University has been awarded a seed fund to investigate whether that variation is important in other ways, for example in influencing thinking or mental health.

The translation of genes to proteins must be carefully regulated. Specialised RNA fragments called microRNAs do this job at an intermediate step between the gene and protein—the RNA level.

Lis Hasholt of the University of Copenhagen will use her seed fund to explore whether microRNAs could confer unexpected benefits in HD, such as protection against cancer.

Another way of regulating how much protein is made is by tagging genes with molecular "notes" called epigenetic markers. Compounds such as histone deacetylase (HDAC) inhibitors, that alter these markers, have been recognised recently as representing a promising potential therapeutic approach to diseases including HD, but first more needs to be known about the epigenetic markers they modify.

Karine Merienne of Strasbourg University will use her seed fund to study them in HD brains.

Seed funds are intended to support pilot studies that will eventually kickstart larger projects, and the application deadline for the next call is **1 July 2015**. More information about the programme and how to apply can be found here.

Update: Clinical and other trials

Jenny Townhill, Central Coordination

2015 will be an exciting year for clinical trials in HD, with more activity than ever before. The following is a summary of those that have been endorsed by EHDN to date.

Two trials sponsored by Teva Pharmaceuticals, Pride-HD and LEGATO-HD, are actively recruiting. **Pride-HD*** is a phase 2 dose-finding and safety study of pridopidine that was covered in the July 2014 edition of this newsletter. Recruitment is expected to be completed in 2015 and all sites are focused on meeting the enrollment deadline.

LEGATO-HD is a phase 2 safety and efficacy study of laquinimod, a compound that, it has been suggested, has an anti-inflammatory effect in the central nervous system. 400 HD patients are expected to be recruited at around 35 study sites in the US, Canada and Europe. The primary objective of the trial is to assess the efficacy of laquinimod using the total motor score of the Unified Huntington's Disease Rating Scale, or UHDRS-TMS (baseline versus 12 months). Additional endpoints are MRI measurements of caudate volume and cognitive, psychiatric and behavioural assessments.

The Pfizer **Amaryllis** trial is a phase 2 safety and efficacy study of a compound called PF-02545920 for the treatment of motor impairment in HD. Approximately 260 subjects are due to be recruited in the European Union (EU), US and Canada. The primary endpoint is the UHDRS-TMS (baseline versus 26 weeks). Secondary endpoints include the total maximum chorea (TMC) score of the UHDRS (baseline versus 13 and 26 weeks) and the clinical global impression-improvement score (baseline versus 13 and 26 weeks). Recruitment is underway and is expected to be completed in 2015.

A multi-centre study examining the efficacy of **deep brain stimulation** for the treatment of severe chorea is due to start recruiting in the first quarter of 2015, in five sites in the UK, Germany, Switzerland and France. A stimulator will be placed in the globus pallidus of 50 patients, who will be followed up for six months. The primary outcome measure will be the UHDRS-TMS (baseline versus 12 weeks). The study is designed to follow up on encouraging results from a previous pilot conducted in Germany.

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

In addition to these clinical trials, the Cardiff HD Physiotherapy Group is conducting two trials of exercise- and physical activity-based interventions:

ENGAGE-HD is an exploratory, randomised controlled trial of a physical activity-based intervention for HD patients, run across eight UK sites. The intervention involves six home visits over 14 weeks by an activity coach, who works with participants to design a programme of physical activity that includes progressive walking and structured home exercise. A control arm will receive time-matched social visits. 26 participants have been recruited to date, and recruitment will continue until July 2015.

*ehdn-newsletter-jul2014.pdf, Page 4

ExeRT-HD is a multi-site, single-blind, exploratory phase 2 randomised trial to assess feasibility, adherence and safety of an aerobic (stationary bicycle), strength and flexibility exercise-based intervention for people with early-to-mid stage HD. There are three participating sites in the UK and one each in the Netherlands, Germany and Norway. The intervention is delivered in the participant's home or at a community gym over 12 weeks, with 20 of the 36 sessions being supervised by a personal trainer and the remainder conducted independently or with the support of a carer or family member. 31 participants have been recruited to date, and recruitment will continue until the end of March 2015.

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

Finally, a CHDI-sponsored **positron emission tomography (PET)** study of levels of the enzyme phosphodiesterase 10A in the brains of premanifest, stage 1 and stage 2 HD patients, and age- and gender-matched healthy controls, is ongoing. It has an adaptive, cross-sectional design, and recruits patients in cohorts (based initially on disease stage), with the results from each cohort determining the composition of the next. The study aims to recruit 45 HD patients and 45 controls in total, and should be completed by the end of 2015. To date, 29 patients and 26 controls have been recruited from six sites in Sweden, Denmark, Norway and the Netherlands. A second, longitudinal study of all patients recruited into the main study is about to start set-up. It will involve follow-up PET scans at 18-24 months after the initial scan.

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Send us your data mining proposals!

Patrick Weydt,
Chair, Scientific and Bioethics Advisory Committee

Through data mining projects EHDN's Registry platform offers its members the possibility to access and analyse a wealth of clinical data and biomaterials for HD research, but researchers' participation is essential to fully realise the platform's potential and maximise benefits for HD families. Formal requirements for a data mining application are kept to a minimum and monthly deadlines ensure smooth and rapid processing. Both the Scientific and Bioethics Advisory Committe and the Executive Committee review applications in a timely fashion to ensure that ethical and scientific standards are maintained without impairing the proposal's momentum. EHDN takes great pride in the high success rate of such proposals and would like to encourage members to make more use of this unique resource. Details about the application process are available online, and EHDN's Central Coordination team, especially Christine Capper-Loup (email: christine.capper-loup@euro-hd.net) and Michael Orth (email: michael.orth@uni-ulm.de), are available to guide members to a successful outcome.

Alert: Fellowship Exchange Programme

EUROPEAN HUNTINGTON'S DISEASE NETWORK

The deadline for applications for the next round of the Fellowship Exchange Programme is **30 March 2015**. The programme is aimed at young neurologists, psychiatrists, psychologists, physiotherapists and clinical geneticists working in clinical practice and research in HD. More information and an application form can be found here.

NeurOmics – applying cutting edge technologies to HD

Cathy Turner, Communication and Dissemination Officer, NeurOmics

The exomes of 1,100 undiagnosed patients are currently being scrutinised as part of a new, EU-funded initiative called NeurOmics that is designed to improve understanding of neuromuscular and neurodegenerative diseases. Samples taken from patients who already have a diagnosis, including HD, are also undergoing RNA analysis as part of the project.

The goal of NeurOmics is to discover new disease-causing and disease-modifying genes in these disease categories. The hope is that this will lead to the development of new therapies, improved phenotyping of patients, an increase in the number of patient cohorts, expansion of inclusion criteria for clinical trials, and the development of new biomarkers for clinical application.

The NeurOmics consortium brings together leading European research groups in 10 rare neuromuscular and neurodegenerative diseases, with innovative industry partners, to apply the most sophisticated genomics, transcriptomics, proteomics and metabolomics technologies to pressing research questions.

The overall coordinator of the project is Olaf Riess of the University of Tübingen; Sarah Tabrizi of University College London leads the HD component. Her team is working with Willeke van Roon-Mom's team at Leiden University on the identification of transcriptomic (RNA-level) biomarkers of HD stage. Quantitative, peripheral biomarkers of this kind will be very valuable in the ongoing development of disease-modifying therapies. 140 TRACK-HD subjects and 150 subjects from Leiden have undergone transcriptome sequencing and analysis of the data has just got underway.

Much of the variability in HD onset and progression is thought to be related to age and CAG repeat number. However, studies suggest that some of the remaining variability is accounted for by other genes, and the identification of these could provide valuable insights into the pathogenic mechanism of HD at the cellular level. With her clinical fellow Davina Hensman and collaborators including Lesley Jones, Peter Holmans and Douglas Langbehn, Tabrizi aims to identify such genetic modifiers. 48 TRACK-HD subjects have undergone whole exome sequencing, and another 191 have undergone SNP genotyping. The analysis and integration of these datasets, including their interrogation for variants that have been linked to HD progression or onset, is underway.

Sarah Tabrizi

Willeke van Roon-Mom

In a third strand of research, Tabrizi and student James Miller are investigating the mechanisms behind innate immune dysfunction in HD. Myeloid cells are known to produce significantly higher levels of pro-inflammatory cytokines when stimulated with lipopolysaccharide, in HD patients as compared to controls, and 150 samples taken from patients and controls have been sent for RNA sequence analysis at deCODE genetics.

Meanwhile, van Roon-Mom's team is looking for longitudinal RNA changes in a group of patients and controls from the outpatient clinic in Leiden. Four years ago, they analysed patterns of gene expression in samples taken from these patients, and proposed a panel of genes that could serve as an HD biomarker in peripheral blood. Now, by analysing changes in those gene expression patterns in the same individuals, they hope to gain insights into HD progression and validate the biomarkers they identified previously.

van Roon-Mom is also participating in the development of an exon-skipping therapy for HD. This makes use of antisense oligonucleotides to remove the exons that code for important proteolytic cleavage sites in the huntingtin protein, making it less toxic. The approach was developed in cultured cells and is now being tested in an HD animal model.

For more information about NeurOmics, please visit: http://rd-neuromics.eu

Update: Enroll-HD

Olivia Handley, Global Project Manager, Enroll-HD

The overarching goal of Enroll-HD is to accelerate the progress of research that will lead to new therapies for HD. Enroll-HD recruited its first participant on 25 July 2012. Two and a half years on, more than 4,000 participants have been recruited from four global regions.

The first Enroll-HD dataset was made available to the public in February, after six months of preparation. Data included in the release had to meet certain criteria. For example, level of monitoring, de-identification and quality control checks had to be completed before data could be included. Every effort was taken to minimise the risk of participant identification. For this reason, certain data were either aggregated (for example, very high CAG repeat numbers), transformed (for example, date of birth changed to age in years) or removed. The HDID, a unique identifier used to protect the participant's identity and cross-reference with clinical data from other HD studies, is never distributed to the public; all data are recoded with an additional unique research ID specifically for the purposes of the release.

Data from approximately 1,500 participants were included in this first release, which can be accessed via the Enroll-HD website. Any interested researcher may request the dataset, but before being granted access they must complete the requisite data use agreement. They will also be asked to provide a brief description (50-200 words) of their proposed project, which will be posted automatically on the Enroll-HD website along with their name and affiliation.

Enroll-HD will continue to release datasets periodically, at least twice a year. But researchers may also submit special requests for data to the Enroll-HD scientific publication review committee, for review and approval. Work is ongoing to implement the online Enroll-HD biosamples catalogue, which will hopefully be available in 2016.

Registry to Enroll-HD transition at a glance

Enroll-HD sites	Number of sites	Number of participants
Total active sites	112	4,623
Active European sites	*49*	*1,726*
European sites in transition	19	–
European sites still to transition	*74*	–

Enroll-HD European contracts	Number of sites
Total European contracts issued to sites	128
Fully executed	*77*

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

Roundup: funding news

Fionnuala Margreiter, Grant Manager

News

- Three HD-related projects were submitted to the rare diseases funding call (stage 1) under Horizon 2020 in late 2014. The call was highly oversubscribed with 421 applications, of which only around 10 will be funded following evaluation of stage 2. One project involving EHDN will now go forward to the second stage. The other two were also highly rated, and alternative sources of funding are being sought for them.

- EHDN is an associate partner in a Marie Curie initial training network project submitted by a Swedish coordinator in January 2015.

- A starting grant proposal related to HD has been submitted to the European Research Council, with EHDN's support.

- If you have thoughts on whether EHDN should be involved in a new initiative called European Reference Networks, please send them to Fionnuala Margreiter at the address above. Calls for network designation will open at the end of 2015.

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

Funding opportunities

- The main funding opportunity for HD research in 2015 is the EU's Joint Programme for Neurodegenerative Disease Research which has opened its call for pre-proposals aimed at supporting transnational research collaborations in three priority areas: longitudinal cohort approaches, advanced experimental models, and risk and protective factors. This is a two-step call with an application deadline for the first step of **10 March 2015**. A minimum of three partners (countries) are required, and five pages of text in the application.

- The international Human Frontier Science Programme supports basic frontier research on the complex mechanisms of living organisms. Research is funded at all levels of biological complexity from biomolecules to the interactions between organisms. The next deadline for applications is **19 March 2015**.

- Up to CHF30,000 is available to Swiss researchers who want to organise an international exploratory workshop with others working in their field abroad. The next deadline for applications is **3 June 2015**.

- The Marie Curie research and innovation staff exchange programme promotes international and intersectoral collaboration through research and innovation staff exchanges. The next deadline for applications is **28 April 2015**.

Scaling up

Jean-Marc Burgunder, Chair, Executive Committee

The new chair of the EC answers questions on his vision for the next 10 years, during which Enroll-HD will replace Registry as the network's centrepiece observational study, and the EHDN will set its sights not just on Europe, but also beyond.

How did you come to work on HD?

With the discovery of the HD gene in 1993, there was a great feeling of excitement. Here was the gene that, all on its own, caused HD. With time, however, it became clear that solving the disease wasn't going to be as simple as we had thought. We certainly had a great advantage, but to make progress we were going to need a new approach—an interdisciplinary approach—and that's how I came into the field.

In the early 1990s I was running a neuromorphology lab at the University of Bern, that had two research programmes looking at gene expression: one focused on the brain, and one on muscle. Besides research, we also diagnosed and treated muscle disorders—muscular dystrophies, dystonias, spasticity and so on.

Over time we saw more and more neurogenetic disorders, including ones that affected the central nervous system such as HD. HD stood at the intersection of my interests in molecular biology, movement disorders and clinical neurogenetics, and it soon became my primary focus. We knew that to tackle it we would need geneticists, anatomists, cell biologists, clinical and translational scientists, and that leading them all there would have to be a clinician. That clinician in turn had to form part of a larger, clinically oriented team that included psychiatrists, occupational therapists, ergotherapists and others. That interdisciplinarity is what we set out to achieve when we created the Swiss HD Centre in a suburb of Bern.

How has the network changed life for HD patients and families, and how will it do so in the next decade?

At the plenary meeting last September my predecessor, Bernhard Landwehrmeyer, expressed cautious hope about our future potential to treat the disease. I fully concur with his sentiment, but I think we are already seeing some of EHDN's initial promise being fulfilled in terms of improvement in standards of care, use of resources and creation of new research centres. These things are coming about just through the expansion of the network. Not only that, but other networks, such as the US-based Huntington Study Group and the Chinese HD Network, are benefitting from the progress that we have made in Europe. In China, where I go twice a year in my role as a visiting professor at several Chinese universities, I'm currently involved in an effort to adapt EHDN materials so that they are applicable to the Chinese HD community.

Is there something special about HD, and the HD community, that makes this kind of collaboration and progress possible?

I think so, yes. The nature of the disease means that the community is highly motivated to help itself, and to do so, sometimes, over generations. That's not true of all those affected, of course; there are those who prefer to distance themselves from the disease as far as they can, for as long as they can. But others are truly devoted, they immerse themselves fully in either care or research or both, and what is amazing to see is the raw motivational power that generates. The group, in this case, is certainly more than the sum of its parts, and one striking manifestation of that is the sheer outpouring of creativity we saw in Barcelona—the documentaries, dance projects and other modes of expression that were on display there.

You've talked—and taught—about the connection between spirituality and medicine, particularly neurology. Could you tell us something about that?

It's a subject that interests me greatly and of course there's an awful lot to be said about it, but one of the messages I try to get across when I teach is that, even in the case of a monogenic disorder like HD, where if

you have the gene your destiny might seem to have been predetermined—and that was certainly the attitude of both doctors and patients in the past—you have choices.

> *"You can choose to confront the disease and to live with a sense of freedom. That's in your power."*

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Part of it is about state of mind, of course, and comes down to each individual's personality and temperament. But it's my hope that as EHDN and the other networks grow and interact, creating a wide base of support for HD research from the clinic to the lab and back again, they will facilitate the development of therapies that will hand that freedom back to those affected in another sense too.

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Wikipedia

Dates for your diary

Save the dates for

- Molecular Mechanisms of Neurodegeneration, Milan, Italy, 28-30 May 2015
- Gordon Research Conference—CAG Triplet Repeat Disorders 2015, Lucca, Italy, 31 May–5 June 2015
- EMBO/EMBL symposium—Mechanisms of Degeneration, Heidelberg, Germany, 14–17 June 2015
- 30th annual Huntington's Disease Society of America convention, Dallas, Texas, USA, 25–27 June 2015