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EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

In memory of Woody Guthrie

EHDN staff Katrin Barth (left) and Mette Gilling accompany Nora Guthrie (in white), daughter of American folk music legend Woody Guthrie. Woody died in 1967, of HD, and in the same year his wife Marjorie—who would have celebrated her 100th birthday this year—founded the forerunner of the Huntington's Disease Society of America. Nora, who lives partly in Germany, decided to mark the three anniversaries with an evening of live music at Berlin's Pfefferberg Theatre. She contacted Michaela Grein of the German Huntington Association (in stripes), who helped her organise the event on 25 September.

CALLING ALL SITES! HD CLINICAL TRIALS NEED YOU...

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Onwards and upwards with EHDN

Jean-Marc Burgunder, Co-Chair, Executive Committee,
and Michael Orth, Science Director

EHDN's objective is to advance research, and it must therefore evolve to keep pace with the state of knowledge about HD. In line with its scientific strategic plan, the working groups are undergoing some reorganisation, and rationalisation, while an HD Science Think Tank has recently been created, and new topic-specific, time-limited task forces are in the pipeline.

Working groups play a critical role in advancing research, because they identify key questions within their specialist domains, as well as new methodologies that can be applied to those questions. They provide a "safe space" where ideas can be generated and then debated among peers.

To make the working groups' activities more transparent to the rest of the network, and to the HD community beyond, the EHDN leadership has encouraged them to provide short mission statements. These will outline their raison d'être, their aims and strategies, and as they come in they will be posted on the section of the EHDN website that is dedicated to the working groups. The hope is that this site will henceforth act as a "shop window", attracting interest in collaboration from the community, including other working groups and researchers not yet involved in HD. Greater clarity with respect to working group activities will also facilitate the network's scientific coordination.

EHDN has established an HD Science Think Tank to complement its existing research efforts. This brings together EHDN staff who are closely involved in supporting scientific research—including members of the Executive Committee, the working groups and Central Coordination—and it engages with the HD research community in three ways:

- Researchers may contact the think tank for help in identifying potential collaborators or funding opportunities, or to discuss scientific ideas
- The think tank welcomes suggestions of research topics, and has provided a contact form on its website via which these can be submitted
- The think tank may occasionally propose specific research topics that could be addressed by a dedicated task force working for a defined period of time

For more information about the HD Science Think Tank, please contact Camille Genoves: camille.genoves@euro-hd.net

At the coalface: dispatches from two working groups and a task force

Systems Modelling Working Group

Christian Néri, University Pierre and Marie Curie

There are two main ways to study HD, and they are highly complementary. One is to study disease mechanisms using experimental biology. The other is to take a systems-level approach, using computer science and informatics to analyse ever-growing quantities of "poly-omic" (transcriptomic, proteomic, functional and other) data. The latter is the focus of this working group.

One strength of the informatics approach is that it provides a holistic view of the disease process. Another is that it sheds light on when in that process certain pathological mechanisms become important, allowing prioritisation of potential therapeutic targets. It has already led to better understanding of the dynamics of the HD process, but it also presents certain challenges.

A current trend in systems modelling of HD involves integrating large data sets in a multidimensional manner—that is, across different layers of molecular regulation, timescales, cell types and so on—in order to generate comprehensive *in silico* models of the disease. However, this requires rich source data and robust data integration methods.

Another challenge is to generate models that reduce data complexity down to a small number of biologically precise hypotheses and targets. The best models achieve the right balance between coverage and selectivity—that is, between highly descriptive source data and good discriminative power.

The goal of this working group is to promote the development of robust integration methods, and to ensure that the output of systems approaches is made available to other working groups—especially those whose focus is genetic modifiers and biomarkers—and hence, to drive the translation of basic discoveries into the clinic.

Karen Jones (left) and Katy Hamana celebrate Wales in The Hague, 2016

Physiotherapy Working Group

Katy Hamana and Karen Jones, Cardiff University

Just over three years ago, the Physiotherapy Working Group launched a project to develop an online information and learning resource to support participation in physical activity for people with HD. The idea emerged from anecdotal evidence, brought to the working group, of a lack of support and information in this area.

The materials that comprise the resource are evidence-based and underpinned by research investigating physical activity in HD from both experimental and experiential perspectives. People with HD and their families and carers also shared their experiences with us, and those experiences make up the "Stories from HD families" part of the resource.

The resource is easy to navigate and provides answers to frequently asked questions, such as, "Why should someone with HD be active?", "What type of activity can someone with HD do?", and "What may stop someone with HD being active?" Users can view short films containing instruction and demonstrations of effective techniques such as strengthening and balance exercises. A workbook is provided, that was developed by the ENGAGE-HD research team, led by Monica Busse and Lori Quinn, as well as tips for overcoming barriers to physical activity. There are also links to external sources of information.

The first version of the resource was launched at the 2016 EHDN plenary meeting in The Hague. During that event, representatives of the European Huntington Association (EHA) and the working group met to discuss a potential collaboration. This collaboration has resulted in the EHA hosting the resource. We are currently evaluating the resource based on users' responses to an online survey. We hope to publish the findings in the coming year, and to use the feedback in further development.

Driving Task Force

Milou Jacobs and Raymund Roos,
Leiden University Medical Center

The Driving Task Force grew out of the Motor Phenotype Working Group and was established because of the importance of driving with HD as a topic in its own right.

The ability to drive a car confers independence and can be indispensable to a person's work, but patients often find it difficult to decide when to stop. Quitting can be associated with depression and social isolation, making it relevant to both clinical care and research.

The mission of the task force, which met for the first time in June, is to develop a set of guidelines for assessing driving ability. The goal is to help patients to continue driving for as long as possible, and to provide advice in a timely fashion. In order to do this, however, more research is needed into driving performance in HD.

The first challenge for the task force is to define fitness to drive. When does someone become unfit to handle a car? This may seem a straightforward question, but the answer has to take into account different countries' rules and regulations where driving is concerned.

We also want to investigate which research assessments are best suited to evaluating driving fitness. Can we use cognitive assessments as a proxy for driving ability, for example, or would decline in motor performance be a better choice?

Two studies are being conducted at the University Medical Center Groningen and the Leiden University Medical Center in the Netherlands, to investigate predictors of driving ability using a driving simulator. These build on two studies carried out at the University Medical Center Leuven, Belgium, in 2012 and 2014.

Update: Clinical trials

Jenny Townhill and Tim McLean, Central Coordination

Calling all sites! As more experimental therapies approach the clinic, pressure is building on HD clinical trial sites to meet the demand for patients and resources. EHDN urges experienced, well-resourced HD centres to join the network of trial-ready sites, and help prevent potential delays in the delivery of new therapies to the clinic.

Three large clinical trials—Pride-HD, LEGATO-HD and Amaryllis—have run concurrently over the past few years. In total, 90 sites have screened 1,313 and enrolled 1,031 participants for these trials. Eleven sites took part in all three of the trials, and 20 in at least two of them. European sites contributed around 75% of the participants.

The more advanced the phase of the clinical trial, the more participants are required. The average phase 3 trial requires around 600 patients, and many more trial-ready sites will be needed to meet that demand, while also supporting phase 1 and 2 trials of emerging therapies.

The HD Clinical Trial Site Certification scheme was devised to support capacity-building with respect to trial-ready sites, and has had an excellent response since its launch in March 2017. It requires sites to register their interest in, and capacity for, participating in trials, and provides an opportunity for small and medium-sized sites to get involved. Now is the time, since at least one large, multinational trial is about to launch its set-up phase. Meanwhile, EHDN is considering other strategies to maximise Europe's clinical trial capacity, such as providing training and guidance for less experienced sites.

Photo: ARTIFOX, Gabriele Stautner

The following is a status update on the clinical trials that EHDN has endorsed.

PRECISION HD1 AND HD2: Endorsed since the last edition of this newsletter and sponsored by WAVE Life Sciences, these phase 1b/2a trials of novel antisense oligonucleotides (ASOs) target the expanded huntingtin allele only, allowing normal huntingtin to continue to be expressed. Two separate though concurrent clinical trials are needed, as the ASOs target different single nucleotide polymorphisms (SNPs) in the huntingtin gene. Unfortunately, not everyone with the HD mutation has these SNPs, which are found—either singly or together—in only around 60% of participants. The study will be conducted at several sites in North America and Europe, and aims to recruit around 50 participants with early manifest, stage 1 or stage 2 HD. For more information, please consult the detailed overview of the trials provided by HDBuzz.

Open Pride: The current focus of this study—the open-label extension to Teva Pharmaceuticals' phase 2 trial of pridopidine, Pride-HD—is recruitment into the Digital Health substudy for activity monitoring. EHDN has endorsed this substudy, and encourages all sites participating in Open Pride to recruit for it. They should do so even if they have as few as one eligible participant, since it will only be with the support of all sites that the recruitment target will be met.

LEGATO-HD: Having completed recruitment in May 2017, this Teva-sponsored, phase 2 safety and efficacy trial of laquinimod is focusing on retaining participants throughout their scheduled 52-week treatment period, before the study ends in mid-2018.

HD-DBS: This investigator-initiated trial of pallidal deep brain stimulation for HD continues to recruit. It has 18 participants randomised (with a target of 50) and another five scheduled for screening in the next few months. The addition of the French site Amiens-Lille, which is currently in start-up, is expected to boost recruitment significantly. Clinicians in participating countries (Germany, Austria, Switzerland and soon France) are encouraged to refer eligible participants to the trial sites. Eligible participants are those with uncontrolled choreic symptoms for which current pharmacotherapy is proving unsuccessful, and who are able to give their consent. For further information, or help in identifying potential participants via the Enroll-HD database, please contact Pauline Kleger: pauline.kleger@euro-hd.net

For more information about, or to provide feedback on, EHDN-endorsed studies, please contact Jenny Townhill: jenny@euro-hd.net

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Sandrine Betuing

Andreas Neueder

Two new seed grants awarded

A group of researchers led by Sandrine Betuing of the University Pierre and Marie Curie in Paris has received seed funding to explore the role of altered sterol synthesis in HD. In 2016, the French group reported that restoration of cholesterol 24-hydroxylase (CYP46A1), an enzyme involved in degrading cholesterol, is neuroprotective in the R6/2 mouse model of HD, and suggested that it could represent a promising drug target in HD. In the brain, cholesterol synthesis relies mostly on astrocytes, whereas neurons eliminate cholesterol that has been oxidised by CYP46A1. Betuing and colleagues will investigate how restoring CYP46A1 in neurons carrying the HD mutation regulates the metabolism of cholesterol and other lipids in the two cell populations.

The second project to have received seed funding in 2017 is led by Andreas Neueder of the University of Ulm in Germany, whose team proposes to study extracellular vesicles. These are tiny parcels of biological material, including protein and messenger RNA, that cells release into the bloodstream in order to communicate with each other—and importantly, they can cross the blood-brain barrier. Neueder and colleagues will measure changes in the composition of these highly mobile messengers, to explore whether those changes mirror the effects on the brain of both mutant huntingtin protein, and potentially, future therapies designed to suppress it. If so, extracellular vesicles could be used as biomarkers in future clinical trials.

Seed funds are intended to support pilot studies that will eventually kickstart larger projects. There will be two calls for applications in 2018 and the next deadline is 1 March 2018. More information about the programme and how to apply can be found here.

Update: Enroll-HD

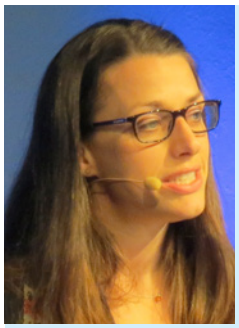
Ruth Fullam, European Manager, Enroll-HD

Enroll-HD celebrates its fourth birthday in Europe this December. Recruitment has exceeded expectations, with nearly 9,000 European participants now enrolled, but Europe has more to give. More than half the sites that were involved in Registry have now been activated in the new study, and the goal is for the remainder to follow suit before the end of 2018.

The transition from Registry, Enroll-HD's predecessor in Europe, started with German and British sites, and was quickly followed by sites in Poland, Italy, the Netherlands and Denmark. However, the sheer scale of the task slowed transition and revealed the start-up trajectory that we had initially envisaged to be unrealistic. More than 130 sites in 16 countries, in which 14 languages are spoken, required not only ethics review board (ERB) approval and site agreements, but also eventual amendments to both. Individual ERBs required local legislation to be accommodated, and each participating institution required a tailored site agreement. Since the primary operational language is English, each adjustment had to be translated.

If our initial plans look overambitious in retrospect, that is mainly because Enroll-HD is itself ambitious. A project on this scale is unprecedented. Registry evolved over a decade, and our goal with Enroll-HD was to "hit the ground running" by building on Registry's strengths. The recruitment figures show that we've done that; it will just take a little longer than we anticipated for the new study to achieve its full potential.

So what next? We have adapted to meet the true challenge, by devoting considerably more resources to the transition process. Since the end of 2016, the number of people working on start-up in Europe has more than trebled, and this has produced tangible results. France saw its first participant enrolled in June 2017 and is adding more sites and participants by the week. Switzerland, Austria, Belgium and Portugal will join the study in the next few months, and Norwegian, Swedish, Czech and Russian sites are expected to follow soon after that. 2018 will prove a pivotal year, as the study moves out of transition and reaches full capacity.



HDClarity starts up

Olivia Handley, EHDN Global Platform Manager

The Enroll-HD platform supports HDClarity, a CHDI-funded, global study for the collection of cerebrospinal fluid (CSF) in HD that was conceived by EHDN's Biomarkers Working Group. HDClarity is now in start-up, with eight sites regularly collecting CSF samples, 21 having been approved to join the study, and a further 19 undergoing assessment. To date, samples have been collected from 127 participants, 80 of whom are enrolled in a separate CSF collection study, HD-CSF, that donates samples to HDClarity.

The goal is to recruit 600 participants at sites in North and South America and Europe, and eventually, to run the study longitudinally. Chief investigator Ed Wild of University College London says that discussions are underway about incorporating testing for neurofilament light protein (NfL) in plasma, into HDClarity, after a recent study suggested NfL could be a powerful biomarker of HD onset and progression.

Marina Peball

Carsten Saft

Fellowship Exchange Programme: Austria and Germany swap notes

Laura Spinney

Marina Peball, an Austrian research fellow in neurology from Innsbruck, spent three weeks in Bochum, Germany this summer, under the mentorship of neurologist Carsten Saft. She will spend a final three weeks there this autumn, thus completing the Fellowship Exchange Programme run by EHDN and the European section of the International Parkinson's and Movement Disorder Society.

Peball, who wrote her medical thesis on HD and has worked with HD patients since 2013, in a group led by Klaus Seppi, wanted to understand how a larger HD centre worked. "We have 50 to 100 patients here in Innsbruck," she says. "Bochum has upwards of 500."

She was impressed by the close collaboration between the HD outpatients department at the Ruhr-University hospital in Bochum, and the centre within the same complex, where basic research is carried out into HD. She learned about ongoing research projects—including a pilot study run by Sarah von Hein on the cardiological effects of the HD mutation. She spent time in the animal facility and with the genetic counselling team, and she observed a person receiving their HD test results for the first time.

Bochum is one of the European centres involved in the ongoing IONIS trial of an antisense oligonucleotide, a potentially disease-modifying treatment for HD, and Peball was struck by her conversations with patients while they waited to take part in it. "It's the first time I've heard patients say that maybe there will be a cure in the future," she says. "It was overwhelming."

After 25 years of working with HD patients, Saft and his colleagues have understood the importance of building a cross-disciplinary team, and have gradually brought in clinicians with expertise in psychiatry, cardiology, the juvenile form of the disease and other specialties. That is one of the strengths of the Bochum centre, he says. But he adds that the learning in the exchange programme hasn't all been in one direction. "In HD there is never a right and a wrong way to treat a patient," he says. "I learnt about Marina's and Klaus Seppi's typical treatment regimes, just as she learnt about ours."

The 2018 round of the Fellowship Exchange Programme will be announced soon; look out for details on the EHDN website before the end of the year.

For information about potential research collaborations and funding opportunities, please follow EHDN's Grant and Collaborations Manager, Fionnuala Margreiter, on Twitter, or contact her via this address: fionnuala.margreiter@euro-hd.net

Follow our Grant Manager, Fionnuala Margreiter, on Twitter **@EHDN_GRANTM** for the latest news on EU funding and events and policy developments in the domain of rare diseases.

HDdennomore lives on

Laura Spinney

New Zealand has commemorated the historic meeting of the global HD community with Pope Francis on 18 May, with its own event in August.

Jo Dysart

Among those who attended the audience at the Vatican were 11 New Zealanders who met the Pope face-to-face and received his blessing—a bonus they hadn't been expecting. Their trip was organised by Jo Dysart of the Huntington's Disease Societies of New Zealand, and funded by that organisation, the Neurological Foundation of New Zealand and the Hugh Green Trust.

"It meant so much to the families who went to Rome," said Dysart. "The hardest thing was leaving some of the families behind." And so on 7 August, she organised a showing of a film of the papal audience to a gathering of the New Zealand HD community at Auckland City Hospital. During the event, 52 rosaries that the Pope had blessed were given out to those who hadn't been able to make the trip.

Steve, who cared for his wife until her death from HD and now cares for his two affected sons, was among those lucky enough to go to Rome. "I'm nearly 80 and caring gets harder as you get older," he said. "Visiting the Pope has recharged me, it was a great privilege that will stay with me forever."

Neuroscientist Richard Faull, one of the creators of the transgenic sheep model of HD and patron of the HD Societies of New Zealand, said that the papal audience was ultimately about humanity, not religion. "This trip has

Richard Faull

been transformational and has changed the lives of the people who went," he said.

Such was the demand to relive the papal audience in New Zealand that similar events are planned.

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STRONGER Together
Sofia · Bulgaria · Sep 2017

EHDN in Sofia

The EHDN was present at the European Huntington Association (EHA)'s "Stronger Together" conference in Sofia in September. Language coordinators running an EHDN exhibition shared information with patients and other members of the HD community who had come from all over Europe and the Middle East. EHDN hopes that the future holds many more such fruitful collaborations with the EHA.

For more information about the 2017 EHA conference, click here.

Adventures in Huntingtonland:

Profile of Alice Rivières

Alice Rivières is a character in a French novel who carries the HD mutation. With her alter ego Emilie Hermant and Valérie Pihet, she set up Dingdingdong, the Institute for the Coproduction of Knowledge on Huntington's Disease, and embarked on a cross-disciplinary journey of discovery. She tells us what she and her fellow travellers have learned so far.

How did your journey begin?

My mother, who was in her 50s, had been behaving strangely for some time, and we finally found out that she had HD. I'm the youngest of three sisters. We're very close as a family, and that knowledge brought us closer, but only after it had shaken us to our roots. I took the test just a few months later—probably too soon, in hindsight. I was 33 years old. The day that I got the result was like a second birth. It took me years to come to terms with it; to realise that, despite being a carrier, I wasn't yet ill.

The person who was born on that day had a new name, Alice Rivières.

Yes. Emilie had always written fiction, because it helped her to understand things, but she had never published anything. After the test she felt a profound need to examine her life. She wrote a novel in a few months, and it was published the following year. Now she had an alter ego, Alice, and being fictional Alice was free to imagine other futures. Valérie and Emilie founded Dingdingdong as a platform for Alice to jump off from, into the world of HD.

What is Dingdingdong's mission?

To bring together artists, researchers in the social sciences and others—we're 17 in all—to explore HD in new ways. Only one of us is a neurologist, because for us, the medical definition of HD is only one small part of it. To understand the rest, the experience of living with the disease, we have assembled a variety of tools, including literature, dance, cinema and painting. We help people with HD express themselves, and we collect their experiences. We have just published a collection of such accounts, called *Le chemin des possibles (The path of possibles)*. Our guiding principle is that the person with HD is the greatest expert on their disease.

Is the goal to change how people with HD see the disease, or how others see it?

Both. You could think of the person with HD as gradually falling out of synch with the world. The gap grows wider with time. But if an outsider understands what that person is experiencing—the frustration of trying and failing to express themselves, say—then the two of them can work together to bridge the gap, and ease the frustration. Clinicians talk about behavioural and psychiatric

problems that can be treated with medication. I have nothing against medication, but there might be other ways—dance, for example. Having said that we're interested in both sides of the conversation, it's also true that we privilege HD carriers, because so far we have heard too little from them.

Tell me about Jimmy Pollard, who is a role model for you.

Jimmy is a nursing home administrator and educator from the Boston area of the US, who in 2008 wrote a guide for carers working with patients in the intermediate and advanced stages of HD, called *Hurry Up and Wait!* For this magisterial contribution to the field, we at Dingdingdong awarded him the honorary title of Professor of Huntingtonian Life. For two years we have been working on a guide that extends the concept to the early stage of HD, called *Absolute Beginners*.

Has Dingdingdong made a difference?

So far I think the main effect of our work has been to destigmatise HD, at least in France. We're trying to have an impact further afield too—more and more of our work is translated, for example, and the English version of our manifesto can be found here. There's still a lot of work to be done. We would like to investigate alternative living environments for HD patients, for example, that allow for individuality within a strong community. And though we are not a patient association, we would like to see more talking groups set up by and for carriers, because the worst thing about HD is the solitude that it imposes.

Back in 2006 you were angry with the world of medicine. Are you still?

No. I've realised that it's not the doctors' job to explore the existential dimension of HD. That's for others to do. For example, doctors are interested in the molecular mechanisms that HD has in common with other diseases such as Alzheimer's and Parkinson's. Alice is also a trans-pathological wanderer: she transmits the experiences of those with HD to people living with other diseases, and she brings their experiences back.

> *"At Dingdingdong we're provocative and proud of it."*

We want to make doctors think differently about HD, but we also work with them. I'm involved in a committee for the definition of HD care protocols, for example. In the end, we all want the same thing—to make Huntingtonland a better place for all those who inhabit it.

To support Dingdingdong financially, or to share your experiences of HD, please contact Alice and her colleagues at the following address: contact@dingdingdong.org

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wikipedia/commons/1/13/Hôtel_de_Ville_de_Bruxelles_01.JPG

Dates for your diary

Save the dates for:

- Society for Neuroscience annual conference, Washington DC, USA, 11–15 November 2017
- European Patients' Forum roundtable on cross-border healthcare, Brussels, Belgium, 4 December 2017
- Digital Health Summit, Brussels, Belgium, 7 December 2017
- 13th Annual HD Therapeutics Conference, Palm Springs, USA, 26 February–1 March 2018
- Enroll-HD Congress, Quebec City, Canada, 20–23 May 2018 (by invitation)
- EHDN2018 Plenary Meeting, Vienna, Austria, 14–16 September 2018 (details to follow)