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EHDN News

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Bernhard Landwehrmeyer

EHDN2014: The network celebrates its 10th birthday

Laura Spinney

The 8th plenary meeting of the European Huntington's Disease Network took place in Barcelona, Spain, from 19 to 21 September 2014, in conjunction with the bi-annual meeting of the European Huntington's Disease Association. Held at the Hesperia Tower Convention Centre in the outskirts of the city, it drew 913 delegates from Europe, the Americas and beyond, and was marked by a spirit of cautious optimism. Ten years into the life of the EHDN, effective therapies are on the horizon, but bringing them within reach will require slow, methodical work. The meeting also provided an opportunity to pay tribute to outgoing chair **Bernhard Landwehrmeyer**, who steered the EHDN so skilfully through its first decade. A full report of the plenary meeting is in preparation, but we would like to use this newsletter to draw your attention to some of the highlights.

Follow this link to find a slideshow of photos and a trailer for the conference.

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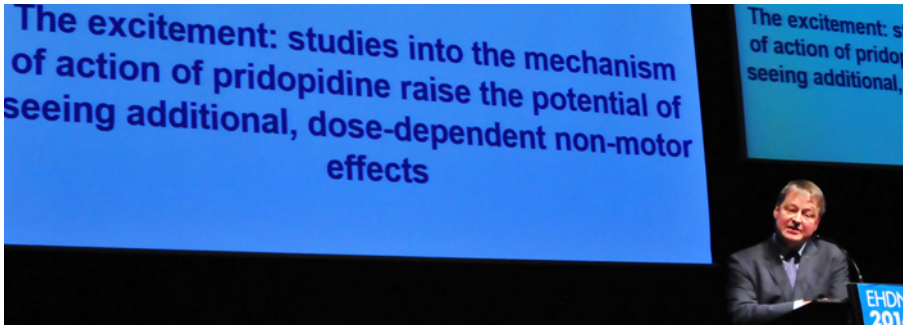


Bernhard Landwehrmeyer

Clinical trials—past, present, future

"The drugs are coming", Bernhard Landwehrmeyer told the conference, and they certainly are, though there are some major hurdles to be cleared before they get here, notably clinical trials. **Sarah Tabrizi** (London) announced a long-awaited trial of a huntingtin (HTT)-lowering drug, ISIS-HTT_{Rx}, developed by Isis Pharmaceuticals. This gene silencing approach, which involves an antisense oligonucleotide (ASO) that blocks human *HTT* messenger RNA (mRNA) and so prevents the synthesis of the protein, is designed to reduce total HTT in the brain's cortex, giving the brain a "huntington holiday" and allowing restoration of connectivity, circuitry and function. It has produced good results in preclinical studies, delaying disease progression and prolonging survival in a mouse model of HD. Safety trials are underway in animals in preparation for a human safety trial which is due to start in 2015.

Bernhard Landwehrmeyer (Ulm) presented Pride-HD, a phase 2 study of pridopidine sponsored by Teva Branded Pharmaceutical Products, of which he is global coordinating investigator. We covered Pride-HD in our last newsletter, so suffice it to say here that part of the excitement about pridopidine is that, although Pride-HD is a trial of its effects on the motor symptoms of HD, it is also known to modulate the release of a range of neurotransmitters, suggesting that it could potentially act on non-motor symptoms too. Recruitment got underway in January 2014 and is expected to be complete by early 2015.

Jan Vesper (Düsseldorf) announced the launch in the next few months of HD-DBS, a multicentre trial of deep brain stimulation for HD. **Ralf Reilmann** (Münster) presented Legato-HD, a phase 2, global trial of the immune modulator laquinimod that is based on the rationale that mutant HTT (mHTT) stimulates microglia and astrocytes in the brain, causing inflammation. The EHDN is collaborating with the Huntington Study Group to support the one-year safety and efficacy trial in 400 HD patients, which is sponsored by Teva. Reilmann also presented a completed phase 2 trial of Siena Biotech's sirtuin 1 inhibitor selisistat, which is thought to prevent mHTT from aggregating in cells. Though the researchers reported increased levels of mHTT in volunteers' blood over the three-month trial, it's not yet clear what that means or whether the drug can bring clinical benefits to patients. **Cristina Sampaio** (Princeton) talked about two PDE10A inhibitors, drugs designed to improve the function of synapses or junctions between neurons, that are in phase 2a trials with Omeros in the US and Pfizer in France. Pfizer has also just launched a phase 2 trial of its compound in four countries, which will be carried out in parallel with a CHDI-sponsored PET study of the drug's action in the brain.

Jan Vesper

Ralf Reilmann

Cristina Sampaio

Ladislav Mrzljak

Leticia Toledo-Sherman

Leslie Thompson

Promising in preclinic

Not yet in clinical trials, but coming closer, are a class of drugs called KMO inhibitors that work by enhancing the neuroprotective function of the kynurenine pathway (KP). **Ladislav Mrzljak** (Princeton) said that CHDI's lead compound, CHDI-246, had performed well in preclinical safety and efficacy studies, and that exciting evidence from a monkey model indicated that it has a longer half-life in primates than in rodents—meaning that it probably remains active long enough to have an effect in the monkey's central nervous system. That particular finding highlights the importance of nonhuman primate models in bridging the translational gap between rodents and humans.

Leticia Toledo-Sherman (Los Angeles) said that CHDI was funding research by Ed Wild's group at University College London (UCL) to establish whether there was a correlation between KP metabolites in cerebrospinal fluid (CSF) or plasma, and disease progression. If so, those metabolites could provide a valuable biomarker of the efficacy of KMO inhibitors in future clinical trials. CHDI has now scaled up production of CHDI-246, and though some further development is required before it can be translated to humans, she thinks such trials will get underway soon.

Leslie Thompson (Irvine) presented two possible approaches to preventing the accumulation of mHTT. One involves modifying the protein itself, and Thompson's group has been looking at ways of enhancing sumoylation, a pathway cells use to degrade HTT. They find that inhibiting an enzyme called PIAS1, which affects this pathway, reduces mHTT levels and is associated with significant behavioural improvement in mouse models of HD. The second approach involves targeting protein homeostasis networks to alter the folding or clearance of mHTT, since we know that it is prone to misfolding. In a proof of concept study, the Irvine team found that aggregated mHTT was cleared more effectively from the brains of HD mice after an injection of TRiC chaperonin complex, a protein that helps HTT fold properly and seems to prevent mHTT from aggregating.

Natural history of a disease

Sarah Tabrizi (London) gave an update on Track-On HD, the follow-up to observational study TRACK-HD, which began in April 2012 and of which she is principal investigator. Emerging data suggest that apathy, negative emotion recognition, finger-tapping speed and structural brain imaging measures may be sensitive predictors of disease onset and progression. New methods that make use of complex maths, such as voxel connectivity profiling, have permitted researchers to track changes in brain connectivity as the disease progresses. As yet unpublished data suggest that the disease is associated with an overall loss of the average connectivity of the caudate nucleus, particularly in its connections with frontal areas of the cortex and the hippocampus. A reorganisation of the connectivity of another striatal structure, the putamen, is also observed, but here the change is an increase—a possible sign of compensation, Tabrizi suggested.

Sarah Tabrizi

Roger Barker (Cambridge) pointed out that invertebrate and vertebrate (rodent, sheep, nonhuman primate and "minipig") models of HD now exist, and have contributed enormously to our understanding of the disease. But animal models also have limitations, not least the fact that they can't speak, which means they can't have symptoms. Findings from such models should be interpreted with caution, therefore, and the model should be chosen according to the question being posed. The key, according to Barker, is to combine animal and clinical studies in thoughtful ways, allowing them to inform each other.

Roger Barker

Bernhard Landwehrmeyer gave an update on Enroll-HD, the successor to another major observational study, REGISTRY. As of 11 September 2014, 102 study sites were active in Enroll-HD—roughly half of the anticipated total—and site activation is due to be completed in 2015. Around 3,000 individuals have already been recruited, including healthy controls, and some of these are already taking part in randomised controlled trials (RCTs). Enroll-HD will accelerate recruitment to such trials, with 1,200 of its participants already expected to be taking part in RCTs by mid-2015. Ultimately, Enroll-HD is expected to recruit 25,000 people, but it won't be allowed to expand faster than its global governance structure allows, since the latter is essential to the platform remaining stable, safe and of high quality. To that end, a second version of the Enroll-HD protocol is in the pipeline.

Bernhard Landwehrmeyer

Biomarkers: the right tools for the job

Blair Leavitt

Beth Borowsky

Doug Macdonald

Cristina Sampaio

The success of a clinical trial depends not just on having a good drug, but also on having reliable methods of measuring the efficacy of that drug. That means having good biomarkers with well-defined endpoints. Observational studies such as TRACK-HD have proved invaluable in supplying new disease biomarkers in recent years, as have brain imaging technologies. **Blair Leavitt** (Vancouver) said that functional MRI and diffusion tensor imaging (DTI) were welcome new additions to the existing toolkit of PET, structural MRI and magnetic resonance spectroscopy. However, as **Beth Borowsky** (Princeton) pointed out, markers of disease progression change at different rates and have different ranges of sensitivity and inflection points. It's not clear *a priori* whether or how they will respond to an intervention, and hence whether they will be useful in clinical trials. Selecting the right biomarker for the task in hand will be critical. With promising HTT-lowering therapies on the horizon, for example, a sensitive assay of HTT in CSF is needed. Such an assay is already available from Rome-based biotech company IRBM Promidis, but it's not yet known if the very low concentrations of mHTT that have been detected in the CSF of HD mutation carriers by Ed Wild's group at UCL, using that assay, will change measurably in response to changes in the synthesis of mHTT in the brain. This particular biomarker should therefore be used for exploratory purposes only at the moment, Borowsky said, and not yet for guiding decisions about whether to proceed with clinical trials. CHDI's strategy, going forward, will be to include many biomarkers in drug trials, so that when effective drugs are finally identified, it will be possible to go back and ask which biomarkers predicted that efficacy and will therefore be useful in future trials.

Doug Macdonald (Los Angeles) said that CHDI has been using another protein quantitation assay, Singulex's Erenna single molecule counting platform, to detect mHTT in CSF with femtomolar sensitivity, and that this platform is currently undergoing preclinical validation at CHDI. To be useful, biomarkers will need to give feedback in real time and be translatable to the clinic, which means they should make use of accessible biosamples and established probes. A key question will be whether a given biomarker is only sensitive to strategies that prevent the measured outcome, or if it can also be used to detect reversibility.

Referring to future clinical trials of CHDI's KMO inhibitor, **Cristina Sampaio** (Princeton) said that decisions about the design of these will depend on whether Wild's group finds that KP metabolites change consistently and measurably in CSF as the disease progresses. If they do, the metabolites will serve as a biomarker through clinical trials 1, 2a and 2b. If they don't, all is not lost since different, indirect biomarkers can be used that probe pathological processes on which the drug is thought to act—neurotransmission disequilibrium, neuroinflammation and neurodegeneration. The choice of biomarker in that scenario will depend on the pathological process a trial's architects are most interested in. The clinical development plan therefore has trade-offs and flexibility built into it.

Jong-Min Lee

Lesley Jones

José Florez

Jan Frich

On disease modifiers

HD is a monogenic disorder, meaning that if you have the mutation you will develop the disease. But within that certainty there is uncertainty. Genome-wide association studies (GWAS) suggest that only about 56 per cent of variation in the onset of HD, as defined by the emergence of motor signs, is determined by CAG repeat length. The remaining 44 per cent must be contributed by so-called genetic and environmental "modifiers", though there may be many of these and the influence of individual modifiers may be small.

Jong-Min Lee (Boston) presented the findings of two large GWAS conducted in 4,000 HD mutation carriers with the goal of finding common genetic variants (single nucleotide polymorphisms, or SNPs) that correlate significantly with age at onset of the motor symptoms of HD corrected for CAG repeat length. This international effort (the GeM consortium, using DNA collected in HD MAPS, PREDICT-HD, COHORT and REGISTRY studies) has pinpointed many potential sources of genetic influence, with the most significant lying on chromosomes 8 and 15. Chromosome 15 is home to both good and bad modifiers, SNPs that can significantly delay or bring forward disease onset respectively.

Lesley Jones (Cardiff) and her team, also members of GeM, have used a mathematical tool called pathway analysis to find out which known biological pathways are over-represented among those genetic regions of interest. Pathways involved in DNA repair turn out to be heavily implicated, as do mitochondrial fission and oxidoreductase pathways.

José Florez (Boston), a diabetes researcher, told the conference that clinical trials can be a useful tool for identifying genetic modifiers, because although an individual modifier's effect may be modest, it can be exacerbated through interaction with a drug or other intervention. He gave examples of trials in which this had happened, and said that in order to maximise their chances of seeing such effects, researchers should work with as large and homogeneous samples as possible, and refine the phenotype of interest as much as possible. He added that there was no correlation between effect size and clinical relevance, with some therapies targeted at genetic modifiers with very small effect sizes having proved highly effective in the clinic.

Jan Frich (Oslo) gave an example of an environmental modifier in the form of physical exercise. He described a one-year programme of intensive, multidisciplinary rehabilitation that his group put in place for early- to mid-stage HD patients, at the end of which they were showing significant improvements in gait, balance, physical quality of life, anxiety and depression. The patients also reported increased self-confidence and a positive impact on their social relations. The intervention now needs to be tested in an RCT and subjected to cost-benefit analyses.

Big Data shines a light on HD

Christian Néri (Paris) gave an overview of what systems biology and Big Data can bring to the HD field, now that so many genetic and molecular data are available. Network analysis is a way of extracting rules or "signatures" of disease from complex datasets, and researchers can use those rules to refine their research questions and select the right models in which to test them. Néri described one such approach developed by his group, as part of a project of the EHDN's biological modifiers working group, called Biogemix. This is a data integration platform into which they have pooled, to date, more than 16 publicly accessible databases of transcriptomic and gene perturbation data. Working with such large bodies of data means that noise is reduced and signals emerge more strongly. The data are also comprehensive, meaning that when they are represented according to graph theory—in terms of nodes and edges—patterns within them become visible in the graph's topology. For example, graphs show that human and worm HD models have in common certain "zipper genes" (genes that link the two networks) that play roles in highly conserved developmental and cell survival pathways and are dysregulated in the disease. That means there is a manageably small number of biologically important genes that researchers should think about prioritising for investigation.

Ruth Fullam interviews Christian Néri for the EHDN website

HD outside the brain

Mutant HTT is expressed in cells and tissues throughout the body, and peripheral pathology is seen early in the disease. But is that pathology "downstream" of nervous system changes caused by the mutant protein, or does it come about via a separate mechanism? The question is important because on it rests another: could disease-modifying therapies be targeted at the periphery?

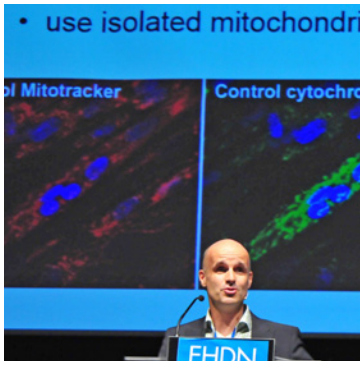
Gill Bates

Gill Bates (London) addressed this question with respect to the cardiovascular and skeletal muscle systems. Her team has observed a range of cardiac abnormalities in HD mouse models, but none of them appear to be *HTT*-related and they found no mHTT aggregation in the heart, suggesting that these abnormalities may indeed be secondary to nervous system ones. When it comes to skeletal muscle, they found atrophy in HD mice that could be reversed by inhibitors of myostatin signalling, a reversal that seems to be mediated by a reduction of mHTT aggregration in the nuclei of muscle fibres, among other things. They concluded that the inhibitor has a disease-modifying effect in mice, but that it remains to be seen if that is also true in humans.

Maria Björkqvist

Maria Björkqvist (Lund) presented the results of a microarray analysis of adipose tissue from premanifest HD mutation carriers which revealed that the expression of more than 400 genes was dysregulated in that group compared to controls. Whether those changes have functional consequences is not yet clear.

Finally, **Michael Orth** (Ulm) presented preliminary data from the European Multi-Tissue Molecular signatures in HD (MTM-HD) project, which is designed to find out more about potential defects in energy metabolism in the muscle of HD mutation carriers. It has produced no evidence of mitochondrial abnormalities in carriers so far, but the work continues.



Michael Orth

Feeding back to the clinic

Alexandra Dürr

Alexandra Dürr (Paris) told delegates that 1,705 predictive genetic tests for HD had been carried out at her centre, the Pitié-Salpêtrière Hospital, between 1992 and 2013. Based on French data, she estimates that only 5 to 25 per cent of those at risk of HD undergo testing, and that of those who request it, only 63 per cent complete the process and receive a result. Of those who receive a result, 70 to 80 per cent report being more aware of possible symptoms of HD in themselves, regardless of their status. This tested population represents an opportunity, so far under-exploited, to perform studies aimed at preventing the onset of symptoms in HD mutation carriers.

Elizabeth McCusker

Elizabeth McCusker (Sydney) presented a case for enlarging the diagnostic criteria of HD. HD is currently diagnosed at the onset of motor impairment, but major studies of the disease's natural history, such as PREDICT-HD and TRACK-HD, have revealed cognitive and imaging changes that precede those motor signs. Besides being better for research, and potentially facilitating the development of new treatments for the non-motor symptoms of HD, a broader, more inclusive set of diagnostic criteria might also benefit patients more directly, McCusker said, since there are treatments available for some of the cognitive and behavioural symptoms that have such a negative impact on them and their families in the early stages of the disease.

David Craufurd

David Craufurd (Manchester) asked whether regular check-ups serve any purpose in HD and found on balance that they did, mainly because of the availability of those symptomatic treatments and the fact they have improved dramatically in recent decades. Also, different treatments become appropriate as the disease progresses. Craufurd suggested that Enroll-HD could provide a foundation for a programme of regular clinical reviews for HD, such as already exists for serious psychiatric disorders in the UK.

Mark Guttman

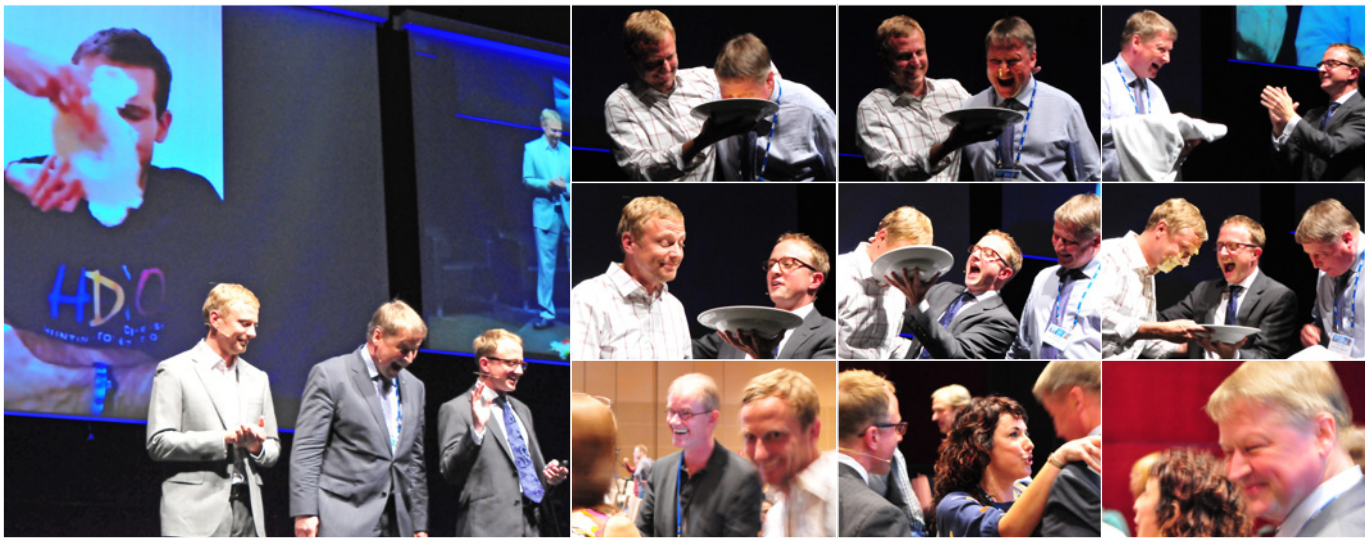
Mark Guttman (Toronto) said that care for HD patients could be improved even before new interventions are approved, and this is the goal of the Enroll-HD care improvement committee (CIC), of which he is a member. He emphasised the importance of outcomes research in achieving that aim, giving the example of a prospective study of cystic fibrosis in which quantitative analysis of outcome measures fed back into care protocols, leading to an average improvement in life expectancy of about eight years. Hoping to achieve something similar, the CIC will analyse existing data from REGISTRY to generate hypotheses which it will then test against Enroll-HD data as they come in. It will also evaluate the different care procedures currently in use at Enroll-HD sites, to see if they lead to different outcomes. A survey of those sites' procedures and patient populations is underway and should be completed by the end of 2014.

Bernhard Landwehrmeyer

Bernhard Landwehrmeyer closed the meeting with his thoughts on how those at risk of HD might cope while waiting for new treatments or a cure to become available. The best way patients and families can contribute to progress in the field while managing their own lives and expectations, he said, was to stay informed, volunteer for clinical trials (for those who find it a useful coping strategy) and maintain a positive attitude.

Business meeting

Following the summer's elections, **Lesley Jones** (Cardiff), **Berry Kremer** (Nijmegen) and **Anne Rosser** (Cardiff) joined the executive committee (EC), while **Stephen Dunnett** (Cardiff), **Christian Néri** (Paris) and **Raymond Roos** (Leiden) stood down. **Jean-Marc Burgunder** (Bern) was re-elected to the EC and took over as chair, while **Patrick Weydt** (Ulm) took up the chair of the scientific bioethics advisory committee (SBAC). **Monica Busse** (Cardiff), **Marina Frontali** (Rome), **Carsten Saft** (Bochum), **Erik van Duijn** (Leiden), **Marta Valenza** (Milan) and **Christine Verellen-Dumoulin** (Gosselies) joined the SBAC, while previous chairs **Maria Björkqvist** (Lund) and **Berry Kremer** stood down, as did previous members **Raphael Bonelli** (Vienna), **Tiago Fleming Outeiro** (Göttingen), **Åsa Petersén** (Lund) and **Ed Wild** (London).



All photos by Gabriele Stautner, Artifox Communication Design, Ulm, Germany

Thanks...

...to all those who made EHDN2014 a success, including the combined organising and programme committee chaired by **Jean-Marc Burgunder** (with members **Astri Arnesen, Jaime Kulisevsky, Bernhard Landwehrmeyer, Jamie Levey, Christian Néri** and **Ralf Reilmann**) and EHDN central coordination (especially **Katrin Barth, Jeton Iseni** and **Meike Munde**). Thanks to **Jeff Carroll** and **Ed Wild** for their inspiring nightly round-ups, and to Bernhard Landwehrmeyer and Jeff Carroll himself for taking the "cream pie challenge" so roundly on the chin. Thanks to all those departing from the various committees who have contributed to the smooth running and evolution of the EHDN over recent years. And last but not least, thanks to sponsors **Teva, Raptor, AOP Orphan, BioRep, Pfizer, UniQure, Evotec, Omeros** and in particular the **CHDI Foundation**, without whom neither the network nor the meeting would have been possible.

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Dates for your diary

Save the dates for

- Rare Disease and Orphan Drug Registries, 3rd international workshop, Rome, Italy, 24-25 November 2014
- CHDI's 10th annual HD Therapeutics Conference, Palm Springs, California, 23-26 February 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