July 2021 · Issue 43

EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Looking Back, Looking Foward…

Catherine Deeprose

Our 43rd issue of EHDN *News* explores the recent setbacks as well as successes in the ongoing quest to find an effective treatment for HD. We open with an article by **Anne Rosser** explaining the facts behind the disappointing trial discontinuations by Roche. Our interview with **G. Bernhard Landwehrmeyer** provides a timely reminder of what we have achieved so far in HD, and critically, lessons learnt and insights into the future landscape of HD research. **Jamie Levey** provides an insider's view into what happens in an EHDN Executive Committee meeting, and **Christine Capper-Loup and Michael Orth** discuss the success of the EHDN Seed Funding programme in driving forward important early-stage research. We also learn how the **EHDN/MDS-ES Joint Fellowship Exchange Programme** has provided the basis for improving services for HD in the Dominican Republic. Our further updates and news converge to remind us of the strength of our HD community going forward.

Photo: G. Stautner, Artifox.com

GENERATION-HD1 and GEN-EXTEND – What Happened and Should We Be Worried?

Anne Rosser, Chair, Executive Committee

In March this year, the HD community unexpectedly learned that dosing in the GENERATION-HD1 trial had been permanently stopped and dosing in the GEN-EXTEND trial had been paused. What happened and what does this mean for HD research?

The GENERATION-HD1 trial, sponsored by Roche, is a Phase III clinical trial of a drug called tominersen. This is an antisense oligonucleotide (ASO) that had been safe, well tolerated and reduced cerebrospinal fluid levels of the

OUR PHOTO EXPERIMENT CONTINUES – SHARE YOUR OWN! SEE PAGE 12

CONTENT — Click the Page

www.ehdn.org

Subscribe here to EHDN *News*:
Please go to the URL below and fill out the online form:
http://www.ehdn.org/news-events/
Please send us your comments, suggestions and overall feedback:
newsletter@euro-hd.net

Imprint:
Editorial Board of EHDN *News*:
Catherine Deeprose, Editor
Gabriele Stautner Artifox Communication Design (Ulm, Germany).

huntingtin protein, including the mutant form, in a previous safety and tolerability trial. Roche set up the GENERATION-HD1 as a double-blind placebo-controlled trial with three arms. In one arm, participants with manifest HD took 120 mg of tominersen every 8 weeks, in the second arm the same dose was given every 16 weeks, and the third arm received a placebo. The trial was planned to follow participants for two years, but the study dosing was terminated early following advice from the Data Monitoring and Safety Committee (DMSC), which is independent from the study sponsor Roche.

Why was the dosing stopped?

It is common in trials of this nature for a DMSC to examine the unblinded trial data at a pre-specified interim point in the trial. This was the case in the GENERATION-HD1 trial, and the DMSC, unfortunately, found that the participants receiving the highest dose of tominersen (120 mg every 8 weeks) over time did increasingly less well than those with less frequent tominersen or placebo. This left little choice except to stop the dosing.

Why did this occur?

This is a question that cannot yet be answered but a number of possibilities can be considered. For example, perhaps the dose was too high and thus, the reduction of huntingtin was excessive? Tominersen knocks down both mutant and wild-type huntingtin protein, and it may be that knocking down huntingtin below a critical level cannot be tolerated over a prolonged period of time. Other possibilities also exist. Perhaps the ASO carried toxicities that weren't revealed in previous, much shorter, trials? Perhaps the participants were not at the optimal disease stage?

Understanding the causes of failure in this study will be critically important for the next steps for tominersen and huntingtin lowering studies more broadly. This will inevitably take some time as GENERATION-HD1 is a huge study and has generated a vast amount of data. Roche has already devoted considerable manpower to this task and has agreed to present their findings at our EHDN virtual scientific meeting in September, so we can look forward to hearing more then.

Has this put the field back?

No – even before knowing the results of the full analysis of the study, it is clear that GENERATION-HD1 has helped to advance our efforts to find a disease-modifying strategy. First, it is the largest interventional study in HD to date and recruited to time. Furthermore, it used a relatively complex intervention – intrathecal delivery – which has helped to raise ambition by demonstrating that we can do large well-powered studies in HD and it has facilitated the setting up of infrastructures that will benefit trials that follow. It is also important to remember that there are other huntingtin lowering agents already in clinical trials (such as Wave's allele-specific ASOs, Uniqure's AAV-micro-RNA, mRNA splicing agents and zinc finger transcriptional repressors) in addition to therapeutic strategies which will tackle completely different pathogenic mechanisms, such as Triplet Therapeutic's plans to target DNA repair enzymes.

> *'GENERATION-HD1 has reminded us that taking new promising treatments to people is a difficult and bumpy ride. However, the study also encourages us that we can dare to believe that disease-modifying treatments will be a reality for HD one day.'*
>
> ***Anne Rosser, Chair, Executive Committee***

GENERATION-HD1 has reminded us that taking new promising treatments to people is a difficult and bumpy ride. However, the study also encourages us that we can dare to believe that disease-modifying treatments will be a reality for HD one day. It is important that we take the time to thoroughly understand the lessons that will undoubtably arise from GENERATION-HD1 and that we continue to move forward with hope (see also our interview with G. Bernhard Landwehrmeyer in this issue). As Albert Einstein commented, *'Failure is success in progress.'*

What Happens at an Executive Committee Meeting?

Jamie Levey, Chief Operating Officer, Central Coordination

Photo: G. Stautner, Artifox.com

The Executive Committee (EC) is the governing body responsible for the EHDN, directing and overseeing network activities, establishing its strategy, and ensuring adherence to the EHDN constitution. The EC meets monthly, endorses clinical trials, approves access to clinical data and biosamples from the REGISTRY study, approves seed fund applications, and guides the planning and organisation of the plenary meetings, among other activities. The members are elected by a majority vote of the EHDN membership for a term of four years (under normal circumstances).

What does the EC discuss at these regularly scheduled meetings?

The meetings are led by the EC chair who moderates the standing agenda items as well as ad hoc, topical items that are current and relevant to the EHDN. The EC meets for a full day three times a year (usually in January, May and September) and hour-long meetings are held monthly in between the diem meetings. A typical full-day meeting (currently hosted on Zoom until we can meet again in person) includes updates on EHDN-endorsed trials and studies, which are usually prepared and presented by EHDN staff who are either ex-officio or guest members of the EC. Updates to observational studies like Enroll-HD, HDClarity and other platform studies are also presented, specifically as pertaining to start-up activities, recruitment and retention issues, site performance, and data protection measures in Europe. A more recent initiative has been to invite the sponsor of an active trial to share the progress and status of their clinical trial. This has been well received by sponsors, and by ensuring that the EC members are appraised and up to date with respect to trial progress, the EC is placed in a better position to advise and assist with any challenges presented by the sponsor.

Another important standing agenda item is the review and approval of the seed fund scheme. The EC considers the reviews and recommendations of the Scientific and Bioethical Advisory Committee to arrive at a unanimous vote for the selection of the seed fund projects presented, and this happens twice each year (see the article by Christine Capper-Loup and Michael Orth in this issue for more on Seed Funds).

The scientific strategy of the EHDN is another key EC responsibility, assisted by the EHDN Think Tank. The Think Tank is a small group of EC members assisted by staff and the previous EC Chair, and provides a platform for discussion and a conduit for bidirectional flow of ideas between EHDN members participating in working groups and task forces and the EC. Think Tank activities are reported at EC meetings and this is enriched by direct presentations from working group lead facilitators. The EC provides advice and assistance as requested but most importantly ensures its oversight responsibility for the research activities supported by the EHDN. The updating and renewal of the overarching EHDN scientific strategy occur every five years and is an activity taken up by a sub-committee of the EC. This is currently in development for the next five years, being led by the Deputy Chair of the EC.

The planning and organisation of the upcoming plenary meeting are regularly discussed at EC meetings. In 2021, the programme originally planned for the in-person meeting in 2020 will occur virtually this September. Future plenary meetings, including location and content, are also part of the discussion as decisions by the EC on where and when, as well as the selection of the programme committee for each plenary meeting need to be taken.

Collaborative projects with other professional organisations also feature regularly at EC meetings. This includes the upcoming HD Education Series and the HD Fellowship Exchange Programme in collaboration with the International Parkinson's and Movement Disorder Society as well as joint activities involving the European Reference Network for Rare Neurological Diseases, Huntington Study Group and various HD patient advocacy groups.

In earlier days of the EHDN, the REGISTRY project occupied a considerable amount of the EC's time and energy. While there are no longer so many requests for the REGISTRY legacy data and samples since the study

closed in 2017, and many participants have continued into Enroll-HD, issues for discussion do arise, such as ethical issues associated with genomic research advances and new technologies that offer exciting opportunities to uncover potential new findings when analysing these data and samples.

The next election for members of the EC will take place in 2022. Normally occurring every two years where approximately half the committee rotates off after their four-year term (staggering member classes), the elections were postponed due to the global pandemic and the terms of all EC members were exceptionally extended. The elections and member rotations will resume in 2022 leading up to the next in-person EHDN plenary meeting in Bologna, Italy.

The EC welcomes the feedback of the EHDN membership. Please feel free to contact the EC at chair@euro-hd.net if you wish to bring any matter to the attention of the EC.

• • •

All photos kindly provided by Lola Díaz Feliz

Lola Díaz Feliz in her office at Fundación Jiménez Díaz Hospital, Madrid, Spain

Laying the Foundations for Improved Services in the Dominican Republic

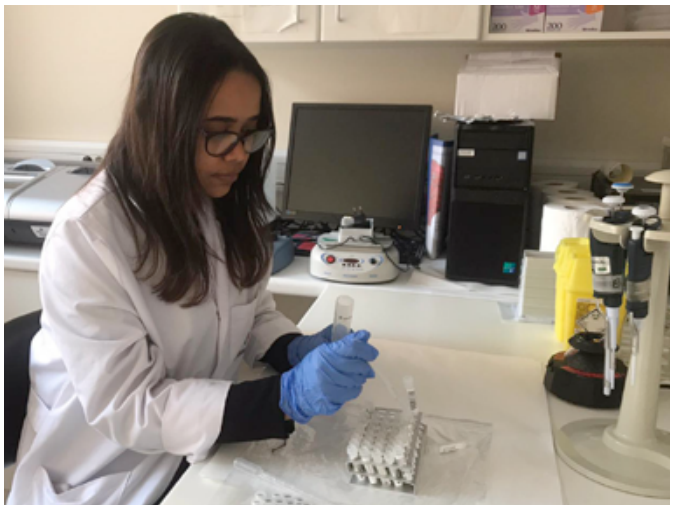
Catherine Deeprose

Lola Díaz Feliz is originally from the Dominican Republic and completed the EHDN/MDS-ES Joint Fellowship Exchange Programme in 2018. Now a Clinical Trial Coordinator at the Movement Disorders Unit at Fundación Jiménez Díaz Hospital and PhD student at the Autonomous University of Madrid, Spain, we catch up with Lola to hear how the fellowship helped drive forward her career in HD.

The fellowship allowed Lola to spend six weeks undertaking clinical observation at the Movement Disorders Unit at the Hospital Universitario Fundación Jiménez Díaz in Madrid, where she is now based. With a background in neurology, she worked with Pedro J. García Ruiz (Head of the Movement Disorders Unit) and his team, gaining critical first-hand experience in HD as well as Parkinson's disease. As part of the team, she completed a wide range of activities, including conducting follow-up visits as part of Enroll-HD, learning more about the study, and how to perform motor evaluations, cognitive tests, and many other clinical assessments.

During her fellowship, Lola met Marta Ruiz, a neurologist at Hospital Universitario Fundación Jiménez Díaz (now at Hospital Universitario Cruces in Spain) and Cici Feliz, a Dominican neurologist working as part of Pedro García Ruiz's team in Madrid. Both neurologists have a particular interest in working with patients affected by HD in the Dominican Republic. At the EHDN plenary meeting in Vienna in 2018, Lola also met Gregory Youden, a physiotherapist based in New York with family ties to the Dominican Republic and a keen interest in extending his work to the region.

These contacts made during the fellowship led to Lola setting up the collaborative project NeuroGen, a non-profit organisation dedicated to working with neurodegenerative diseases in the Dominican Republic, and specifically HD. The aim is to provide local and foreign assistance for patients with HD and their families, which sadly, most lack the economic resources to be able to access independently. HD is considerably under-recognised in the Dominican Republic and without specialised resources. As Lola describes, this work is important because *'You can't work on a problem you*



Lola Díaz Feliz working in the laboratory.

Lola Díaz Feliz working with a family.

don't know about, and NeuroGen is the first step in addressing this.'

Lola explains that the principal objective of the NeuroGen collaboration is to determine the number of patients affected with HD in the Dominican Republic. The next step will be to visit patients in their homes and take blood samples back to Spain for genetic testing at Madrid's Hospital Universitario Fundación Jiménez Díaz.

Lola and her collaborators will then be able to characterise these patients according to their clinical tests, genetic tests, classification and treatment received. The team will conduct periodic visits to areas with the highest prevalence of affected families, and offer training for patients and family members. Personnel will also be trained to diagnose HD. Furthermore, close links with the team at Hospital Universitario Fundación Jiménez Díaz will be maintained through monthly telemedicine videoconferences.

Lola firmly believes that the fellowship has played a critical role in allowing her to take forward her career and she is now also completing a PhD under the supervision of Pedro García Ruiz and Miguel Angel García Cabezas at the Autonomous University of Madrid. When asked about her longer-term plans, Lola elaborates that *'My main objective is to change the current situation regarding HD in the Dominican Republic, and to work tirelessly as a specialist in movement disorders. Completing the EHDN/MDS-ES Fellowship has brought me closer to achieving that ambition.'*

'We are delighted that the EHDN/MDS fellowship has given Lola a chance to put her energy and enthusiasm into helping the HD community in her home community by establishing additional contacts, further developing her own clinical and research expertise and ultimately using this knowledge to set up NeuroGen to improve the situation for HD patients and their families in the Dominican Republic.'

Fionnuala Margreiter
Grants & Collaborations Manager

Outcomes of the EHDN Seed Fund Programme

Christine Capper-Loup, Scientific Project Manager and Michael Orth, Science Manager

Photo: G. Stautner, Artifox.com

Preliminary data can make all the difference in arguing one's case more convincingly in a grant application. To help researchers generate that precious pilot data, EHDN's Seed Fund scheme provides funding up to 50,000 EUR. From the scheme's inception in 2008, 379 seed fund applications have been submitted. The number of projects received at each deadline can vary, ranging from five to 27 over the past ten years (Figure 1). To date, 78 seed funds have been awarded out of a total of 379 applications. Most applications have come from Western Europe, and in particular, the UK (82 applications, of which 28 were approved) and Germany (61 applications, of which 18 were approved; Figure 2).

We request annual follow-up information for active projects. Based on the information received, 56 of the 78 funded projects are considered to have completed, and the majority of these projects have completed within 12 months. From funded projects, 58 publications have been generated to date, and include publications in *ELife, PLoS Biology, PLoS One, PLoS Currents, Experimental Neurology, European Journal of Neurology, and Journal of Huntington's Disease*. The average time between the approval of the project and first publication is 3 years. The total funding delivered for all seed fund projects to date is approximately 2.8 million EUR, with more than 11 million EUR having been generated as follow-on funding from major funding bodies including the UK Medical Research Council, CHDI Foundation, German HD association, and the French Research National Agency.

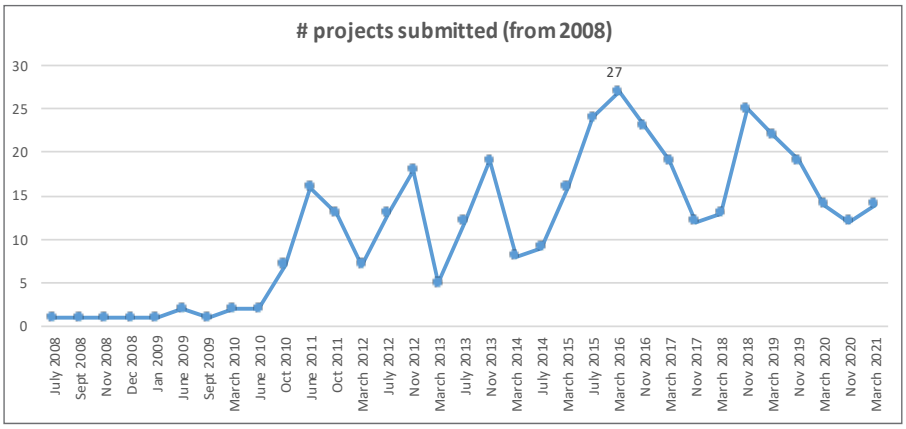


Figure 1: Number of projects submitted at each deadline from 2008 (total of 379). From 2011, the minimum number of projects received was five (March 2013) with a peak of 27 (March 2016).

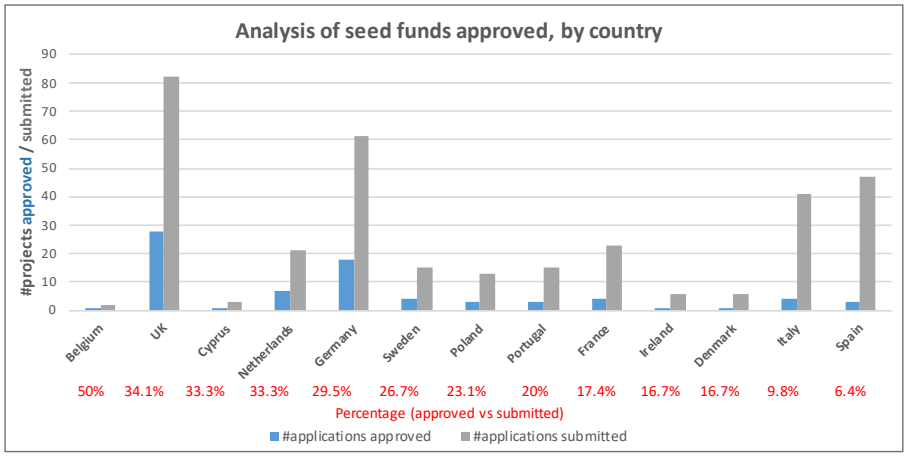


Figure 2: Number of projects approved (blue bar) and submitted (grey bar) per country (scale on the left). The percentage of approved vs submitted projects per country is given in red.

The number of publications produced with seed fund money, and in particular the further funding that applicants have been able to obtain using their pilot data, are both testament to the success of this programme.

If you are interested in applying, you can find further information here, click here for a description of the review procedure, or contact Christine Capper-Loup directly (Christine.Capper-Loup@siloah.ch).

Photo provided by Tom Massey

How does this drive forward clinical practice and research in HD?

This research highlights the importance of the early recognition and treatment of psychiatric and cognitive symptoms in HD gene carriers. The majority will experience some of these symptoms, often early in the disease course, with a significant negative impact on their daily lives. Future research should focus on defining HD-specific psychiatric/cognitive problems so that they can be targeted and assessed in clinical trials of therapeutics.

Publication Spotlight

Recently, the Registry Members of EHDN published the paper 'Timing and Impact of Psychiatric, Cognitive, and Motor Abnormalities in Huntington Disease' in the international journal *Neurology* (https://doi.org/10.1212/WNL.0000000000011893). Senior author Tom Massey, Clinical Academic Fellow in Neurology at Cardiff University, explains why this research is so important.

What were the key study questions?

What are the prevalence, timing, and functional impacts of psychiatric, cognitive, and motor symptoms in people with manifest HD?

How was this tested?

We analysed retrospective, cross-sectional data in a large population of 6,316 individuals with manifest HD from the observational REGISTRY study. Data came from clinical histories and each patient completed an HD clinical characteristics questionnaire that assessed eight symptoms: motor, cognitive, apathy, depression, perseverative/obsessive behaviour, irritability, violent/aggressive behaviour, and psychosis. We looked for associations between individual symptoms and functional outcomes.

What were the main findings?

We found that as the age at onset increased, motor presentations became more likely, and non-motor presentations less likely. Overall, 64.8% of our HD population reported at least one psychiatric or cognitive symptom at or before the onset of motor symptoms, with depression being the most common. The presence of each non-motor symptom predicted poorer functional capacity scores.

Get in touch with the Think Tank!

The EHDN's HD Science Think Tank brings together EHDN members and staff who are closely involved in supporting scientific research – including members of the Executive Committee, Central Coordination and the working groups – 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 Think Tank, please contact Kristina Bečanović: kristina.becanovic@euro-hd.net

Photo provided by Kristina Bečanović


Photo: Jenny Townhill


Photo: G. Stautner, Artifox.com

Update: Clinical Trials

Jenny Townhill and Tim McLean, Central Coordination

The following studies have been endorsed by the EHDN. Endorsement of a study protocol follows review by the EHDN Scientific and Bioethics Advisory Committee, which makes its recommendations to the Executive Committee. If endorsed, a formal letter of endorsement is then issued to the study sponsor, allowing them to inform relevant regulatory authorities and/or ethics committees that the study protocol has been reviewed and endorsed by a group of expert HD scientists and clinicians. The endorsement may also be posted on the EHDN website, signalling the same message to the HD community.

There are currently eight EHDN endorsed trials and studies that are active or in start-up (see Table 1), and notable updates are provided below. Further discussion on the discontinuation of the Roche GENERATION-HD1 and GEN-EXTEND trials and the Wave PRECISION-HD1 and PRECISION-HD2 trials can be found in the article by Anne Rosser and the interview with G. Bernhard Landwehrmeyer in this newsletter.

PRECISION-HD1 and-HD2

Dosing for these Wave-sponsored trials and their corresponding open label extension studies was stopped with immediate effect from 29 March 2021. Final study visits were performed over the following weeks, and all studies terminated in mid-May.

WVE-003

Wave's first HD candidate using their modified antisense oligonucleotide (ASO) with novel backbone chemistry (WVE-003), is anticipated to begin dosing this year. This compound targets SNP3, one of the single-nucleotide polymorphisms (SNPs) that are most commonly found in association with the HD gene, and estimated to occur in approximately 30% of people with HD. The previous PRECISION-HD1 and -HD2 trials targeted SNP1 and SNP2, respectively. Participants will be pre-screened to check they have SNP3 prior to participation.

GENERATION-HD1

It was announced that dosing would be stopped in the Roche GENERATION-HD1 Phase III trial of tominersen on 22 March 2021, and paused in the open label GEN-EXTEND trial whilst a full unblinded analysis is conducted. Currently, participants are being encouraged to continue to attend follow-up visits for both studies.

HD-DBS

This multi-centre trial exploring the safety and efficacy of deep brain stimulation in HD will shortly complete recruitment, with the last participant scheduled for randomisation in June 2021, bringing the total number recruited to 48. The final study report is expected in 2022.

DOMINO-HD

Following a delayed start caused by the COVID-19 pandemic, this study is now open to recruitment in the UK and Spain, with sites in Germany and Poland expected to open during the course of 2021. For more information visit: https://www.cardiff.ac.uk/centre-for-trials-research/research/studies-and-trials/view/domino-hd

PROOF-HD

This ongoing trial of pridopidine recruited the first participant in October 2020, in the USA, with the first participant recruited in Europe in the UK in April 2021. For more information visit: https://huntingtonstudygroup.org/proof-hd/

HDGeneTRX2/AMT-130-2

UniQure has recently announced the initiation of this European trial, which is expected to start recruitment in

the second half of 2021. This open label surgical trial is linked and will be run in parallel to the UniQure North American trial, HDGeneTRX1/AMT-130-1 randomised, double-blind, sham-controlled trial.

Table 1: EHDN-endorsed Trials and Studies
(Active or in Start-up)

Registration ID	Sponsor	Trial name	Phase	Intervention	Mechanism of Action	Estimated Enrolment	Location(s)
NCT02535884	Heinrich-Heine University, Duesseldorf	HD-DBS	II	Deep brain stimulation	High-frequency stimulation of the globus pallidus	50	Austria, Germany, Switzerland
NCT03761849	Hoffmann-La Roche	GENERATION-HD1	III	RG6042/ tominersen	Allele-nonselective ASO	909 (completed enrolment: 791 participants)	Australasia, Canada, Europe, Japan, USA, Latin America
NCT03842969	Hoffmann-La Roche	GEN-EXTEND	OLE	RG6042/ tominersen	Allele-nonselective ASO	1,050	USA, Canada, Europe
NCT04120493	UniQure Biopharma B.V.	AMT-130-02 HD Gene TRX2)	Ib/II	rAAV5-miHTT	miRNA nonselective (gene therapy)	15	UK, Germany, Poland
NCT04556656	Prilenia	PROOF-HD	III	Pridopidine	Sigma-1 receptor (S1R) agonist	480	Australasia, USA, Canada, Europe
TBD	Wave Life Sciences Ltd.	WVE-003	Ib/IIa	WVE-003	Allele-selective ASO	36	Canada, Europe
NCT04406636	Triplet Therapeutics	SHIELD-HD	N/A	N/A	N/A	60	USA, Canada, Europe
N/A	Cardiff University	DOMINO-HD	N/A	N/A	N/A	300	Ireland, Poland, Spain, Switzerland, UK

Note. ASO = antisense oligonucleotide; OLE = open label extension

• • •

Update: Enroll-HD

Olivia Handley, Enroll-HD Global Platform Manager

The focus of the Enroll-HD update in this issue is HDClarity, the longest-running study to use the Enroll-HD platform. Here, we describe what HDClarity is, why it is so important, and why we need more participants to take part.

What is HDClarity?

HDClarity is the largest ongoing study collecting cerebrospinal fluid (CSF) in HD and is funded and supported by the CHDI Foundation. The study sponsor and coordinating centre is University College London, and Ed Wild leads the initiative as Chief Investigator.

Photo: G. Stautner, Artifox.com

Why is HDClarity so important?

HDClarity is an important initiative aiming to facilitate therapeutic development for HD. As the number of therapeutic trials continues to increase – in particular, those focusing on the development of novel therapeutics – we need to better understand potential biomarkers for HD. Such biomarkers are necessary to evaluate how well novel therapeutics reach their intended target and have a biological effect, their effectiveness in improving clinical signs and symptoms, and finally, to track disease progression over time. To this end, CSF is an ideal biospecimen due to its close proximity to the brain.

Until HDClarity started in 2016, there was no high-quality CSF collection in a well-characterised, longitudinal cohort of HD participants. HDClarity has created that opportunity.

Who can take part?

HDClarity is open to all Enroll-HD participants who have been tested and confirmed to have the HD gene expansion (with or without symptoms of HD) and healthy control participants.

Where is HDClarity happening?

HDClarity is running in 26 sites across seven countries and plans are currently underway to expand the number of countries and sites.

How many people are taking part in the study?

Over 500 participants have already been successfully screened and have attended at least one sampling visit. However, we are targeting a recruitment goal of 1,200 participants. This means the number of participants needs to increase almost three-fold!

What is next for HDClarity?

HDClarity is providing the largest, longitudinal CSF collection for HD. But this precious resource is exhaustible and in high demand by researchers. For HDClarity to meet the needs of the scientific community, we rely upon continued commitment from HD families. 'There's an old proverb: If you want to go far, go together. All the progress we've ever achieved in HD has been a team effort involving researchers, clinicians, and HD-impacted families,' noted Ed Wild. 'HDClarity has the potential to dramatically accelerate the development and testing of new treatments, but we want to go far – fast! We need more clinical sites and more patient and control volunteers if we're going to bounce back from the Covid pandemic and get the large number of samples we need.'

As a game-changer in the research arena for HD, the ongoing work of HDClarity is critical if we are to answer more scientific questions and further facilitate much-needed therapeutic development in HD. As lockdown restrictions begin to lift around the world, we are now in a position to resume this research with renewed vigour. If you would like to find out more about HDClarity, please contact hello@hdclarity.net.

> *'All the progress we've ever achieved in HD has been a team effort involving researchers, clinicians, and HD-impacted families.'*
>
> ***Ed Wild***

Countries participating in HDClarity:

- Canada
- Germany
- Italy
- Poland
- Spain
- UK
- USA

Countries coming soon:

- Austria
- Australia
- Portugal
- France
- Norway
- Switzerland
- New Zealand

Update: New Seed Funds Awarded

Catherine Deeprose

The EHDN has recently awarded seed funding for two exciting projects.

Silvia Gines Padrós at the University of Barcelona, Spain, has been awarded funding for her proposed project on neuronal dysfunction in HD.

Most aspects of nervous system function rely on crosstalk (interactions) between neurons and nonneural cells known as glia, particularly the specialised star-shaped glial cells known as astrocytes. Importantly, this neuronal-astrocyte communication implies the release of different factors that may influence both types of cells and modulate neuronal function. This project will decipher whether HD brain pathology in the striatum relies on neuronal-autonomous processes or whether astrocyte-neuron crosstalk is playing an essential role.

Itamar Ronen at Leiden University Medical Centre, Netherlands, has been awarded funding for his proposed project on the association between iron dysregulation, neuroinflammation and clinical measures in HD.

As with other neurodegenerative diseases, damage to neurons in HD seems to be associated with inflammation in the affected brain region. At the same time, many neurodegenerative diseases are associated with a build-up of iron in affected brain areas, particularly in activated microglia. This project will utilise magnetic resonance imaging to determine the distribution of iron in the brain and test the association of this with cerebrospinal fluid markers for neuroinflammation and neurodegeneration as well as clinical measures of disease progression and severity.

Seed funds are intended to support pilot studies that will eventually kickstart larger projects. The next deadline for applications is 1 November 2021. More information about the programme and how to apply can be found here or you can contact Christine Capper-Loup (Christine.Capper-Loup@siloah.ch) for further information.

Update: Funding Opportunities

Fionnuala Margreiter,
Grants & Collaborations Manager

Three new funding opportunities of relevance to HD have recently been announced.

In the new Research and Innovation programme Horizon Europe (2021–2027; 95.5 Billion EUR), one of the calls in the work programme includes a specific focus on the development of new effective therapies for rare diseases. The current deadlines for this two-stage call are: Stage 1 – February 2022 and Stage 2 – September 2022.

The European Research Council has announced a call for Advanced Grants in any area of research with a deadline of 31 August 2021. Applicants should be active researchers with an established track record.

Finally, the European Cooperation in Science and Technology has announced a call for networking projects, including workshops and other networking activities in a wide range of science topics. The next deadline is 29 October 2021.

Follow our Grants and Collaborations Manager on Twitter @EHDN_GRANTM for the latest news on EU funding and events and policy developments in the domain of rare diseases.

Images:
Zalamea la Serena, Badajoz, Extremadura – Credit Asociación Extremeña de Huntington

Cáceres, Extremadura – Credit Asociación Cacereña de Huntington;

Madrid – Credit Asociación de Corea de Huntington Española;

Baleares – Credit Associació Balear de la Malaltia de Huntington;

Send Us Your Photos!

These beautiful photographs are generously shared with us by Asuncion Martinez, President of the Asociación Jóvenes Huntington, Spain.
'Light It Up 4 HD' was one of the activities conducted as part of Huntington Disease Awareness Month in May this year. As we can see, Spain was especially active in this activity!
Asun provides a little bit of history by explaining *'On 4 May 2015, Jamie a volunteer from the Huntington Society of Canada (HSC) was instrumental in lighting up the CN Tower to raise the visibility of Juvenile HD (in purple) and HD (in blue) and Huntington Disease Awareness Month, held each May. When the sun set on 4 May, hundreds of thousands of Canadians saw the CN Tower lit up in purple and blue. And our HD community lit up with pride.'* (From the webpage of the Huntington Society of Canada).
Asun further explains, *'Since 2015 this initiative had been growing worldwide. To me, it is very inspiring to see the HD community fighting together. The HD community is so unique!'*

Our photo experiment continues!

Whether you're affected by HD personally, or you're a carer, clinician or scientist working in the field, we'd like to publish your images in the newsletter. If you have a photo that provides an insight into your daily life, that you think might interest or inspire other EHDN members – or make them think differently about the disease – please send it to us along with a few words explaining who you are and what the image shows: **newsletter@euro-hd.net**

EHDN Remote Meeting

This year, the EHDN Remote Meeting will take place via Zoom over three half-days from **Thursday 9 September to Saturday 11 September 2021** (14:00–19:00 CEST each day). Following on from the success of the EHDN Remote Meeting in September 2020, the event once again promises lively exchange about HD research and updates on the latest news in the field. In addition, the results of the voting on the adoption of the amended EHDN Constitution (set to open from mid-summer) will be presented at this meeting.

- Registration is open until September 2021. The full programme is available here.
- Abstract submission has been extended to Sunday 4 July 2021.

Please contact ehdn2021@euro-hd.net with any questions.

Please also note that the **EHDN Plenary Meeting** will take place in Bologna from **16 September to 18 September 2022**. We very much look forward to seeing you in person there!

• • •

Huntington's Disease Alliance UK and Ireland: National Awareness Campaign

Joanne Dobbie, Head of Fundraising, Huntington's Disease Association

In 2020, the four national charities supporting people living with HD across the UK and Ireland came together to form the Huntington's Disease Alliance UK and Ireland to develop a national awareness campaign around HD.

#FamilyMatters was launched in May 2021 covering various aspects of awareness raising including the #FamilyMatters website, which invited anyone affected by HD to share their stories about living with this devastating disease. A series of films shows the lives of people affected by HD in various ways, from partners to parents to children. These films are giving people the opportunity to tell the world about their experiences.

We have also carried out a comprehensive survey, one of the largest of its kind for people living with HD and you can read the findings here.

The Alliance has been working with celebrity ambassadors including George Rainsford, who portrayed someone with a diagnosis of HD on the UK BBC drama Casualty, and Sarah Winckless, an Olympic medallist and double world champion rower, who has tested positive for the Huntington's gene. George and Sarah have generously given their time and support leading to lots of newspaper, radio and television interest from the media. Reactions to the campaign have been very positive and we hope to build on this each year.

• • •

Huntington's Disease Association

Huntington's Disease Association: Upcoming Events

The Huntington's Disease Association (HDA) will be hosting their annual family event and AGM (including

Photo: Huntington's Disease Association

keynote talks and workshops) online this year due to the ongoing COVID-19 situation. Further information will be released closer to the event date, so keep an eye on their website in the coming months.

In addition, the HDA are holding regular virtual carers meetings, Juvenile HD Zoom meetings and online coffee mornings (telephone 0151 331 5444 or email info@hda.org.uk for more information on these).

Finally, an exciting array of fundraising activities are planned throughout the year. From climbing Snowdon, running marathons and taking part in a Halloween walk, there's something for everyone. Visit the 'Events' section of the HDA website to see what activities are planned for 2021, as well as upcoming webinars.

• • •

Annual Huntington's Disease Therapeutics Conference

The 16th Annual Huntington's Disease Therapeutics Conference: A Forum for Drug Discovery & Development took place 27–29 April 2021. Highlights included clinical trial updates from Wave Life Sciences and Roche, and discussion on upcoming developments in the therapeutic pipeline for new ways to treat HD, including novel genetic technologies. An informative and engaging blog on the proceedings can be found at https://en.hdbuzz.net/304.

• • •

European Huntington's Association: May Awareness Month 2021

Astri Arnesen, President, European Huntington Association

The 2021 May Awareness Month has been different from those in previous years due to the pandemic and the restrictions that still are in place in most countries. Nevertheless, this May, the HD community has been more active than ever. We have all learned to make more use of online activities and opportunities, and during May, this was apparent with hundreds of posts on social media, webinars and other online activities all over Europe. The European Huntington Association (EHA) coordinated some activities and made a nice logo and a Facebook Frame. We also asked all the EHA member associations to promote the Call for Action document in which we advocate for better access to treatment and care for all patients. The petition has been sent to politicians, clinicians and other stakeholders and by the end of May achieved 257 signatures. We would be grateful if all EHDN members would also support us and sign the petition.

EHA also organised a series of webinars, with topics including the latest news from Roche and Wave Life Sciences, a webinar with Alice Wexler – 'Life with HD Comes in Many Flavours' and two featuring young men from HD families, Dimitri Poffé and Adriano Meireles.

And last, but not least, many associations throughout Europe and beyond took part in Light It Up 4 HD, posting photos on Instagram with #LightItUp4HD.

• • •

MDS-ES and EHDN Joint Online Course Series: Huntington's Disease: From Foundational Principles to Assessment and Treatment

Free HD Virtual Clinical Training Course

EHDN is delighted to announce that a free HD virtual clinical training course developed together with the Movement Disorders Society-ES will be held in October 2021. Registration is open now. MDS-ES and EHDN Joint Online Course Series: Huntington's Disease: From Foundational Principles to Assessment and Treatment (movementdisorders.org)

All photos: G. Stautner, Artifox.com

Taking Stock:

Interview with G. Bernhard Landwehrmeyer

G. Bernhard Landwehrmeyer is one of the founding members of EHDN and served as the first Chair of the Executive Committee of EHDN from 2004 to 2014. He is a Full Professor of Neurology at the University of Ulm, where he also directs the Huntington Disease Centre. Since 2011, he has been the Principal Investigator of ENROLL-HD. He shares here his insights and perspectives on past, current and future HD research.

To start, could you summarise what you view to be the biggest achievements in HD research over the past ten years?

For me, there have been three major achievements. The first is the establishment of a global study into HD – ENROLL-HD. In the context of the European HD network, we had REGISTRY which started in 2004 and was an observational, longitudinal prospective cohort study. In parallel, mostly in North America but also Australia and in some parts of Europe, the Huntington's Study Group was conducting a similar natural history study called COHORT (Cooperative Huntington Observational Research Trial). From 2011 onwards, both were combined into one truly global platform and expanded the reach to South America and Asia.

> *'Given that HD is a rare disorder, to make real progress both in understanding and advancing treatment options, it is vital that the HD community works together and I am proud that this has been achievable.'*

HD exists in every single country in various proportions relative to the population. Given that HD is a rare disorder, to make real progress both in understanding and advancing treatment options, it is vital that the HD community works together and I am proud that this has been achievable. While there are still countries that we would love to incorporate into ENROLL-HD, we are making progress in creating a unified, global response to the global problem that is HD.

The second achievement, obtained through these large observational studies, the efforts of many family members affected by HD, and more than 200 study sites across the globe, was the development of a critical mass of data and biomaterials that enabled meaningful genome-wide association studies. These sought to identify genetic modifiers of HD, and as many will recall, the first study led by James Gusella and the GeM-HD Consortium was published in 2015 followed by another in 2019. This work led to

G. Bernhard Landwehrmeyer at the EHDN Plenary Meeting, Barcelona 2014

emphasising that the critical predictor of onset as well as age of death in HD appears to be the dynamic length of CAG repeats – more so than the polyglutamine length of the translated product.

The third major achievement from my perspective is that a study aiming to downregulate the further production of mutant huntingtin gene products was completed using antisense oligonucleotides (ASOs). This compound was developed originally by Ionis Pharmaceuticals and then licensed to Roche, and is what we know as tominersen. This work showed that with intrathecal injection (that is, injection directly into the cerebral spinal fluid) of ASOs, you can, in a dose-dependent fashion, lower mutant huntingtin in cerebral spinal fluid, demonstrating target engagement. In other words, tominersen was doing exactly what we hoped it would do. Critically, this work showed that in real people, in real life, we could modify the mutant gene products that are beyond doubt important for the pathophysiology of HD.

But of course, the recent Roche and Wave Life Sciences trials discontinuations have been met with huge disappointment across the board. Can you describe your own response to these events?

For me personally, these trial discontinuations are bad setbacks – but no more than that. Furthermore, in my view, the two setbacks are quite different. The Wave study was a Phase I/IIb study, so an early study in terms of clinical development. The intention was to explore whether the compound would be able to achieve target engagement, evidenced by the lowering of mutant huntingtin in CSF. The hope was to see something similar to what we had observed with tominerson but unfortunately, this was not the case. We need to remember though, that by default, any Phase I study runs this sort of risk and that is why we do them. The Roche study discontinuation is a different ball game altogether to my mind because we are talking about a Phase III study where the hope was to demonstrate efficacy. A far larger number of HD patients participated (more than 800) and therefore the implications are far more extensive and the high visibility of this trial impacted the entire HD community.

G. Bernhard Landwehrmeyer at the EHDN Plenary Meeting, Barcelona 2014

G. Bernhard Landwehrmeyer being interviewed at the EHDN Plenary Meeting, Barcelona 2014

It is important to keep in mind that after the successful completion of the previous Ionis/Roche Phase I and IIa studies demonstrating target engagement in a dose-dependent fashion combined with good clinical tolerability and safety, it made sense to go for a Phase III study. Often in clinical development, you would do a proper dose-finding study to determine which doses works best before that. However, this would have taken quite some time – perhaps 2 years at least, and would have required a large number of participants (about the same number enrolled in the Phase III study).

Given the data available at the time, and the conceptual thinking that it is important to reach all relevant brain areas affected in HD, it appeared important to create a steep concentration gradient. Thus, the decision was made to go for rather high doses administered in close temporal proximity.

In retrospect, there were some warnings that potentially the dose chosen, or the dose regime chosen in the GENERATION-HD1 study might come with problems but to this day, I believe that the decision made sense at the time and I personally supported it.

We all hoped that tominerson would deliver on the promise of changing the relentless downward trajectory of HD, and in the most optimistic version, might even reverse some of the signs and symptoms. That clearly did not happen. But I think the evidence available currently suggests – at least to me – that the disappointing findings so far may be the consequence of an unfortunate choice of dose in the sense of too high an exposure and not evidence for this approach being unhelpful altogether.

What is unfortunate, currently, is that we are losing time. In HD, the pressure of time is like having a time bomb wrapped around your chest and this is true, unfortunately, for a number of disorders, including cancer. We need new horizons and new treatments to be delivered in a timely fashion. And that is the real setback here. The sad thing is that we have not been more successful in delivering on the promise of modifying the course of HD tomorrow as opposed to in a couple of years. Nonetheless, I remain hopeful that in my professional lifetime, I will see truly disease-modifying therapies in the clinic.

What lessons do you think may be learned from these recent trial setbacks?

One potential lesson is that the enthusiasm to deliver disease-modifying therapies tomorrow instead of later, is not always conducive to the best decision making. The eagerness to make a difference and the pressure to do something today may get in the way of doing everything in the most thorough way. I think it is always going to be a complicated balance, not least because there are always things you don't know. My impression regarding the Roche trials is that we were perhaps a little bit overenthusiastic and therefore, moved faster, than now with the benefit of hindsight, we should have.

And now, looking forward, what strengths do you feel the HD community can offer?

I believe one of the biggest strengths of the HD community is its resilience – and this was tested by the recent clinical trial setbacks without doubt, but remains impressive. In my daily practice, I continue to be impressed by the inventiveness of people to deal with the objectively, very, very difficult situations imposed on them and their families by HD. Many people are coming up with amazing solutions to really hard problems.

The other salient feature of the HD community is the collaborative spirit. I think it is fair to say that many fields of medicine are very competitive (and this includes HD research). This was particularly prominent in the time of gene hunting. There is only one group that eventually, can uncover a gene and although other groups will be working on it, there will be only one winner. This can induce an unhealthy competitiveness. But even during the period of gene hunting, the HD community (thanks to numerous people, Allan Tobin included) worked to achieve a collaborative spirit, which is not an easy thing to do. This is something that I really like about the HD community – the readiness to collaborate. In a way, this is facilitated by the fact that HD is a rare disease and so working together comes naturally. Nobody on this planet has an outpatient clinic that is large enough to address all the important research questions in HD, so there is a need for collaboration.

G. Bernhard Landwehrmeyer with Astri Arnesen and Bea de Schepper, both EHA, at the EHDN Plenary Meeting, Barcelona 2014

G. Bernhard Landwehrmeyer with Jeff Caroll and Ed Wild taking the 'cream pie challenge' at the EHDN Plenary Meeting, Barcelona 2014

G. Bernhard Landwehrmeyer with Raymund Roos and Sarah Tabrizi, at the EHDN Plenary Meeting, Den Haag 2016

When discussing collaboration, I also refer to our HD families who are a critical component in their willingness to work with clinicians and scientists in such a non-selfish fashion. Again, that has to do with the hereditary character of the disorder, in my opinion. If I talk to research participants in my centre, very often, they tell me, 'It's not about me, it's about my children. I want a better future for my children.' I think that is exactly the spirit that one needs for research. This is an important strength of the HD community.

As COVID-19 restrictions continue to ease across Europe, how do you envisage HD research progressing both in the near and more distant future?

The COVID-19 pandemic and the associated restrictions obviously imposed on research in a number of ways. But the pandemic also opened up new opportunities. I don't want to in any way sugarcoat the challenges that were induced by the pandemic and the tragedies that affected many families. But what I think is important to note is that people started to realise that there are new and important ways to be in touch and to communicate remotely.

Many of my participants, including elderly ones who are not particularly familiar with the digital era, started to lose the fear of exploring these new tools, such as using Facetime on their mobile phones and taking part in virtual visits with their physician. This reflects learning on both sides – we cannot do everything remotely (such as blood draws, for example) but there is still a lot that we can do. We all started to appreciate that it might be more efficacious for optimising treatment to see people more frequently. Because we're talking about a movement disorder (or at least, that's one aspect of HD), we need to look at whether certain medications are doing their job or have detrimental effects. Of course, remote consultations do not allow comprehensive assessment, but they do give the clinician the opportunity in a time-efficient fashion to be more frequently in touch and ensure that a better balance is achieved relating to the benefits and side effects that come with all medications.

In addition, as physicians, we now have the opportunity to visit people virtually in their homes and that is always extremely informative. In the old days, physicians would go to people's homes and be able to open the door and observe important details such as how the patient and their family are coping with daily tasks, for example. This type of understanding of the broader context is only apparent if you visit someone in their home. Now, we can ask someone to take their phone and using their camera, walk us through their home, and this insight is really helpful for the physician to obtain a more realistic impression of the situation and work in a multidisciplinary way, because we can engage physiotherapists, counsellors, and so on, as well as relatives. For people living, say, an hour or even two hours away from an HD centre, it's an enormous effort for caregivers, relatives and partners to make that visit and be able to discuss their situation, what could do done to help, and their perspectives. If people can focus on these issues rather than the logistics of getting to clinic, the difficulties preventing people from getting help can now be more easily overcome, and that gives us real reason for hope in terms of patient care.

G. Bernhard Landwehrmeyer at the EHDN Plenary Meeting, Vienna 2018

Finally, what is the key question that will we need to look at in future research?

A major issue that I believe we should focus on is what I like to call environmental modifiers. It is obvious that factors such as how you live your life and how fit you are, impact many aspects of disease. Studies in Venezuela looking into environmental and genetic modifiers have shown that, particularly in somewhat deprived circumstances, the environment plays a critical role. For example, if you do not have enough to eat, given the high energy consumption that is a hallmark of HD, you are likely to have a less favourable course of the disease. If there is nobody to train you to improve your muscle strength, you will find it more difficult to maintain independence because you don't have the appropriate training.

'I remain hopeful that in my professional lifetime, I will see truly disease-modifying therapies in the clinic.'

Currently, we have a fairly reasonable idea of what genetic modifiers there may be, at least for some aspects of the disease. The next big frontier will be understanding environmental modifiers. Does it make a difference how you live your life in the early stages of HD, if you are active for example, or if you get enough sleep? We have only very limited knowledge about these factors at this point in time and this is why by concept we wanted ENROLL-HD to be global. For instance, in Latin America, there are a lot of genetic descendants of people from Europe but their circumstances are quite different. By highlighting differences in circumstances, we will get a better sense of potential intervention points.

This is an important perspective. It is clear that our genetic make-up is of impact but it is equally likely that for HD and many disorders, our environment and how we live is important too. To disentangle this in a disease that has a defined root cause and for which we have identified genetic modifiers, is going to be productive and give us important insights into HD but also beyond HD. This is why continuing our global, observational studies and broadening the path to a more extensive characterisation is quite important to my mind.

• • •

Follow us on Twitter:
@EHDN_*News*

Reader Survey:
Tell Us What You Think Of EHDN *News*

Dates for your diary

Save the dates for:

- Accessing the community with Huntington's disease webinar Friday 2 July 2021. Please note that attendees are required to register in advance.

- EHDN Remote meeting, Thursday 9 September to Saturday 11 September 2021. Registration is open until September 2021. The deadline for abstract submission has been extended to 4 July 2021.
- International Parkinson and Movement Disorder Society International Congress, 17 September to 22 September, 2021.
- FENS The Brain Conference: RNA Mechanisms and Brain Disease in Rungstedgaard, Denmark, 20 October to 23 October 2021. Early registration ends 10 July 2021, regular registration ends 3 August 2021.
- EHDN Plenary Meeting in Bologna, Italy, 16 September to 18 September 2022.