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EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Photo: Jeremy Bishop

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Reflecting, Learning and Moving Forward

Catherine Deeprose

Our March issue of EDHN News coincides with the anniversary of one of the most significant advances in the history of HD – the publication of the paper unveiling its genetic cause. The trajectory of HD research was forever changed and because of this, 23 March each year will now be HD Gratitude Day, in recognition of the tremendous input of all the families and researchers involved. Our article, led by Cristina Ferreira and Katrin Barth, explains the importance of this date and encourages everyone to get involved. In addition, Yury Seliverstov shares his reflections on the very human cost of the Ukraine conflict on HD families and G. Bernhard Landwehrmeyer provides a poignant and personal tribute to Christiane Lohkamp. Amongst lots of exciting updates, we have the pleasure of meeting Flaviano Giorgini, who shares his insights on working in the HD field, being part of the HD community, and the importance of reflecting, learning and moving forward.

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Photos: Cristina Ferreira

Cristina Ferreira demonstrates the Gratitude Day Logo Play Challenge in action! To memorise it, use this limerick by Jimmy Pollard:

Flat hands facing each other
Great! Here's another!
Thumbs meet tip to tip
Three little ones dip
Now you're making H-Hands, my brother!

The logo was conceived and designed by Cristina Ferreira´s daughter (Sofia Sena), and further interpreted by the Factor-H designer Manyee Lieu. The position of the hands represents Huntington, Hope and Humanity – the vectors of this partnership and the three humanitarian values of Factor-H. The eight stars are present in recognition of the Venezuelan flag. The heart-hand around these is symbolic of our global partnership and unending gratitude. The original concept is that the Gratitude Day Logo can be freely replicated, all around the world, just using our own hands.

23 March: Anniversary of the Discovery of the HD Gene
A Day to Celebrate
A Day to Show Appreciation

Cristina Ferreira, Katrin Barth, Asuncion Martinez, Jimmy Pollard, Catherine Deeprose, Ignacio Muñoz-Sanjuan

This year marks the 30th anniversary of the discovery of the HD gene. After a long and difficult quest, on 23 March 1993, a collaborative team of researchers in multiple laboratories (The Huntington's Disease Collaborative Research Group) published their landmark paper on the genetic basis of this devastating family disease. Finally, the cause of HD had been isolated: a single mutation of a gene on chromosome 4.

While one gene was found to be responsible for HD, the work behind the discovery involved many researchers who worked collaboratively and shared data across continents. As thousands of samples were needed, the discovery wouldn't have been possible without the many HD families around the world who shared their family

histories and donated blood for DNA extraction along with their precious time and energy.

In the area of Maracaibo, Venezuela, the prevalence of HD is the highest known in the world and this specific population became the focus of intense research efforts. Every spring for more than 20 years, Nancy Wexler led an international team of researchers and clinicians on a month-long visit to examine, study and care for HD families in this region. This team traced the path of the disease through 10 generations in a family tree that included more than 18,000 people, and during these visits, the Venezuelan HD families generously and consistently donated blood and other biological samples.

This project ultimately led this collaborative group of researchers to the detection of the critical difference on a single gene, located on chromosome 4, which they named the Huntingtin gene. Everyone with a number of CAG triplets (cytosine, adenine and guanine) above a certain threshold eventually would develop HD, whereas individuals with repeats below that threshold were not affected.

This foundational discovery revolutionised HD research. The discovery of the gene also made predictive, prenatal and pre-implantation genetic diagnosis viable options for families, which enables individuals carrying the HD mutation or at-risk for HD to bear children while avoiding passing on the disease. These advances now play an enormous role in allowing individuals to prepare for the future. It also catalysed research efforts by enabling the generation of animal and cellular models of HD, to investigate the precise mechanisms of disease and to test potential therapeutics, allowing the study of HD in the laboratory. Beyond the HD field, the discovery of the HD gene was pivotal in advancing human genetics research more broadly, including the study of the human genome.

The gene discovery was a tremendous milestone. Many investigators working today in HD research and care became interested in HD while participating as postdocs, students or junior clinicians with the research teams in Venezuela. The partnership between families, therapists, scientists, doctors and everyone else in the HD field has evolved and strengthened in the last 30 years. One thriving example is the European Huntington's Disease Network (EHDN), the foundation of which was led by G. Bernhard Landwehrmeyer (who was involved in the work in Venezuela) and others who formed part of the research group in 1993.

The search for treatments is ongoing. The gene discovery was a significant milestone but now, 30 years later, we strive to silence the effect of the mutation.

Today, families in Venezuela are not only suffering from HD. They are also suffering in conditions of extreme poverty and vulnerability, in one of the poorest areas of the world.

But unlike HD, poverty is already curable. Since 2012, Factor-H has been working to support these HD families and has built an infrastructure to ensure funding is provided where it is needed the most in the Venezuela area. Factor-H works closely with local non-governmental organisations in Maracaibo to implement their programmes through the work of employees and volunteers. These activities range from providing access to medical care, supporting caregivers and at-risk youth, and providing basic assistance to the most vulnerable families. Donations to support this are important, needed, and of course, well-received. All donations go entirely to support these programmes.

We want to show the Venezuelan HD families and their successors our gratitude for their vital contributions to the discovery of the HD gene and in doing so, providing a vision of hope for the future. For this reason, 23 March is now HD Gratitude Day.

This is the 'call to action day', to all who feel impacted by HD or stand in empathy with the HD community, in any way, anywhere. We invite you to take part in thanking the Venezuelan HD families for making our research achievements possible. So, team up with your colleagues in HD and share photos, celebrate the gene discovery and donate to Factor-H.

From this year forward, 23 March will be a day to recognise, reflect upon and express our collective gratitude for the partnership between families and scientists that allowed this tremendous achievement.

So, team up with your colleagues in HD and share photos, celebrate the gene discovery and donate to Factor-H.

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Factor-H

Starting as a project in 2012, Factor-H has grown through the successful completion of programmes with HD communities in Latin America. Now a charitable US-based charity, 2019 marked Factor-H's first full year of operations as a non-profit organisation. The work of Factor-H is dedicated to enabling HD communities in Latin America to exit the poverty and disease cycle, offering a better chance to live with dignity and hope, and facilitating a less difficult future for new generations of at-risk children.

Factor-H is asking individuals and their families, allied healthcare professionals, and staff in clinics, laboratories and offices all around the world to get involved.

And there are lots of ways this can be done, on social media and in person! Find out more and follow Factor-H on social media:
W: https://factor-h.org/
F: https://www.facebook.com/factorh.org/
YouTube: https://www.youtube.com/channel/UCPGADaoHc1IOkj6BSJ-WHbA
Twitter: @FactorH_LatAm
LinkedIn: https://www.linkedin.com/company/factor-h-hd/

Further Reading
https://www.nytimes.com/2020/03/10/health/huntingtons-disease-wexler.html
https://dana.org/article/we-found-the-gene-huntingtons-disease-after-the-cheering/

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Bearing Witness to the Ugly Reality of War

Yury Seliverstov, Neurologist and Researcher, Ulm University

For millions of people in Ukraine, 24 February 2022, marked a critical turning point. Overnight, life was redefined as that which took place before and after the start of war. Although some people may try to pretend that nothing has really changed and that life goes on, war affects everyone without exception — some directly and some indirectly, some at the start and some a little later. This is the ugly reality that we are currently bearing witness to.

Yury Seliverstov

Photo: Yury Seliverstov

While the inevitably serious long-term consequences of the war are yet to come, the HD community has already been impacted. When I worked as a movement disorder specialist in Moscow, I worked with people with HD not only from Russia but neighbouring countries, including Ukraine. I stayed in contact with many of these people and share here some of the insights I have gained into how the war is affecting their lives.

In Ukraine, while some people were evacuated, some were simply physically unable to leave and are now trying to somehow survive under fire and bombing.

Meanwhile, in Russia, many highly qualified doctors and researchers who do not support the war left the country – creating even more obstacles for the people with HD to receive adequate care. But also, many who disagree have been forced to stay, either because of problems with relatives or a lack of financial means to leave the country. This means they must now try to avoid potential persecution.

For the foreseeable future, access to participation in cutting-edge clinical trials is closed to the country. The long-awaited launch of Enroll-HD has also been suspended, and people with HD are now unable to participate as easily in the activities of our international HD community. Some people, perhaps out of misguided patriotism, may declare that the country does not really need all that anyway. But I believe that to declare such a thing in today's world is

not only foolish but denies the enormity of the destruction and suffering that is being inflicted.

This ongoing and severe stress continues to place unprecedented pressure on people with HD and their carers and relatives. In September, some people identified as premanifest HD mutation carriers tried to hide in other countries to escape conscription, while others tried to prove to the so-called medical board at the conscription sites that they could not and did not want anything to do with the war.

It is clear that the wounds that continue to be inflicted through this war will not heal for a long time, and unfortunately, it is hard to envisage a quick, humane and reasonable resolution to the unleashed conflict.

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In Memory of Christiane Lohkamp

G. Bernhard Landwehrmeyer,
Ulm University

At the very end of 2022, on 31 December, Christiane Lohkamp passed away at the age of 81 years, having endured years of decline in her strength and abilities that progressively limited her independence. When darkness shaded her, death was a welcome guest, relieving her of advanced Parkinson disease. Her death, however, leaves the EHDN and HD community at large deprived of an exemplary, strong and inspiring advocate for HD.

Photo: Kindly provided by G.B. Landwehrmeyer

Christiane Lohkamp

Christiane's life was shaped in many ways by HD. Her husband Uwe developed behavioural issues all too often associated with HD well before developing the characteristic motor signs and cognitive decline. Both Uwe and Christiane were unaware of any family history at the time of their marriage and conceiving children, and the diagnosis of HD was both challenging and delayed. It was hard living with Uwe. When Uwe was no longer able to work, Christiane stepped in and succeeded him in his demanding job at the Landesamt für Denkmalpflege (State Office for Preservation of Monuments) Baden-Württemberg in 1988. Christiane could step in because she was a trained architect with a degree from the Technical University Karlsruhe, inspired by her father, a well-respected Professor of Architecture at Stuttgart University, Günter Wilhelm. It was difficult to raise their two children, Anne and Mark, as she juggled the tasks of being the sole breadwinner, parent and caregiver – a situation all too familiar to HD families. In addition, there was the worry whether her tall, beautiful daughter, an aspiring model who made it to Los Angeles, and her son might have inherited the expansion mutation in the Huntingtin (HTT) gene from their father.

It turned out that both Anne and Mark inherited the expansion in the HTT gene. Mark died not quite 40 years of age from HD. Anne is still alive, living in the most advanced stage of HD, having been unable to communicate with her mother in recent years. Effectively, Christiane lost both her children to HD. Christiane experienced the joy of becoming a grandmother; however, Anne's daughter was born preterm and suffered perinatal complications resulting in impairments limiting her developing independence. The bad luck didn't stop here: as if having one neurodegenerative disease running in the family wasn't enough, Christiane herself started to develop the symptoms and signs of Parkinson disease in her late sixties.

However, Christiane never let HD (or her own health challenges) define her life. She had every reason to

turn to bitterness and to complain that fate had dealt her an unfair share of misery. But she never did. Instead, she turned to helping others facing HD. Starting in 1990, she become an engaged and active member of the German HD advocacy (Deutsche Huntington-Hilfe – DHH), first in her local chapter at Stuttgart, then at the national and international levels. Christiane helped to form new regional chapters of HD advocacy in underserved areas, first within, and shortly after, outside of Germany. These activities led her to be elected chairperson of the DHH in 2000 as well as of the International Huntington Association (IHA). In addition, she supported research into understanding HD, as well as forming clinical centres of expertise and care excellence while empowering families by making translations of caregiver support materials available in several languages. All these contributions made Christiane a natural choice to serve as the representative of the European Huntington Association (EHA) when the European HD Network formed its first Executive Committee in 2004, a role which she undertook for 6 years.

Christiane understood the impact of HD on the lives of HD-affected families. She also knew that everybody facing HD has to find their own way. There is no 'one-size-fits-all' path forward – all choices are, by necessity, deeply personal. As such, she never forced her own views and preferences on the people she interacted with but instead encouraged reflection. For example, Christiane authored a booklet to help people with a parent carrying the HTT gene expansion mutation and struggling with whether to opt in or opt out of predictive genetic testing. Her booklet, 'Denkanstösse – Food for Thought', alerts readers to a range of perspectives, the critical questions to ask yourself in the process, and the difficulty of knowing yourself well enough to predict whether preserving an inner equilibrium with good as well as with bad news might be possible. Fittingly, Christiane was chosen to represent patient advocacy as a founding member of the first German National Ethical Council, appointed by the then chancellor of Germany, Gerhard Schröder.

Christiane knew how to live. And how she lived! She enjoyed exchanges and travel, her interests were broad, she was willing to consider the unconventional and her views were always very well-articulated – it was great fun to be with her. Above all, however, she was a great source of inspiration in how she braved adversities. Inevitably, she eventually grew tired, and expressed her wish to transcend all her troubles (having tasted the bitter bread) in the knowledge that this could not happen in the flesh.

We miss Christiane. The EHDN will remember her contribution and her life, and will honour her memory.

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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 K. Bečanović

Photo: Gabriele Stautner · artifox.com

Olivia Handley

Photo: Ruth Fullam

From left to right: Ruth Fullam, Jenny Callaghan, Selene Capodarca

Photo: Christine Capper-Loup

Christine Capper-Loup

Photo: Gabriele Stautner · artifox.com

Jenny Townhill

New Director Appointments

Congratulations to the EHDN Management team who have recently been made directors in recognition of their valued work and contributions: Olivia Handley, Jenny Townhill, Jenny Callaghan, Ruth Fullam, Selene Capordarca, Katrin Barth and Christine Capper-Loup.

Photo: Gabriele Stautner · artifox.com

Katrin Barth

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Photo: Aurelio Cordi, webmaster and volunteer of the association, provided by Wanda Danzi

Roberta Cellini, Giuseppe Paladina and Giacomo Mascaro receiving the award

Transforming Memories into Actions

Wanda Danzi, Vice-President, Asso one Italiana Còrea di Huntington Roma OdV (email: lettere@aichroma.com)

In honour of the late and sadly missed medical geneticist, Professor Marina Frontali, we established an award to recognise the authors of a scientific publication deemed by the scientific consultants of AICH-Roma OdV to represent particular interest and innovation in the HD field. After the careful evaluation of papers published in 2021 and 2022, the prize was awarded to Effect of Immersive Virtual Reality by a Computer Assisted Rehabilitation Environment (CAREN) in Juvenile Huntington's Disease: A Case Report, by Roberta Cellini of IRCSS Centro Neurolesi 'Bonino-Pulejo' and co-authors at our conference held in December 2022.

ERN-RND Joint Webinars 2023

The European Reference Network for Rare Neurological Diseases (ERN-RND) organises joint free educational webinars on rare neurological and movement disorders with the European Academy of Neurology (EAN). These 1-hour webinars take place throughout the year and are presented by international experts. They discuss various aspects ranging from more general clinical features, examination, disease diagnosis, medical interventions, and disease management to more specific ones such as the use of scales or imaging. Adult and paediatric neurology are both covered.

Further information about ERN-RND webinars in collaboration with EURO-NMD and the EAN is available here: https://www.ern-rnd.eu/education-training/webinars/

Huntington's In Mind – A Campaign

Vicki Rutland, Huntington's Disease Association

In May 2022, the Huntington's Disease Association launched a campaign to mark Huntington's Disease Awareness Month. The theme was chosen following research undertaken with Roche in collaboration with ourselves and the Scottish Huntington's Association looking at the provision of services for people across the UK who had been diagnosed with HD.

One of the stark findings from the research was the number of people who spoke of the difficulty in accessing mental health services. The campaign was designed to help people understand how mental health can be affected by HD and we put a call out to the community for people who were willing to share their stories.

At the heart of the campaign were three films. David, Charlie and Alison (pictured) shared their experiences of mental health and the impact of HD in a series of films. The stories were featured across both printed and broadcast media – including The Independent, The i News, Daily Express and more. Our celebrity patron George Rainsford talked about the campaign on ITV's Loose Women and BBC Morning Live, reaching a national audience.

The campaign included a resource for professionals and people in the community with information on mental health and HD, and also gave us a chance to reach out to new stakeholders via podcasts and invited presentations.

A Catalyst for Action

Huntington's Disease Awareness Month needs to be a catalyst for action for healthcare professionals and parliamentarians. Working with the Scottish Huntington's Association and Huntington's Association Northern Ireland, an Early Day Motion was proposed that included a call for access to mental health services. From this, Hilary Benn (MP) became a parliamentary champion for HD, with a parliamentary debate held in Westminster Hall in November 2022. Attended by members across the parties, Helen Whately (Minister of State for Social Care) closed the debate by emphasising the clear need for mental healthcare and support for people with HD, and an assurance this would now be addressed.

We are grateful to M&F Health for their creative input and Roche for providing funding.

'What the team have been able to achieve with the #HuntingtonsInMind Campaign has been pivotal to opening up further conversations about Huntington's disease. Not only raising awareness of the rare disease but also the mental health implications of testing, caring and being diagnosed with Huntington's disease. Will forever be proud to of been involved in this campaign along with David and Alison!'

Charlie, contributor.

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Local Language Coordinator (LanCo) Meetings

Luz Lopez, Local Language Coordinator for Spain since 2019

Three times each year, the entire EHDN team gathers for one or two days, somewhere in Europe, to catch up and discuss the latest trends/developments/best practices, and so on. These meetings allow the local language coordinators (LanCos) to interact with each other, as well as to meet with the EHDN management team. They also provide a good opportunity to have face-to-face meetings and receive individual feedback. The event location changes for every meeting but it usually takes place in one of the major European hubs (recent examples include Prague, Bologna and Barcelona) making it quick and convenient for everyone to travel to the event from their home base.

Barcelona LanCo Meeting

The last LanCo meeting took place in Barcelona (18–19 January 2023). This was also the occasion to celebrate the 10-year anniversary of Enroll-HD, together with the site investigators and staff at the local Enroll-HD sites, HD families/lay associations and members of the Enroll-HD management team.

Over this two-day event, participants attended 15 thematic sessions of approximately 45 minutes, each presented by different subject-matter experts from the EHDN and Enroll-HD management team, including professors, neurologists, psychologists, as well as LanCos.

Photo provided by Luz Lopez

Luz Lopez

As usual, the presentations were followed by Q&A sessions, which allow attendees to share thoughts and best practices, clarify questions or concerns, and make suggestions for future developments. Some of the topics discussed in Barcelona were the EHDN's new Scientific Strategy, peripheral tissue manifestations in HD, the latest developments in clinical trials, site certification and HD participant recruitment.

A Personal Perspective

I always find LanCo events to be a great opportunity to strengthen relationships and collaboration between the international community of LanCos as well as with EHDN management. For me, the highlight of the meetings is the satisfaction I get from feeling part of a larger family whose combined efforts are contributing to advancing our understanding of HD.



Photos: Gabriele Stautner · artifox.com

Update: Clinical trials

Jenny Townhill and Tim McLean, Central Coordination

The following studies have been endorsed by 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 and shared on social media, signalling the same message to the HD community.

The studies reported below are of investigational compounds, where safety and efficacy have not been established. There is no guarantee that the outcome of these studies will result in marketing approval.

Key updates since the last newsletter are provided below for EHDN-endorsed trials and studies; please refer to Table 1 for a summary of the main study information.

ASK-HD-01-CS-101 (Asklepios Biopharmaceutical, Inc. [AskBio])

This surgical open-label phase I/II study evaluating the safety and efficacy of BV-101, a novel gene therapy targeting cholesterol metabolism dysfunction opened to recruitment in Q42022. Up to 18 participants will be enrolled at two sites in France.

VIBRANT-HD (Novartis)

This study was designed to detect and assess early safety signals in the development of branaplam in the treatment of HD. In December 2022, Novartis shared the news there will be no further dosing of branaplam in the VIBRANT-HD study and that the development of branaplam for HD will not continue. The study had previously been paused following the detection of side effects in some participants. A review of additional follow-up data showed that many participants who received branaplam had signs or symptoms of peripheral neuropathy. There was also an increase in a marker of neuronal damage [neurofilament light chain (NfL)] and some MRI findings suggesting an increase in the volume of the lateral ventricles.

Branaplam did lower mutant huntingtin protein (mHTT) in the cerebral spinal fluid as expected. However, given the safety findings, it is very unlikely that it is safe to explore other doses or other dosing frequencies.
All participants who received the study drug will continue to be followed up for one year after their last dose of branaplam to monitor recovery and gather more data about these safety signals and how they may change over time.

DIMENSION, SURVEYOR and PURVIEW (Sage Therapeutics)

Recruitment is continuing into the two phase II trials, DIMENSION and SURVEYOR, assessing the effect of an orally administered NMDA receptor modulator, SAGE-718, on cognitive performance and functioning. A further phase III open-label study of SAGE-718, PURVIEW, has started recruitment and will enrol a total of 300 participants, comprising participants from DIMENSION and SURVEYOR as well as an additional cohort of de novo participants who were not enrolled in the phase II studies. The PURVIEW trial has been granted partial endorsement; the transition of DIMENSION and SURVEYOR participants to PURVIEW has been endorsed, however, as the de novo cohort has no placebo arm, and no data currently exists to provide appropriate matching of participants, this additional cohort has not been endorsed.

HDGeneTRX1 and HDGeneTRX2 (uniQure)

Last summer, unexpected severe side effects, including localised inflammatory responses, that were suspected to be related to the study drug were reported by uniQure for some participants that were treated with the higher dose of AMT-130. At the time, the trial data safety monitoring board (DSMB) recommended temporarily delaying further enrolment into this higher-dose group pending a full safety review. Following this

review of safety data, the trial DSMB determined that it was safe to proceed with recruitment into the higher dose group and additional safety measures, including closer post-surgical monitoring, have been included in the assessment protocol.

PIVOT-HD (PTC Therapeutics)
Recruitment continues into this 12-month phase IIa study of orally administered PTC518 (a small molecule huntingtin-lowering compound) in Australia and Europe. Currently, the study is on hold for sites in the US as the FDA has requested additional data to allow the study to proceed. Preliminary data are expected to be reported early in 2023.

GENERATION HD2 (F. Hoffman La Roche)
This phase II study of intrathecally administered tominersen, a huntingtin-lowering antisense oligonucleotide (ASO), will evaluate the safety, biomarkers and efficacy trends of different dose levels of tominersen in people with prodromal (roughly equivalent to HD-ISS Stage 2) or early manifest HD (roughly equivalent to HD-ISS Stage 3). Approximately 360 participants will be enrolled across 15 countries, and each participant will have at least 16 months of treatment with either tominersen or placebo.

The study has started screening, with the first sites activated in the US and Spain at the start of 2023, and additional sites in North America, Europe, South America and Oceania expected to open in the coming months. Details will be posted on clinicaltrials.gov as individual sites are activated and are ready to start screening potential participants.

SELECT-HD (Wave Life Sciences)
This phase Ib/IIa study of an allele-selective ASO continues to recruit participants. Preliminary data were reported last year on

Table 1: EHDN-endorsed Trials and Studies

(Active or in Start-up)

Registration ID (Clinical Trials.gov)	Sponsor	Trial name	Phase	Intervention	Mechanism of Action	Target Enrolment	Location(s)	Status
NCT05541627	BrainVectis, a subsidiary of Asklepios BioPharmaceutical, Inc. (AskBio)	ASK-HD-01-CS-101	I/II	BV-101	Cholesterol metabolism dysfunction (AAV gene therapy)	18	France	Recruiting
NCT05686551	F. Hoffman La Roche	GENERATION HD2	II	tominersen	ASO	360	North America, Europe, Oceania	Recruiting
NCT05111249	Novartis	VIBRANT-HD	IIb	branaplam	Small molecule mRNA splicing modifier	75	USA, Canada, Europe	Treatment terminated; participant follow-up
NCT04556656	Prilenia Therapeutics	PROOF-HD	III/OLE	pridopidine	Sigma-1 receptor agonist	480	USA, Canada, Europe	Participant follow-up
NCT05358717	PTC Therapeutics	PIVOT-HD	II	PTC518	Small molecule mRNA splicing modifier	TBD	Australia, France, Germany, Netherlands, UK, USA	Recruiting
NCT05107128	Sage Therapeutics	DIMENSION	II	SAGE-718	NMDA receptor modulator	178	Australia, Europe, North America	Recruiting
NCT05358821	Sage Therapeutics	SURVEYOR	II	SAGE-718	NMDA receptor modulator	80	North America	Recruiting
NCT05655520	Sage Therapeutics	PURVIEW	III	SAGE-718	NMDA receptor modulator	300	Australia, Europe, North America	Recruiting
NCT05475483	SOM Biotech	SOMCT03	IIb	SOM3355/ bevantolol	VMAT2 inhibition	129	France, Germany, Italy, Poland, Spain, Switzerland, UK	Recruiting
NCT04406636	Triplet Therapeutics	SHIELD-HD	N/A	N/A	N/A	60	USA, Canada, Europe	Complete
NCT04120493	UniQure	HD GeneTRX2	Ib/II	rAAV5-miHTT	miRNA nonselective (AAV gene therapy)	26	Germany, Poland, UK	Recruiting
NCT05032196	Wave Life Sciences	SELECT-HD	Ib/IIa	WVE-003	Allele-selective ASO	36	Australia, Canada, Europe	Recruiting

Note. ASO = antisense oligonucleotide; OLE = open-label extension; VMAT2 = vesicular monoamine transporter 2

the first two of the three single-dose cohorts, showing that a single dose of WVE-003 reduces mHTT in cerebrospinal fluid (CSF) and that WVE-003 was in general, safe and well-tolerated. Normal htt levels were consistent with allele selectivity. There is no apparent difference in dose response between the two dose groups analysed to date. Based on these findings, the originally planned number of participants that will be included in each single dose cohort has been increased to gather additional data on dose response and the percentage reduction of mHTT in CSF. Additional biomarker and safety data for the single-dose cohorts are expected in the first half of 2023.

SHIELD-HD (Triplet Therapeutics)
This study is now closed. Seventy prodromal and early manifest HD gene expansion carriers were enrolled in this 96-week natural history study, and the last 96-week visit was completed towards the end of 2022. The primary objectives of the study were to assess DNA damage repair (DDR) gene expression, and somatic instability (SI) of the HD gene and to examine associations between DDR gene expression, SI and markers of disease progression which included validated and novel clinical outcome measures, wet biomarkers such as NfL, and neuroimaging.

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Update: New Enroll-HD Periodic Data Set (PDS6) is Now Available!

Olivia Handley, Enroll-HD Global Platform Manager

Data from the Enroll-HD study are made available to the research community every 1–2 years – these are known as periodic data sets or 'PDS' releases. Since the first periodic dataset was made available in 2015, there have been hundreds of data downloads, leading to over 100 peer-reviewed publications, and many more posters, presentations and collaborations. The Enroll-HD PDS remains a unique and powerful research tool, informing our understanding of HD and, in combination with biosamples, allowing us opportunities to identify new therapeutic targets and biomarkers.

The sixth PDS release was announced on 9 January 2023. This most recent release is the largest to date, containing data from 25,550 Enroll-HD participants. In addition to Enroll-HD study data, this release also includes data from different sources: REGISTRY[1] and additional clinical data (ad hoc[2]) (*Table 2*).

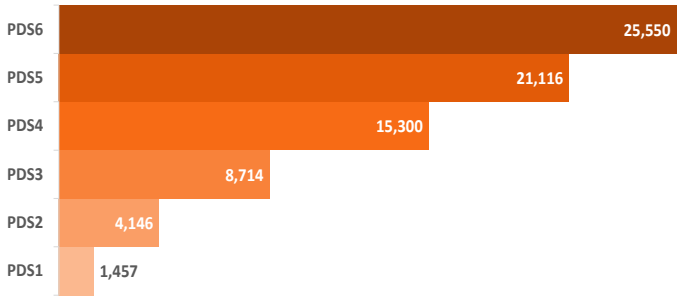
[1] REGISTRY is a European observational study of HD running from 2004 to 2015. The PDS includes individuals who participated in REGISTRY then enrolled in Enroll-HD and consented to the migration of their REGISTRY data into the Enroll-HD dataset.

[2] Ad hoc data refers to data collected on a subset of Enroll-HD participants at routine clinical visits outside of the Enroll-HD and REGISTRY studies, and comprise HD assessment data (e.g., UHDRS Motor).

Photo: Gabriele Stautner - artifox.com

The PDS6 Overview document provides a high-level summary of the data set, including information on the data source and inclusion criteria, as well as data on sample size, number of visits, sample characteristics, and coverage (data availability broken down by geographical region, participant category and visit count). A few of the figures (*Figures 1 and 2 and Table 2*) from that document are provided below and illustrate sample size and visit counts across consecutive Enroll-HD PDS releases.

Figure 1. Enroll-HD sample size by PDS release



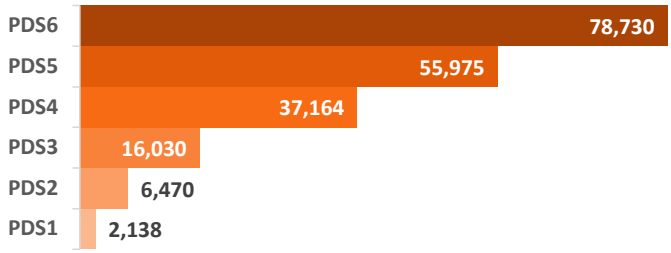
There are 95,040 visits (baseline and follow-up visits only; all sources) in PDS6, of which 78,730 were Enroll-HD visits.

Table 2. Number of visits in PDS6 by data source.

Data source	Participants	Visits
Enroll-HD	25,550	78,730
Registry 3	4,337	10,114
Registry 2	2,153	5,178
Ad Hoc	316	1,018
TOTAL		*95,040*

Participant number indicates the number of Enroll-HD participants with visit data available for the indicated data source (maximum N = 25,550)

Figure 2. Enroll-HD visits only (baseline and follow-up only) by PDS release



Each PDS release is accompanied by supporting documents designed to describe, explain, and help end users work with the data. Anyone interested and/or in receipt of the PDS is encouraged to review these documents which are available on the Documentation page of the Enroll-HD website.

Accessing PDS6

Who can access PDS6?

If you are a researcher at a recognised research organisation, you can request data and/or biosamples. You will need institutional authorisation to sign data and/or biosample use agreements. Please visit the Access page on the Enroll-HD website for more information on the document package to submit with your application.

What do I need to do to access PDS6?

You will need to submit the following via email to accountsetup@enroll-hd.org:

- **PDS6 request form**
- **Data Security Questionnaire**
- **Technical and operational security measures (TOMs)**

Once your application has been approved, a Data Use Agreement will need to be signed and executed with your institution. The PDS6 dataset will then be delivered electronically (typically in 4–6 weeks). It is available in two formats (.csv and .r).

Enroll-HD PDS releases are made available free of charge. Please visit the Access page on the Enroll-HD website for more information. The Enroll-HD publication policy is available on the Enroll-HD website.

Acknowledgements
Thanks to Jen Ware and Eileen Neacy for their review of this article.
This article uses material directly taken from the Enroll-HD PDS6 Overview document prepared by the Enroll-HD PDS team.

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Update: HDClarity

Seema Maru, HDClarity Study Coordinator, and Alex Lowe, HDClarity Research Assistant

HDClarity Current Site Status

With the growing numbers of clinical trials exploring novel therapeutic approaches for treating HD, HDClarity was designed to:

- **Generate a high-quality CSF collection and plasma samples (from blood) to evaluate biomarkers and pathways to enable the development of novel treatments for HD**
- **Collect high-quality clinical data for each participant using Enroll-HD core assessments**

All HDClarity participants must be part of the Enroll-HD study and HDClarity is aiming to recruit 2,500 participants worldwide. The study opened in 2016 under Protocol Version 2 (CLR2) and consisted of a single Screening (SCR) and Sampling Visit (SMP) within 30 days and an Optional Repeat Sampling Visit (RPT) 4–8 weeks after. Protocol Version 3 (CLR3) provided participants with the option to re-enrol into the study again on an annual basis by signing a new consent form. These longitudinal visits over three years (Y0–Y3) have now

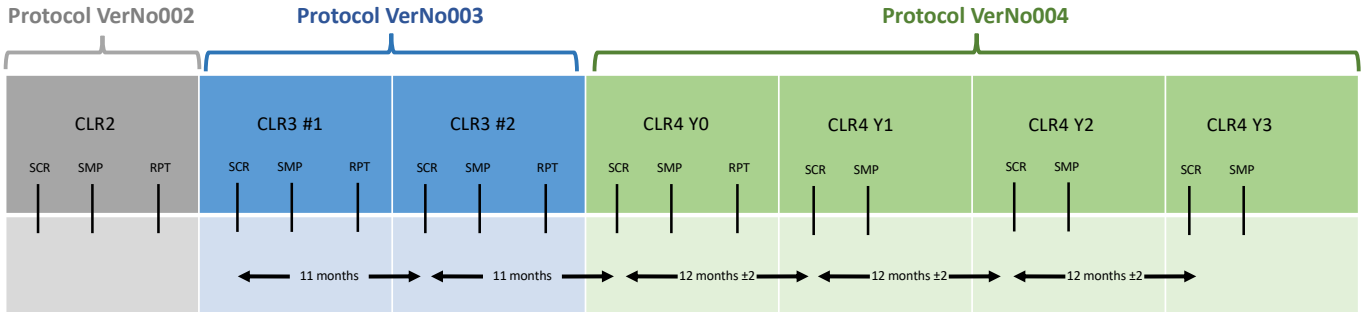

Figure 3. Participant Visit Schedules for all Study Protocols

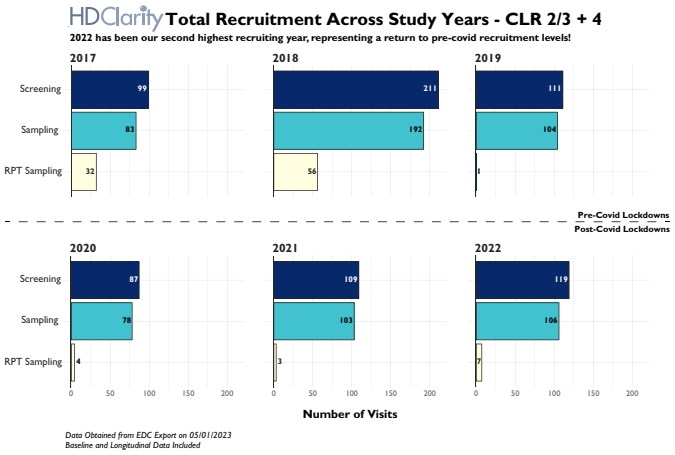

Figure 4. Total Recruitment Across Study Years, 2017–2022

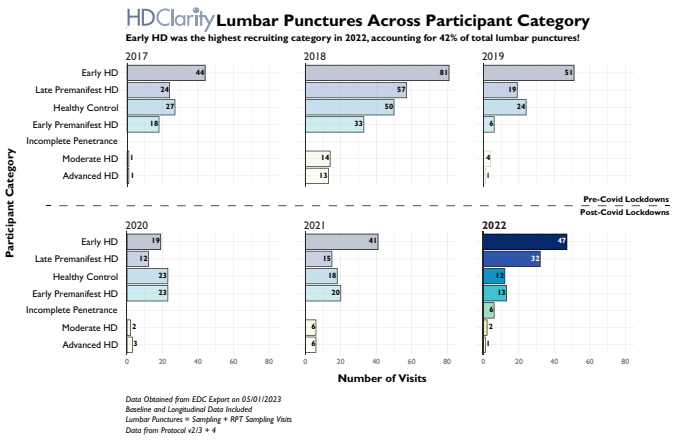

Figure 5. Lumbar Punctures Across all Participant Categories

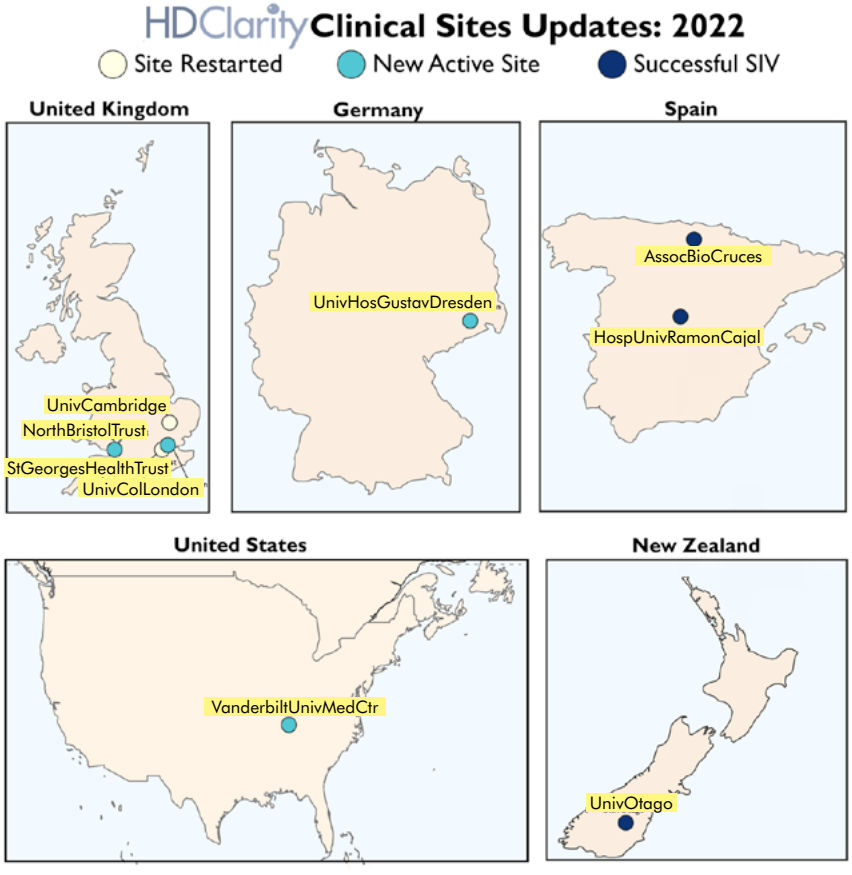

Figure 6. HDClarity Clinical Site Updates: 2022

been embedded in the new Protocol Version 4 (CLR4) which received UK ethics approval in October 2021 *(Figure 3)*.

Total Recruitment

The study is currently recruiting Healthy Controls, Premanifest HD (early and late) and Manifest (early, moderate and advanced) HD participants. In Protocol Version 4, two additional categories were added: 'Juvenile' participants and 'Incomplete Penetrance' (CAG repeats of 36–39).

Since 2016, the study has conducted over 1,500 study visits *(Figure 4)* and 769 Lumbar Punctures for CSF collection *(Figure 5)*. The highest recruiting year was 2018 (pre-COVID) and 2022 (post-COVID).

Our current and actively recruiting sites are located across the UK, Canada, USA, Germany, Italy, Poland and Spain. In 2022, the study opened new sites in Great Britain, Germany, Spain, the USA and New Zealand *(Figure 6)*.

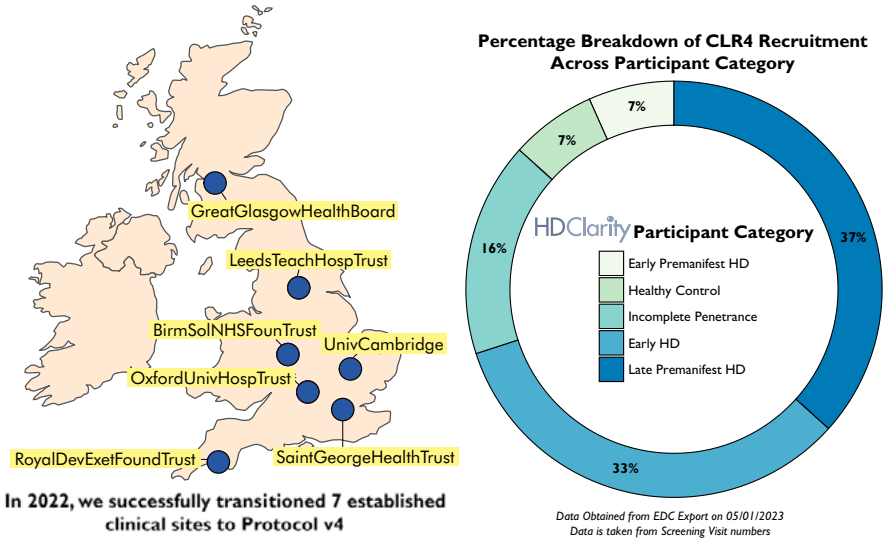

Figure 7. UK HDClarity Sites Operating on CLR4 Protocol Version 4

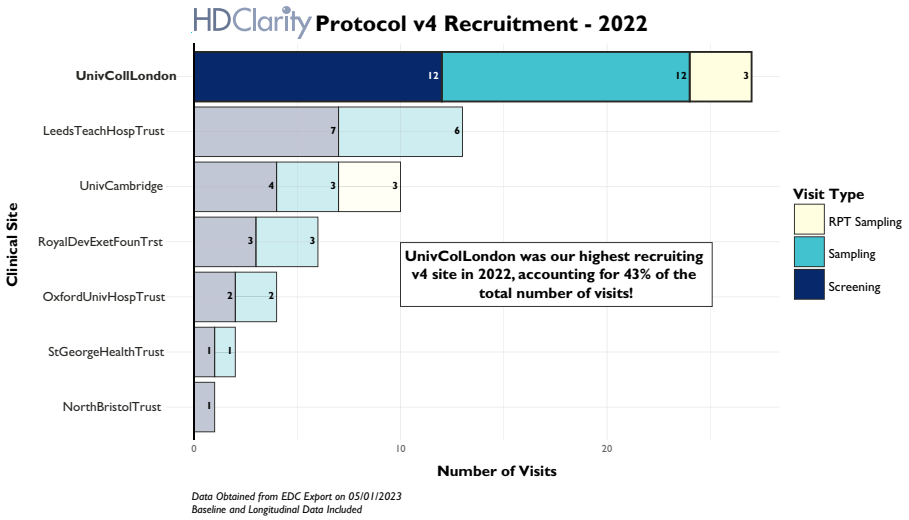

Figure 8. Protocol Version 4 Recruitment: UK Sites

Longitudinal Visits

The introduction of Protocol Version 4 results in participants consenting to four Annual Screening and Sampling Visits at Y0, Y1, Y2 and Y3 after the first initial visit, with re-consent thereafter.

We are pleased to announce that in 2022, seven established HDClarity UK sites can recruit participants under Protocol Version 4 *(Figure 7)* and currently University College London Hospital is the highest-recruiting UK site *(Figure 8)*.

Further Information

Further information on HDClarity is available at www.hdclarity.net and the study team, led by Professor Ed Wild are always happy to answer any questions.

For more information and details on participating in HDClarity, please email hdclarity-cc@enroll-hd.org.

Interested in Participating?

Enroll-HD enroll-hd.org

U.S. National Library of Medicine ClinicalTrials.gov clinicaltrials.gov

HDClarity hdclarity.net

@HDClarityStudy

Update: New Lesley Jones Seed Funds Awarded

Catherine Deeprose

The EHDN seed fund programme has been renamed in honour of Professor Lesley Jones, who was deeply involved in the review of applications.

Photo provided by David Harrison

David Harrison

David Harrison at the University of Cardiff has recently been awarded funding for his project on the prenatal effects of mutant huntingtin. Even though most HD symptoms appear in later life, the genetic cause is present from conception. This project will use a mouse model of HD to better understand the embryonic brain and its placenta, potentially providing new directions in the search for preventative interventions.

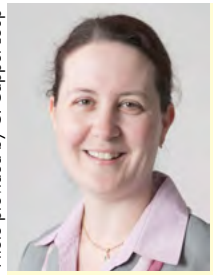

Photo provided by C. Capper-Loup

The Lesley Jones Seed fund programme is intended to support pilot studies that will eventually kickstart larger projects. The next deadline for applications is 1 November 2023.

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) or Kristina Bečanović (kristina.becanovic@euro-hd.net) for further information.

Photo provided by K. Bečanović

Update: Funding Opportunities

Photo: Gabriele Stautner, artfox.com

Fionnuala Margreiter,
Grants & Collaborations Manager

- A new FENS /IBRO exchange fellowship programme for researchers has recently been announced. Find out more at https://www.fens.org/careers/grants-and-stipends/grant/fens-ibro-perc-exchange-fellowships
- The HD Clinical Fellowship Programme 2023, sponsored jointly by the EHDN and MDS-European Section, recently closed for applications. The results of the evaluation are expected in early April.

Find out about current research funding programmes and keep up to date with opportunities on the EHDN website: https://ehdn.org/hd-clinicians-researchers/grant-manager/ and follow me on Twitter @EHDN_GRANTM

Our photo experiment continues!

Please get involved in sharing your photos!

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**

Photos provided by Flaviano Giorgini

Rocking It Up: An Interview with Flaviano Giorgini

Alongside a high-flying rock career, Flaviano (Flav) Giorgini, Professor of Neurogenetics at the University of Leicester in the UK, has been driving forward our understanding of the biological underpinnings of HD for many years. We met with Flav to hear more about his diverse interests and being a member of the HD community.

How did you get involved in HD research?

I completed my PhD studies at the University of Washington in Seattle, and at this time, I was focused on fundamental biological studies. These weren't disease-related but when I finished my PhD, I was keen to do more applied, disease-related research that would be more directly beneficial to people. And as it happened, there was a new principal investigator in the department next door, and he had just started a laboratory looking at the role of protein misfolding in HD and using model systems to do this. This was probably in 2003 and I was immediately excited – as a trained geneticist, I saw this would be a great opportunity to apply my knowledge to better understanding rare diseases.

'When I first came into this community, I found it to be a really amazing and supportive place and I think this is still the case.'

At this time, a lot was going on in terms of trying to understand protein misfolding in the cells of the brain as a cause of neurodegenerative disease and also the potential impact of genes in modifying the toxicity of mutant huntingtin. This was, of course, before any of the genome-wide association studies took place but the work was based on the similar principle that there may be genes that we can target to somehow modify the progression of the disease.

In 2006, I came to the University of Leicester in the UK – which means I have been here for 17 years! The EHDN had started just a few years before and the Europe-wide network that emerged in providing structure and support for the HD community, comprising clinicians, researchers and HD families, has been invaluable.

I began by starting my own research group and trying to identify interesting genes that may be relevant in causing HD and may also be potential therapeutic targets. This has mainly involved laboratory work in yeast and mammalian cells, and most recently, work in fruit flies which we've found to be a really good system for looking at HD.

What does it feel like to be a longstanding part of the HD community?

When I first came into this community, I found it to be a really amazing and supportive place and I think this is still the case. While still relatively small, people in the HD community tend to know each other (or know of each other, at the very least). This makes for a really supportive environment. I think there's always been a huge interest in supporting early-career researchers, from different backgrounds and different genders. The main focus is on working together, talking together, and sharing data. I joined this community because I wanted to work in disease, and when I got to know the community more, I was thrilled to be part of it.

Squirtgun

What sort of research are you currently involved in?

My research 'self' is still focused on HD although these days, we do some other things as well. Protein misfolding-based neurodegeneration remains a core interest but over the years we've been doing quite a bit of work with Parkinson's disease models and more recently, we've been doing work related to the Tau protein, which is very much linked to Alzheimer's disease but also, Tau pathologies are associated with a lot of neurodegenerative disorders more generally. We've also been working on schizophrenia. Some of the metabolites that we're interested in in the context of neurodegenerative disease look like they may also play a role in schizophrenia and some other related disorders.

'I think there's always been a huge interest in supporting early-career researchers, from different backgrounds and different genders. The main focus is on working together, talking together, and sharing data.'

And in this time, you also built up a reputation in punk rock! Tell us more…

I've been in punk rock bands since 1984, so a long time – gosh, getting on almost 40 years! I went through various different bands, but in the mid-1990s, my brother and I formed a band called Squirtgun. I would call this melodic punk, some people would call it pop punk, similar to Green Day or Blink 182 but more melodic. We signed to a pretty well-known independent label called Lookout! Records which is also where Green Day got their start and in the mid-1990s, we did a fair amount of touring, released a few albums, had videos on MTV, songs on movie soundtracks… and that kind of thing. I think we did pretty well for an independent band!

I took a break between being an undergraduate and PhD student to focus on music. Later, the band kept going and I remained a non-touring member but I'd jump in occasionally. In the later 1990s, it was more for fun than work and although we never got huge, we worked with a lot of well-known people. Blink 182, for example, opened for us, as did a band called Anti-Flag, an American punk band. In January this year, Anti-Flag released a new album which made the top ten in Germany!

How does music fit into your life now?

I've always kept music as part of my life. I've done a few solo albums that were mainly acoustic guitar with a folky feel and I've always kept a bit of the melodic punk thing going as well. Even now, I'm still doing music. Since the pandemic, I've run a music project called the Phase Problem and we record all our work

virtually. I do the songwriting and singing and playing the guitar but have joined up with other band members from around the UK for the recordings.

For me, music provides a mindfulness sort of relaxation. I have my guitar here in my office and I can jam along if I need a break. When I pick up the guitar, I get lost in music, it clears my mind of everything else and it recharges me. I think it's really important because creativity in science comes from being able to relax your mind and let yourself think. I feel one of the biggest problems in society right now is that we don't have time to actually think because we are constantly bombarded with everything – like email. We need time to reflect on things if we are to learn and move forward.

Photo: Gabriele Stautner · artifox.com

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Dates for your diary

- **HDYO's International Young Adult Congress** will take place 17–19 March 2023 in Glasgow, Scotland. The event is primarily aimed at young adults from HD families around the world. Find out more here.
- **The 4th ERN-RND Winter school** takes place online 23–25 March 2023. Registration closes 15 March. The course is dedicated to neuroimaging issues in patients with symptoms of rare neurodegenerative/genetic disorders.
- **The 18th Annual Huntington's Disease Therapeutics Conference**: A Forum for Drug Discovery & Development will take place 24–27 April 2023 in Dubrovnik, Croatia. Registration has already sold out but a waiting list is available.
- **An educational webinar** (jointly organised by the ERN-RND, EURO-NMD and EAN) will be presented by Sarah Tabrizi (University College London) on Huntington Disease: New Insights into Molecular Pathogenesis and Therapeutic Opportunities. It takes place 27 June 2023, find the sign-up details here.

Alhambra, Granada/Spain

By Slaunger, Own work, CC BY-SA 3.0

- **The International Congress of Parkinson's Disease and Movement Disorders** takes place in Copenhagen, Denmark, 27–31 August 2023. The deadline for Abstract submission is 15 March. More details can be found at mdscongress.org
- **The 11th IBRO World Congress of Neuroscience** takes place 9–13 September 2023 in Granada, Spain. Early bird registration closes in May.
- **The European Huntington's Association congress** takes place in Blankenberge, Belgium 19–22 October 2023. Registration will open soon and further details are available here.

Would you like to share an upcoming event with our readers?
Please email the details to newsletter@euro-hd.net