EHDN 2022 Plenary Meeting

Report prepared by Catherine Deeprose and Michael Orth

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The EHDN Plenary Meeting 2022 was held 16–18 September in Bologna, Italy. This was our first face-to-face plenary after the COVID-19 hiatus and the opportunity to meet in person was warmly welcomed, despite the considerations involved with gathering a large crowd of people together in one place. It was attended by 853 participants, out of the 933 who had registered. All sessions were recorded and are available online along with photographs. A summary of the meeting was published in the November issue of the EHDN newsletter and meeting abstracts for the poster presentations have been published in a supplement to the September issue of the Journal of Neurology Neurosurgery & Psychiatry.

Friday 16 September

The meeting commenced with a warm welcome and introduction from Anne Rosser (EHDN Chair/Cardiff University, UK), Astri Arnesen (President of the European Huntington's Association) and Patrick Weydt (EHDN Deputy Chair/University of Bonn, Germany).

The opening **Keynote Session**, '**150 Years of Huntington's Disease**' was chaired by Anne Rosser and Charles Sabine. **Charlotte Raven**, British journalist and author of 'Patient 1: Forgetting and Finding Myself' opened with 'Living with HD' – a personal and poignant account of her journey, accompanied by reflections on her highflying yet often controversial media career. She recounted being the first patient to receive tominersen (then known as IONIS-HTTRx) and shared her pride at being part of the search for a cure. She was joined by daughter **Anna Sheahan** who shared her perspectives on the challenges of being 'a part-time carer and part-time daughter… growing up in the shadow of HD', but also the hope and direction that stems from the HD community. **Ed Wild**, Professor of Neurology at University College London, UK, shared how his experiences working as Charlotte's neurologist have provided further insights into the day-to-day realities of the disease.

Next to present was **Gillian Bates**, Professor of Molecular Neuroscience at University College London, UK, with 'Mutant Huntingtin: Molecules, Models, Medicines'. After recapping on the importance of the cytosine, adenine and guanine (CAG) repeat size, Bates presented converging data from animal and human post-mortem studies supporting the role of the exon 1 huntingtin (HTT) protein in HD pathogenesis. She elucidated the hypothesis that exon 1 is responsible for the aggregation of mutant HTT (mHTT) and described some of her work developing HTT bioassays to specifically measure this and subsequent experimental work. Bates concluded with a theoretical model of exon 1 HTT as the pathogenic consequence of somatic instability in which the expanded region of CAG repeats continues to expand over time, and highlighted the potential for HTT1a and exon 1 HTT as new therapeutic targets.

The final speaker in this keynote session was **Elena Cattaneo**, Professor of Pharmacology, at the University of Milan, Italy, with 'Huntingtin: Evolution, Structure, Function'. Referring to the biology of the origin of life, Cattaneo described how with the progression of evolution, we see an increase in CAG size associated with species with progressively more advanced nervous systems. She discussed how this observation provided the impetus for experimentally introducing normal huntingtin into a plant (Arabidopsis) and studying the evolutionary history of the polyglutamine (polyQ) tract in huntingtin. Finally, we heard how exciting new results utilising the human CAGinSTEM platform to detect CAG instability are informing our understanding of HD pathogenesis.

Next, Anne Rosser and Sarah Tabrizi (University College London, UK) presented '**In Memory of Professor Lesley Jones (1957–2022)**' in recognition of the sad and unexpected passing of our friend and colleague in June this year after a short illness. We heard how Lesley spent most of her professional life at Cardiff University, UK, where she completed her first degree and PhD before being appointed as a scientist and lecturer, and then in 2012, Professor in Neuropsychiatric Genetics. Having started her career working across several neurodegenerative diseases, Lesley increasingly focussed on HD, for which she is now best known. With a range of collaborators across the globe, Lesley was central to the activities of the Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium and was a world leader in the explanation of HD gene modifiers. At the time of her death, Lesley was a core member of the EHDN Executive Committee and Think Tank, and her contributions in these roles were characterised by energy and engagement. Lesley made immense contributions to our understanding of HD at every level and published critical papers that will remain highly influential in the field. She worked across cell biology, mouse behaviour and the genetics of HD, pioneering efforts that are resulting in new therapeutic targets and possibly new treatments. Lesley is also known for making huge contributions to our understanding of Alzheimer's disease, being among the first to recognise the central role of glial cells in its pathogenesis. A much-loved and respected figure, Lesley was well known for her sharp intellect, good sense and kindness, and in particular, her careful attention to the needs of young scientists and strong support of women in science. She also cared deeply about patients and families. We have lost a good friend, a supporter and a truly remarkable woman whose inspiration will be carried into the future with our new generations of scientists.

Plenary Session I: New Genetics of HD was chaired by Hoa Huu Phuc Nguyen (Ruhr-Universität Bochum, Germany) and Flaviano Giorgini (University of Leicester, UK). **Darren Monckton** of the University of Glasgow, UK, spoke on 'Cis-acting Genetic Modifiers and Somatic Expansion in Huntington's Disease'. Reporting findings derived from Enroll-HD and genome-wide association studies (GWAS), and further research with a South African HD population, he described new implications for understanding the HTT repeat and disease pathway in HD, reminding us of the value of human genetics and the need to study diverse human populations in elucidating HD biology.

Next to speak was **Larissa Arning** of Ruhr University Bochum, Germany, with 'Non-pathogenic CAG Tract and Gray Matter Microstructure in the Human Brain'. Arning summarised the neurodevelopmental hypothesis of HD which suggests that the CAG repeat-expansion is the pathological extreme of a more general mutational process contributing to normal brain function and development. However, only a few studies have previously examined non-pathogenic HTT CAG size. She reported her analysis of cognitive, intelligence and magnetic resonance imaging scanning data in healthy participants. Findings suggested that while an increasing number of HTT CAG repeats below the disease threshold do not impact cognition, increases in the physiological length may influence the densities of cortical myelinated axons and the impact of this is yet to be determined.

Remaining on the theme of CAG repeat length, **Joseph Hamilton** (University College London, UK) spoke on 'FAN1 as a Genetic Modifier of Huntington's Disease'. Human stem cell models of HD have shown that FAN1 suppresses somatic expansion at the *HTT* locus although the mechanism of action is unclear. Hamilton reported recent findings from Tabrizi's laboratory and others that converge to show that FAN1 is a powerful modifier in HD whereby somatic stability can be mediated through two mechanisms. The first is through binding MLH1 (part of the DNA mismatch repair pathway) and the second is through nuclease activity, which likely promotes accurate repair at the *HTT* locus. This proposes new therapeutic targets for preventing expansion of the CAG repeat.

The final speaker in this session was **Galen Wright** of the University of Manitoba, Canada, with 'Huntington Disease Genomic Modifiers: Emerging Biological, clinical and Therapeutic Insights'. He opened by noting the importance of genomic modifiers of HD age of onset in disease management for both prediction (e.g., allowing genetic counselling) and prevention (e.g., informing the

development of potential therapeutic targets). Wright then presented HD as a case study illustrating the power of human genetics research, citing key studies and highlighting new avenues for therapeutic development, namely, targeting somatic repeat instability and DNA repair as an attractive alternative to targeting HTT given its role as an essential gene.

Parallel Session 1: HTT Structure and Function was chaired by Chiara Zuccato (University of Milan, Italy) and Frédéric Saudou (Grenoble Institute of Neurosciences, University Grenoble Alpes, France). **Stefan Kochanek** of Ulm University, Germany, opened with 'HTT/HAP40 Complex in the Pathophysiology of HD'. Building on the discussions earlier in the day on different disease mechanisms and how they work together to cause HD, he explained his current focus is on two proteins: HTT and huntingtin-associated protein 40 (HAP40). He reported data illustrating interactions between HAP40 and polyQ-expanded HTT, the evolution of HAP40, and finally, the expression and stability of HAP40. Kochanek pointed to the need to better understand the consequences of interaction between HTT and HAP40, and the potential for HAP40 to be used as a biomarker in HD.

Next to speak was **Frédéric Saudou** with 'Huntingtin and the Transport of Neurotrophic Signals in Axons'. He described how huntingtin is involved in vesicular transport along microtubules and is altered in disease. He described the development of a microfluidic device which has allowed the study of the corticostriatal circuit in HD, confirming disruption to this and the potential for the cortex, and in particular, axonal transport for therapeutic intervention. His work has further shown that the compound ML348 (an acyl-protein thioesterase 1 inhibitor) restores the phenotype in HD mice and may have promise for HD therapeutics.

The final speaker in this parallel session was **Hilal Lashuel** of the Swiss Federal Institute of Technology Lausanne, Switzerland, on 'Disentangling the Sequence, Cellular and Ultrastructural Determinants of Huntingtin Fibrillization and Inclusion Formation'. In discussing the mechanisms of HTT aggregation, he proposed that inclusion formation is the missing link in our understanding of HD and reported new insights from a series of studies supporting this. He also discussed recent efforts to bridge the divide between the simplistic models and approaches offered by current in vitro systems and the complexity of huntingtin aggregation and pathology in neural cells.

Parallel Session 2: Digital Endpoints was chaired by Ralf Reilmann (George Huntington Institute, Germany) and Ahmad Aziz (German Center for Neurodegenerative Diseases, Germany). The first speaker was **Marcus D'Souza** of University Hospital Basel, Switzerland, who presented 'A Perspective from Multiple Sclerosis Bridging to Huntington Disease' in relation to digital endpoints (e.g., the capture and documentation of clinical measures). He provided details on the basics of digital endpoints in general and discussed how assessments such as the Huntington's Disease Integrated Staging System (HD-ISS) could be used electronically. Further, he discussed how the advantages of this approach would give insights into the pathophysiology of HD and real-world challenges, as well as how it might improve personalised care and outcomes in phase 3 trials.

Jonas Dorn, of F. Hoffmann-La Roche Ltd, Switzerland, followed with 'Lessons Learnt from the Roche HD Digital Monitoring Platform'. The Digital Monitoring Platform (dMP) has been used in several studies as part of the tominersen development programme (including GENERATION HD1), amassing data from more than 1,000 participants so far. While interpretations of data in GENERATION HD1 are limited due to differences in the participants who continued versus those who stopped providing digital data, new findings suggest that individual tests of the Roche dMP can capture disease progression earlier and more sensitively than the composite Unified Huntington's Disease Rating Scale (UHDRS) score, particularly in individuals with HD-ISS stage 2.

The final speaker in this parallel session was **Robin Schubert**, of the George Huntington Institute in Germany, who presented 'Lessons Learnt from Q-Motor and Q-Cog in HD Trials'. The digital Q-Motor system quantitatively assesses motor function and also cognition (Q-Cog). Schubert presented data from different studies (PRIDE-HD, LEGATO-HD and AMARYLLIS) in which Q-Motor showed greater sensitivity than the UHDRS-Total Motor Score primarily due to the absence of placebo responses. He also discussed recent work increasing the cognitive load in tasks and the translation of traditional pen and paper tests.

Plenary Session II: Approaches to Quality of Life and Clinical Management of HD was chaired by Alzbeta Mühlbäck (Ulm University, Germany) and Giorgos Papantoniou. First to speak was **Tess Persson** with 'Coping with Symptoms of Huntington's Disease'. She described her experiences of being diagnosed with HD and being part of an HD-affected family. Sharing her personal account of various cognitive, mental and physical challenges, she shared insights into how yoga/mindfulness, cognitive behavioural therapy, exercise and maintaining daily routines (which can be a daily struggle) have been helpful.

Bernhard Landwehrmeyer of Ulm University (Germany), then spoke on behalf of Stephen McKenna (Galen Research, UK) on 'Quality of Life and PROMs for HD'. He discussed the need for and value of quality of life measures developed specifically for individuals with HD – including the early stages of HD – as well as their caregivers/companions. He described how a needs-based model was adopted to inform the development of items for the new HD-specific measure which has undergone psychometric validation. The measures will be available for the HD community and researchers with a view to inclusion in future clinical trials.

Åsa Petersén of Lund University in Sweden took a different perspective in her presentation 'Understanding Emotions and Psychiatric Aspects of Huntington's Disease'. Noting that psychiatric difficulties are more often found in HD (e.g., depression, psychosis, obsessive-compulsive disorder and suicidality) than would be otherwise expected, she explained the need to take a multifactorial approach to understanding these, citing examples including the stress and vulnerability model and changes to the emotion regulating circuities in the brain as part of HD. She concluded that while psychiatric symptoms can be reduced in HD, more research and better therapies are still needed.

The final presenter was **Duncan McLauchlan** of Cardiff University, UK, with 'Management of the Psychiatric Symptoms in Huntington's Disease'. After presenting further evidence supporting the considerably higher prevalence of psychiatric disorders in HD, he considered the current treatment guidelines and current lack of evidence base. McLauchlan then asked whether HD pathology contributes to psychiatric disorders, and whether the underlying mechanisms may differ. Using depression as a model, he presented data showing that the cognitive mechanisms associated with depression in HD differ from the general population, and finally noted that antidepressants also differ in their efficacy in HD. A lively panel discussion with the presenters and chairs concluded this session.

The **Working Groups Session** was chaired by Michael Orth (University of Bern, Switzerland) and Kristina Becanovic (Karolinska Institute, Sweden). After the chairs provided an overview of the EHDN working groups (WGs) and task forces (TFs) and the purpose of these, presentations were delivered by lead facilitators for the Incidental Findings TF, Cognitive Phenotype WG, Imaging WG, Physiotherapy WG and Systems Modeling WG.

After a **Short Communications Session** with selected poster presentations, the first day came to a close with the highly anticipated and equally well-received **Special Lecture** by **Nora Guthrie**, chaired by Michaela Winkelmann (German HD Association) and Patrick Weydt. After a busy day of science

and statistics, we welcomed this moving account of her family experiences of HD accompanied by poignant photographs and music.

Saturday 17 September

Day 2 opened with **Plenary Session III: Update on Ongoing Clinical Trials**, chaired by Sarah Tabrizi and Astri Arnesen. The first speaker was **Michael Hayden** of **Prilenia** with an update on the phase 3 PRidopidine Outcome On Function in Huntington Disease (PROOF-HD) study. This was designed to replicate and further assess the beneficial effects in maintaining total functional capacity (e.g., working, performing household tasks) observed in PRIDE-HD (an exploratory phase 2 dose-finding study). We heard that the FDA has now granted fast track designation for pridopidine in the treatment of HD and study results are anticipated in early 2023.

Next to speak was **Ricardo Dolmetsch**, representing **UniQure** and the AMT-130 HD programme. AMT-130 targets exon-1 of the HTT gene through direct injection into the striatum and is currently under investigation in a double-blind, sham-controlled phase 1/2 study in the USA and an open-label trial in Europe. In both studies, the low dose (6×10^{12} gc) continues to be well tolerated and in the USA study, we see the predicted increases in cerebral spinal fluid (CSF) levels of neurofilament (NfL) protein after surgery and lowering of mHTT. Administration of the high dose (6 x 1013 gc) is currently on hold pending a full safety review.

Danlin Xu spoke on behalf of **Wave Life Sciences** on WVE-003, which is designed selectively lower mHTT by targeting a specific single nucleotide polymorphism (SNP3) that is commonly found on the expanded CAG allele. In contrast to typical mHTT-lowering approaches, WVE-003 spares wild-type HTT (which is important for healthy brain function) and is under investigation in SELECT-HD, a phase 1b/2a trial. Preliminary data suggest that WVE-003 has improved exposure in CSF compared to earlier compounds and activation of sites and recruitment is ongoing.

PTC Therapeutics was represented by **Amy-Lee Bredlau** who discussed PTC518, an orally available pre-mRNA splicing modifier that lowers HTT in the blood and brain of HD mice. A phase 1 trial has confirmed the compound is well-tolerated and shows mRNA and protein lowering in healthy volunteers. The PIVOT-HD phase 2 study started in the first quarter of 2022 and is looking at safety and efficacy in HD during 12-month randomised treatment with PTC518 compared with placebo.

Speaking on behalf of **SOM Biotech** was **Catherine Scart**. SOM3355 (bevantolol hydrochloride) is a vesicular monoamine transporter 2 inhibitor and was originally developed and commercialised for the treatment of hypertension, in which it showed a good safety profile. Expected benefits in chorea were confirmed in a phase 2a proof of concept study and a phase 2b study comparing the effects of two doses with placebo is now underway with completion expected in June 2023. An open-label extension study is also planned.

Irina Antonijevic of **Triplet Therapeutics** presented on their antisense oligonucleotide (ASO) approach and in particular, TTX-3360 and the rapid development of this, in part informed by their natural history study SHIELD-HD. Minimal adversity of TTX-3360 at therapeutic doses was recently observed in animal studies, and Triplet has several backup molecules with improved characteristics (e.g., greater potency). In summarising, Antonijevic noted that SHIELD-HD has now transitioned to CHDI and that Triplet is looking for a partner to support the ASO programme.

The **Panel Discussion** that followed included the chairs, speakers, Dina de Sousa and the audience. Interesting topics included the value of preclinical work and the volume of work that goes into the drug development process and the need for more sophisticated biomarkers.

A second **Short Communications Session** with selected poster presentations was then chaired by Katrin Lindenberg (Ulm University, Germany) and Anne Nørremølle (University of Copenhagen, Denmark).

The **EHDN Business Meeting** was conducted by Anne Rosser and Patrick Weydt. Members of the existing Scientific and Advisory Board (SBAC) and the Executive Committee (EC) had agreed to extend the duration of their positions over the COVID pandemic to the current election. In a change from previous elections, a slate of SBAC candidates had been proposed to ensure appropriate cover of important areas of excellence and expertise. Thanks were given to the members stepping down, namely, Kathrin Reetz, Kristina Becanovic, Esther Cubo, Leonor Correia Guedes, Paola Bellosta, Jennifer Hoblyn, Katrin Lindenberg, Karine Merienne, Saul Martinez-Horta, Martha Nance and Daniel Zielonka. Ahmad Aziz will continue to chair the SBAC to provide continuity, and incoming members Sandrine Betuing, Marta Biagioli, Silvia Gines, Davina Hensman Moss, Jiří Klempíř, Duncan McLauchlan, Hoa Huu Phuc Nguyen, Mayke Oosterloo, Willeke van Roon-Mom, Niels Henning Skotte and Chiara Zuccato were extended a very warm welcome. The patient representative, statistics advisor and ethics advisor (Dina de Sousa, Peter Holmans and Heidi Benzten, respectively) are appointed through a separate process. Dina de Sousa is now the European Huntington Association's appointed member to the EC.

Moving on to the EC, Ralf Reilmann, Raymond Roos and Sandrine Humbert received thanks for their contributions and then the election results were announced. Patrick Weydt was re-elected and newly elected members Åsa Petersén, Monica Busse and Ed Wild each introduced themselves on stage and shared their vision for working with the EHDN as part of the EC. Kathrin Reetz (previously SBAC Chair) was also newly elected to the EC but could not be present.

Rosser then reviewed the criteria that clinical trials must adhere to be endorsed by the EHDN and illustrated the range of studies that have been endorsed since 2018. She also reviewed data mining and seed fund applications. Since 2018, 12 Registry data mining applications were approved and 139 seed fund applications were made with 20 being awarded. The seed fund programme has been renamed to honour Professor Lesley Jones and applications can be made in March and November each year.

The Think Tank assists the EC and interacts with WGs and TFs and inputs into the fellowship programme but is also available for discussions with EHDN members upon request. Recent initiatives include the Digital Assessments in HD WG, Advanced Therapies Surgical WG, Dysphagia TF and Incidental Findings TF. Areas of special focus over the past few years include imaging and quality of life.

We were reminded that the objective of the Fellowship Programme is to provide clinical multidisciplinary training in HD to young professionals currently working in underserved areas. This is offered in collaboration with the International Parkinson and Movement Disorder Society – European Section (MDS-ES) and typically six places are available each year. While the programme was paused in 2021 and 2022 due to COVID-19, the plans to resume in 2023 are nearly complete and the deadline and process for applications (January/February 2023) will be finalised shortly. Updates will be provided on the EHDN website.

Other activities include the continued development of the site certification scheme, EHDN/MDS training webinars, a virtual platform to discuss the Roche study, and the development of a new scientific strategic plan (previous plans had been made in 2011 and 2017). Development of the strategic plan is currently underway and this is intended to run from 2023 for 4–5 years. More updates on this will be available soon!

Finally, thanks were given to all those working behind the scenes to support this work, and in particular, the EHDN Central Coordination team, the Ulm 'container' office (led by Bernhard Landwehrmeyer) and CHDI for funding.

Parallel Session II: The Use of Biomarkers in Clinical Trials of Neurodegenerative Disorders was chaired by Maciej Figiel (Polish Academy of Sciences, Poland) and Lauren Byrne (University College London, UK). **Henrik Zetterberg** of the University of Gothenburg (Sweden) and University College London (UK) presented 'Neurofilaments as Biomarkers Across Neurodegenerative Disorders'. Providing a brief history, he noted that in 1996, increased levels of the NfL protein in CSF were associated with neurodegenerative diseases and with HD in 2009. There is evidence that CSF NfL can be normalised pharmaceutically (e.g., in multiple sclerosis), suggesting its potential as a biomarker in HD. He concluded that improved knowledge of biomarker stability and disease-relevant longitudinal change in relation to NfL and other convergent outcomes will inform clinical research in HD.

Douglas Macdonald of the CHDI Foundation then presented 'A Novel Ultrasensitive Assay to Measure Huntingtin Protein in a Polyglutamine Length-independent Manner'. Pointing to the need for additional HTT protein biomarker assays for clinical use, Macdonald described the development of CHDI_HTT_143 which selectively measures *total* huntingtin (wildtype HTT and mHTT combined). Data were presented supporting the sensitivity and validity of this assay, which also provides a measure of HTT in premanifest HD participant CSF samples. Studies will now look at repeat and longitudinal samples as well as the clinical utility of the assay.

Next, **Aline Delva** of University Hospitals, Leuven/KU Leuven, Belgium, presented an update on iMAGEmHTT with 'First-in-Human Evaluation of Novel Mutant Huntingtin PET Radioligands 11C-CHDI-180R and 11C-CHDI-626'. She reported dosimetry data in healthy volunteers showing 11C-CHDI-180R is a promising PET radioligand in targeting mHTT aggregates (and that 11C-CHDI-626 is not suitable). In a phase 1 study of 11C-CHDI-180R, the volume of distribution data showed considerable individual variability and overlap between groups but exploratory analyses with the cerebellum as a pseudo-reference region reduced variability and allowed the determination of significant differences in the cortical regions between people with HD and healthy controls.

Parallel Session II: Neurodevelopment/Pediatric/Juvenile HD was chaired by Sandrine Humbert (University Grenoble Alpes, France). **Mariacristina Capizzi**, also of University Grenoble Alpes, opened with 'Developmental Defects in Huntington Disease Show that Axonal Growth and Microtubule Reorganization Require NUMA1'. She explained that although HD is considered an adult disorder due to the mutation in the HTT gene, the mutated protein is expressed from the foetal stage. Noting that converging evidence may suggest a developmental contribution to corpus callosum alterations, Capizzi presented studies illustrating disorganisation of the microtubule cytoskeleton during development in HD.

Radhia Kacher of the Paris Brain Institute, France, then spoke on 'Propensity for Somatic Expansion Increases Over the Course of Life in Huntington Disease'. She presented long-term data from HD participants tested 10–20 years apart as well as foetal and post-mortem data which, taken together, showed that CAG somatic expansion increases in HD through life, with a trajectory that starts as stable in the developing foetal cortex to one marked by highly active expansion in older age as symptoms progress.

Finally, **Ferdinando Squitieri**, co-founder and chief scientific officer of LIRH Foundation and Head of Huntington Unit at CSS-Mendel Institute Rome, Italy, presented 'Huntington's Disease in Kids' and opened by explaining that when HD starts before the age of 18, it is known as paediatric-onset HD and when it starts before the age of 10, paediatric/childhood HD – starting in the first years of life. He noted that there are important differences, however, in addition to the age of onset, such as fast

disease progression, short lifespan, atypical clinical presentation and liver steatosis, necessitating the study of HD approaching post-mortem brain and peripheral organs from kids with highly expanded CAG mutations >80 repeats. He proposed that research should identify the factors contributing to the more severe progression seen with younger onset, and that this should go beyond the nervous system.

Parallel Session III: White Matter Changes in HD was chaired by Åsa Petersén and **Mahmoud Pouladi** (University of British Columbia, Canada), who was also the first speaker with 'Oligodendrocyte Dysfunction in Huntington Disease Models'. After explaining how oligodendrocytes and myelination are critical for neuronal function, Pouladi described work using mouse models showing that both innate (developmental) and adaptive (regulated by neuronal activity) forms of myelination are altered in HD and furthermore, how such defects in myelination are at least partly due to direct effects of mutant HTT on oligodendroglia. Finally, he noted that oligodendroglial dysfunction contributes to white matter and myelination abnormalities and other neurological manifestations of HD.

'Early White Matter Pathology in the Fornix in Huntington Disease' was the focus of the second speaker, **Sanaz Gabery** of Lund University, Sweden. Pointing to the psychiatric symptoms that can appear early in the progression of HD, Gabery noted that the limbic system and in particular, the fornix, may be involved. Post-mortem data has shown the fornix is smaller in HD and data from IMAGE-HD has shown that fornix volume correlates with depression and performance on neurocognitive tests. He presented further data showing that myelin breakdown and transcriptional changes in HD may account for this.

Following on from this, **Anna Williams** of the University of Edinburgh, UK, started the final presentation with 'Glial-specific Transcriptomic Changes in Huntington's Disease'. Work in this laboratory is focused on understanding and manipulating myelin pathology, and in particular, the therapeutic potential of glia. **Sunniva Bøstrand** (also of the University of Edinburgh) continued the presentation by describing her recent work showing that altered glia are in abundance in HD and further work demonstrating the altered expression of the PDE1A gene in oligodendrocytes, opening up its potential as a therapeutic target.

Meanwhile, **Parallel Session II: Multidisciplinary Care** was chaired by Ruth Veenhuizen (Atlant and Amsterdam University Medical Center, the Netherlands) and Monica Busse (Cardiff University, UK). First to present was **Ruth Veenhuizen** with 'Challenges in HD Treatment and Care: Moral Case Deliberation'. We heard how this structured process facilitates the discussion of ethical issues arising in the workplace between participants and is argued to enhance proficiency, professional collaboration and quality of care. Veenhuizen presented a step-by-step guide to decision-making and determining the next steps using this approach.

Una Jones of Cardiff University, UK, was next to present on 'Moving Against Resistance: Implications for Physiotherapy and Physical Activity'. She acknowledged that while intervention studies and current guidelines all support the importance of exercise in HD, many individuals do not embrace it, prompting the question of how evidence-based practice can be implemented in the context of behavioural, cognitive and movement problems. Jones discussed how a person-centred approach to goal setting, the development of individualised plans and specific physiotherapy expertise can facilitate physical activity.

'Managing the Transition from Independence in Daily Living' was the focus for **Manon van Kampen** of Atlant, the Netherlands. Challenges to independence and all that entails (e.g., for self-care, feeding, well-being) when challenged in the course of HD require a careful balance in terms of care and management. van Kampen discussed practical tips for guiding this, including the need for being

honest and clear, facilitating decision-making, being aware of environmental factors impacting the individual and focusing on residual capacity in day-to-day tasks.

Also speaking from Atlant was **Margret Knoll** with 'Nutrition Decision Making', with a specific focus on individuals for whom oral nutrition is no longer possible or safe due to challenges in eating and drinking. She emphasised the importance of discussing tube feeding in a timely manner and presented case studies to illustrate effective management (including the use of moral deliberation as discussed earlier). To wrap up this session, the speakers and chairs convened for a **Panel Discussion**.

The Keynote Lecture '**Lessons Learnt from Other Neurodegenerative Disorders'** was chaired by Patrick Weydt and presented by **Dieter Edbauer**, Professor of Translational Neurobiochemistry at the German Center for Neurodegenerative Diseases with 'Vaccines and Small Molecules to Target Dipeptide Repeat Proteins in C9orf72 ALS (Amyotrophic Lateral Sclerosis)/FTD (Frontotemporal Dementia)'. ALS and FTD are both neurodegenerative diseases and though present quite differently clinically, they share the common mutation of the repeat expansion in the C9orf72 gene. Edbauer described his elegant work dissecting C9orf72, and highlighted the role of repeat-associated non-AUG (RAN) translation in causing neurodegenerative diseases such as ALS and FTD, and also HD. We heard how these new insights into ALS and FTD disease pathology are informing several avenues of intervention which are currently in development, including immunotherapy, and the research efforts that are overcoming challenges and defying expectations in this 'mission impossible'.

Cristina Sampaio chaired the next **Keynote Lecture**, titled '**HD-Integrated Staging System – A Primer for Use in Clinical Research**' and presented by **Sarah Tabrizi**, Professor of Clinical Neurology & Neurogenetics at University College London, UK. Tabrizi explained the importance of medical staging systems, noting that relying on motor symptoms for the diagnosis of HD is not only imprecise but occurs late in the disease trajectory. She explained the development of the HD-ISS by the Critical Path Institute HD-Regulatory Science Consortium WG. We heard that with the HD-ISS, HD is still defined by genetic testing. However, disease progression is classified into four Stages (0, 1, 2, 3), covering the entire lifespan, with individuals in each stage sharing predefined, common characteristics. This classification usefully creates a framework for intervention before clinical motor diagnosis. As Tabrizi noted, there are many advantages to using the HD-ISS in clinical research, but ultimately, it paves the way for trials and treatments earlier in the progression of HD with the hope to prevent or delay disease progression.

Roche's **Peter McColgan** presented a Special Report on 'Towards an Understanding of the Post-treatment and Mechanistic Aspects of Tominersen', chaired by Jean-Marc Burgunder (University of Bern, Switzerland). Despite treatment (120 mg tominersen every 8 or 16 weeks versus placebo) being stopped, an impressive ~77% of participants completed the final study visit. McColgan described analyses showing that the initial increases in the rate of ventricular volume increase with tominersen seen at 37 weeks decreased at later timepoints and post-treatment. In addition, further analyses showed that rates of disease progression in the post-treatment period did not differ between tominersen and placebo. Finally, we heard how mechanistic studies have led Roche to believe that lower doses of tominersen may mitigate unwanted effects such as ventricular volume increase, setting the scene for further research.

Day 2 concluded with a **Round Table Discussion** on '**What do Results from Clinical Trials Mean?**'. Chairs Jean-Marc Burgunder and Patrick Weydt were joined by Henrik Zetterberg, Bernhard Landwehrmeyer, Jessica Koehli, Anne Rosser, Peter McColgan and Irina Antonijevic. Questions were also invited from the audience and stimulating discussions emerged on several topics, including the importance of converging evidence from different biomarkers in clinical trials, discussion about what has been learned from recent studies and also the importance of meetings such as these in providing a forum to advance the HD field.

Sunday 18 September

The final day of the meeting opened with **Plenary Session IV: Advanced Therapies for HD**, chaired by Anne Rosser and **Romina Aron-Badin** (French Alternative Energies and Atomic Energy Commission, Molecular Imaging Research Center, France) who also provided an introduction and overview of the challenges of delivering advanced therapies to the brain, including difficulties in bypassing the blood-brain barrier with different administration routes and novel delivery devices.

Liam Gray of Cardiff University, UK, then presented 'Challenges to Surgical Delivery of Advanced Therapy Medicinal Products (ATMPs)'. Noting that while direct delivery of therapeutics to the brain has specific advantages, it also comes with significant challenges, including accuracy and access in the pathological brain. Gray reviewed the available technologies available to help minimise these various challenges but summarised that knowing whether or not the ATMP has worked remains problematic. This led Gray to the question of 'how do we make delivery visible?' and the introduction of the EHDN Surgical Delivery TF and the proposed work plan of this newly established group.

Cheney Drew, also of Cardiff University, remained on this topic with 'Challenges of Trialing Advanced Therapies in HD'. Drew presented an overview of the alternatives to the 'gold standard' of randomised controlled trial in clinical research, including the 'trial within a cohort' design in which a prospective cohort of participants provides consent for routine longitudinal assessments at specified time periods. She concluded with a personal reflection on the value of the participant voice in clinical research and called on researchers to engage with the full breadth of the HD community to find ways to deal with the inherent challenges in HD research.

Next, **Anne Rosser** presented 'What is New: Cell Therapy', and opened with an explanation of the aims of cell therapies which includes support/rescue of host cells and replacing cells lost to the disease process. She reported on the status of several human ES-derived neural progenitor studies, including the progress of an Investigational New Drug application to the Food and Drug Administration by the Thompson group for ESI-017 hNSCs. She also discussed translational constraints associated with cell therapies and the global platforms set up to address these challenges (EHDN Advanced Therapies WG and Stem Cells for HD). Rosser concluded with a discussion on using HD as a model for translating cell therapies for neurodegenerative diseases.

Last to speak was **Jan Vesper** of Heinrich Heine University Medical Center, Germany, who took a slightly different approach in his presentation 'Deep Brain Stimulation (DBS) of the Globus Pallidus (GP) in Huntington's disease (HD): A Prospective, Randomised, Controlled, International, Multi-centre Study (HD-DBS)'. We heard that following a successful pilot study, the HD-DBS study was conducted. However, no statistically significant differences were seen for the primary endpoint which was a change in motor symptoms, 12 weeks after surgery. Vesper explained that while some patients may benefit, the predictors of this remain unclear and he concluded that pursuing DBS as a treatment at the current time is unsupported. So far, DBS cannot be recommended to treat HD.

This session was wrapped up with **Discussion** between the chairs, speakers and audience, who were invited to ask questions.

Plenary Session V: Update on Planned Clinical Trials was chaired by Tim McLean (EHDN) and Bernhard Landwehrmeyer. **Nathalie Cartier-Lacave** on behalf of **AskBio** was the first to present with 'Restoring Brain Cholesterol Metabolism Using Gene Therapy in Huntington's Disease'. Given that brain cholesterol metabolism is impaired in HD – notably, the CYP46A1 regulatory enzyme, AskBio has been working to restore this. They have found beneficial effects of doing this in mouse models of HD and also that BV-101, an adeno-associated virus gene therapy that encodes CYP46A1, has a

favourable safety profile in non-human primates. An open-label phase 1/2 dose-finding study will now evaluate the safety, tolerability and preliminary efficacy of BV-101.

Aaron Koenig then presented on behalf of **Sage Therapeutics** with 'The PERSPECTIVE Program: Evaluating the Effect of SAGE-718 on Cognitive Function in Patients with Huntington's Disease'. Koenig explained that cognitive impairment in HD is associated with lower levels of 24S-HC, an endogenous NMDA receptor positive allosteric modulator (PAM). SAGE-718 is a novel, investigational NMDA receptor PAM currently being evaluated in three trials. DIMENSION will assess the effect of SAGE-718 on cognitive performance and functioning in HD and SURVEYOR will establish the clinical meaningfulness of cognitive endpoints in HD by linking cognitive changes to real-world functioning outcomes. An open-label study will then assess the long-term safety of SAGE-718.

Peter McColgan spoke again on behalf of **Roche**, this time to announce a new 'Phase II Dose-finding Study of Tominersen'. We heard that GENERATION HD2 aims to evaluate safety, biomarkers and clinical efficacy trends in response to intrathecally-administered tominersen compared with placebo, in individuals with prodromal and early manifest HD. The study doses will be 100 mg tominersen every four months, 60 mg tominersen every four months or placebo. Every participant will receive tominersen or placebo for at least 16 months, in a common close design, with the possibility of an optional open-label extension study, based on supportive data at the end of the study. The study will include approximately 360 participants and is expected to run in 15 countries.

The last speaker was **Henk-André Kroon**, representing **Annexon Biosciences** with 'Results from a Phase 2 Study of ANX005 in Patients with Manifest Huntington's Disease'. ANX005 is a monoclonal antibody that inhibits C1q, the initiator of the classical complement pathway (part of the immune system). Complement activation correlates with disease severity and functional decline in HD, and we heard that in a small phase 2 study, ANX005 showed C1q target engagement in blood and CSF, was generally well-tolerated, and was associated with clinical improvement and decreased neuroinflammation. These findings will be confirmed in a larger, placebo-controlled clinical study which will start in 2023.

In the very final session of the meeting, Åsa Petersén announced the poster awards presented in honour of Lesley Jones: Maximilian Wagner of Ulm University, Germany, Laura Heraty of Cardiff University, UK, and Laurent Cotter of the French Alternative Energies and Atomic Energy Commission, Molecular Imaging Research Center, France. **Patrick Weydt** and **Anne Rosser** then brought the meeting to a close, expressing gratitude to everyone who had participated and made the meeting such an outstanding success, and finally, inviting everyone to the 2024 EHDN plenary meeting in Strasbourg, France!