EHDN 2021 Remote Meeting

09–11 September 2021

Report prepared by Catherine Deeprose

The EHDN Remote Meeting was held over three half-days (09 September to Saturday 11 September) via Zoom due to the continuing pandemic situation. An impressive total of 865 participants (out of 1,065 who had registered) attended over the course of the meeting. All presentations, discussions and posters were made available 'on demand' via the meeting platform from 13 September to 10 October 2021 and are now available on the EHDN website (http://www.ehdn.org/ehdn2021/). Meeting abstracts have been published in a supplement edition of the *Journal of Neurology Neurosurgery & Psychiatry*.

Thursday 09 September[1]

The meeting was opened with a warm welcome from current EHDN Executive Committee Chair Anne Rosser, previous EHDN Chair Jean-Marc Burgunder, and President of the European Huntington's Association (EHA), Astri Arnesen.

The first keynote session, 'From fruitfly biorhythm genetics to Huntington's', was presented by **Charalambos P. Kyriacou**, Professor of Behavioural Genetics at the University of Leicester, UK. Kyriacou started by describing his early work with Jeffrey Hall at Brandeis University, where he discovered the rhythmic components of the Drosophila courtship display and how mutations of the period gene influence this, following on from Ron Konopka and Seymour Benzer's seminal demonstration that the gene regulates the Drosophila biological clock. We heard how Michael Rosbash (Brandeis University) and Jeffrey Hall then started molecularly identifying the period gene, while at the same time, Michael Young (Rockefeller University) and his colleagues started working on the same idea. Key papers published by both groups in 1984 showed that a piece of DNA from the period locus could restore circadian rhythms in mutant, arrhythmic Drosophila and the groups continued to consolidate this work, culminating in a model of the Drosophila circadian clock. The circadian clock gene model was later shown to be very similar to that of mammals, confirming the relevance of flies to understanding human sleep and circadian rhythms. Kyriacou related how his interest in HD had been prompted due to a family connection with the disease, and explained how subsequent work with Susanna Campesan, Flaviano Giorgini and colleagues confirmed the role of the metabolic kynurenine pathway in modulating neurodegeneration in a Drosophila model of HD. Kyriacou elaborated on how this work was developed by utilising Drosophila in modelling neurodegeneration to explore therapeutic targets in HD. The keynote was concluded on a personal note, with Kyriacou providing an update on his family connection to HD that had been the trigger for his interest in the field.

The first plenary session, 'Genetic Modifiers of HD: DNA Damage and Somatic Expansion of Repeats', was chaired by Lesley Jones (EHDN Executive Committee and Cardiff University, UK) and Davina Hensman Moss (St George's University of London, UK). The session was opened by **Vincent Dion** of Cardiff University, UK, with 'A Gene Editing Approach to Contract CAG/CTG Repeats'. Dion started by reminding us that longer repeats cause more severe disease at an earlier age, which means that if we can take a long repeat and shrink it down to a non-pathogenic size then this should bring benefits to patients. To try to achieve this, researchers have removed the repeat track altogether in multiple different systems in multiple different diseases. The general concept is to induce double-stranded breaks using the gene editing technique CRISPR-Cas9 on either side of the repeat track to

[1] The EHDN Business Meeting is summarised at the end of this report.

remove the underlying cause of the disease. However, some difficulties are associated with this, including the lack of specificity. As such, Dion and his colleagues have been working on an alternative approach using a Cas9 nickase that cuts only one of the two strands of DNA to specifically target only the repeat track, and this provides contractions. We heard how striking data from Dion and his colleagues have confirmed the utility and safety of this approach and ongoing research is aiming to address outstanding questions, including the underlying molecular mechanism of CRISPR-Cas9-induced contractions.

Bob Lahue at the National University of Ireland, was next to speak on 'Using Histone Deacetylase 3 Inhibition to Rein in HD Expansion Mutations'. We heard how work in his laboratory has identified the role of histone deacetylase 3 (HDAC3) enzymes in modifying other target proteins by changing post-translational modification. More specifically, Lahue explained, HDAC3 seems to work on a very important protein called MutSβ which drives the repeat CAG expansions that occur in HD. Work in Lahue's laboratory has shown that RGFP966 inhibits HDAC3, and in doing so, can block the activation of MutSβ and thus block expansions. Lahue provided the analogy of thinking about the expansion mutations in HD as an 'out of control genetic train', arguing that if we can slow down that train, we can slow down the deterioration of the brain in HD. Lahue noted the genome-wide association studies that have informed this work, leading to confirmation of the crucial role of HDAC3 as well as MutSβ for driving expansions, and the observation that HDAC3 and MutSβ work in the same pathway to achieve this. The presentation ended with data showing that administration of RGFP966 in mice before the onset of symptoms of HD suppressed huntingtin (HTT) expansions in the brain, slowed neurodegeneration, protected cognitive function, helped normalise the pattern of transcription and was also well tolerated, pointing to the potential for RGFP966 as a therapy in HD.

The third speaker was **Vanessa C. Wheeler** of the Center for Genomic Medicine, Massachusetts General Hospital, USA. Wheeler's presentation, titled 'Dissecting Genetic Modifiers of HD: Towards Understanding Mechanism', began with the observation that genome-wide association studies have provided significant insight into the pathogenesis of HD in recent years. She described how longer somatic expansions in the brain are associated with earlier onset of HD, and how quantification of somatic expansion across a wide range of central and peripheral tissues has revealed common patterns of instability. Wheeler continued to describe how HTT and ataxin 1 CAG expansion are highly correlated, and presented a two step model for pathogenesis in HD that involves a repeat expansion component and a toxicity component. Wheeler showed how the knockout of genes using CRISPR can be used as a tool to test whether human onset modifier genes alter somatic expansion and to explore potential genetic interactions. She concluded that further work including the dissection of human modifier alleles is now needed to better understand mechanisms and optimal therapeutic approaches.

Before the second plenary session, **Matthew Ellison** provided an announcement on the global work of the HDYO in providing support for young people and their families. He explained this is achieved in part through the HDYO website, where supportive information is available in 14 languages. HDYO also organises youth camps to provide experiences for teenagers and young adults. Although these services have been provided for free, he noted that HDYO would gladly welcome donations to support this work and encouraged delegates to contribute.

The second plenary session was on advances in cognition research, chaired by Jaime Kulisevsky and Saul Martinez-Horta, both of the Biomedical Research Institute Sant Pau, Spain.

Michael Orth (EHDN Science Director and of the University of Bern, Switzerland) opened with 'Visual System Integrity in Huntington's Disease. Orth is interested in the 'what', 'where' and 'how' of visual objection recognition and discussed how attention helps us focus our vision and how movement can be anticipated through assessment of the visual scene. Such assessments in vision are critical in

social interaction and misperceptions can lead to difficulties in day to day life. In HD, the transfer and speed of transfer of information to the primary visual cortex are intact, and the neuronal density of the primary visual cortex is comparable to controls. Nonetheless, a large number of studies point to vision abnormalities in HD and there are certainly structural and functional abnormalities. Visual cognition is of huge practical importance (consider, for example, the impacts on social cognition, movement and balance, and driving capability). Orth concluded that future research will benefit from focusing more specifically on visual cognition, selecting appropriate neuropsychological measures, and integrating data from several modalities (e.g., imaging, functional and behavioural assessment).

The final presentation in this session was **Julie Stout** of Monash University in Australia. Her talk 'Hippocampal-dependent Memory in Huntington's Diease' began with clinical anecdotes of memory complaints. While impairments in learning and retrieving information present the biggest problem, closer inspection also indicates problems with storage. This pattern is clear, for example, on word list learning tasks, and hippocampal pathology and atrophy are seen early in HD. Stout discussed two studies from her laboratory, the first being on autobiographical memory, defined as 'recollections of personally experienced events'. She found that individuals with HD recall fewer autobiographical events and these events in lesser detail than healthy controls. The second study focused on spatial memory and navigation. Here, Stout found deficits in early HD on the navigation component of a computerised 3-D task compared to healthy controls, but not in pre-manifest HD. In the object location component, both the pre-manifest group and early HD group showed deficits. Stout concluded by emphasising the importance of episodic memory deficits in HD, and highlighted the importance of better understanding how these deficits affect functioning as well as imagining and future-orientated thinking.

The next session consisted of short communications, chaired by Esther Cubo of the Hospital Universitario Burgos in Spain, and Lauren Byrne of University College London in the UK. **Filipa Júlio** of the EHA spoke first on 'Research Participation: The View of Persons at Risk and Persons with Premanifest Huntington's Disease'. Given the current lack of treatment for HD, research remains critical and those with traditionally lesser involvement in research need to be engaged. Individuals at risk for HD and those with premanifest HD completed a short online survey (N = 525) to determine the influencing factors of research participation. Júlio highlighted that motivation to take part in research is high, despite limited research experience and literacy. This work is providing a knowledge base for the latest EHA project 'Moving Forward' to increase participation in HD research, and Júlio noted the key role for patient organisations in fostering engagement.

Next, **Idaira Rodriguez Santana** of HCD Economics in the UK presented 'Huntington's Disease Burden of Illness (HDBOI): Study Methodology, Sample Representativeness and Fieldwork Risk Mitigation Strategy During the COVID-19 Pandemic'. Data on 2,094 patients were collected from physicians in the USA, Germany, Italy, Spain, France and the UK, and were considered representative of the countries and stages of HD studied. Santana noted how the pandemic negatively impacted patients and caregivers, particularly in relation to health resource use and mental health. This study provides novel data on health resource use by HD stage, increasing the evidence base of the HD community.

Speaker **Peter Holmans** of Cardiff University, UK, was next with 'Comparison of models for estimating Age at motor onset in HD'. Holmans explained that given the established influence of CAG length on HD age of onset (AOO), the power to detect other risk factors is increased by taking it into account and modelling the effect of CAG length as accurately as possible. Using the Enroll-HD PDS5 dataset, the researchers compared the Langbehn (2004) model which assumes a log-linear relationship between CAG length and AOO with that proposed by Kaplan (2007), which models CAG expansion in cells directly, with onset occurring when CAG lengths exceed a pathogenic threshold in a sufficient proportion of cells. Holmans provided data indicating improved accuracy for the Kaplan

model relative to that of the Langbehn model and noted that this approach may allow the inclusion of patients with CAG >56 when predicting AOO in genome-wide linkage and association studies.

'Skill-Based Dysphagia Training as an Intervention for Individuals with HD' was the topic for **Emma Burnip** of the University of Canterbury, New Zealand. She opened by explaining that while dysphagia is highly prevalent in HD and associated with aspiration pneumonia, the leading cause of death, there is a lack of evidence to support dysphagia rehabilitation. Skill-based training for dysphagia aims to enhance cortical modulation to improve the safety and efficiency of swallowing. Burnip reported on a study of 12 adults with HD and dysphagia who had completed two weeks of training. Findings confirmed the feasibility of the intervention and benefits for swallowing-related quality of life but not the effectiveness or duration of treatment effects.

The final speaker was **Rebecca Mason** of the HDYO with 'Introducing JOIN-HD: The Juvenile Onset Initiative for Huntington's Disease'. Mason explained the aim of this patient registry (JOIN-HD) is to identify patients, increase understanding, facilitate future research and identify unmet needs. Mason noted that since pre-registration opened in March 2021, 17 registrations from six countries have been received and work is now in progress preparing a platform for stage 1, establishing a family advisory group, obtaining EHDN approval, increasing recruitment and securing additional funding.

Anne Rosser, Jean-Marc Burgunder, Sandrine Humbert (Grenoble Institute Neuroscience, France) and Bernhard Landwehrmeyer (Ulm University, Germany) reconvened at the end of the day to share their perspectives and insights on this exciting first day of presentations.

Friday 10 September

The focus of the third plenary session was clinical trials, chaired by Ralf Reilmann of the George Huntington Institute in Germany, and Dina de Sousa of the EHA and also Board Member of the EU HD Association.

Scott Schobel of F. Hoffmann-La Roche Ltd, Switzerland, presented 'Roche: An Update from the Tominersen Clinical Development Programme'. After recapping on the iDMC's decision to stop tominerson dosing in the GENERATION HD1 trial, Schobel noted that ~85% of patients currently remain in the study for clinical and safety follow-up. He also recapped on the observation that 120 mg tominerson given once every 8 weeks had an 'unfavourable safety profile' whereas the same dose given once every 16 weeks while having a safety profile comparable to placebo, showed no apparent observable benefit. Schobel updated that simple univariate analyses (e.g., the timecourse of one biomarker over time in an active arm compared to placebo) commenced recently and the more interesting multivariate analyses (e.g., the relationship between change in one biomarker on another biomarker outcome) is yet to be completed. Questions in relation to the future for tominersen and HTT-lowering approaches can be answered, and shared with the HD community in due course.

Next to present was **Maurice Zauderer** of Vaccinex Inc in the USA on 'SIGNAL/Vaccinex – Results and Lessons Learnt'. He began explaining that SIGNAL was a randomised, placebo-controlled trial in cohorts of early manifest and prodromal HD given pepinemab (VX15) or placebo. In general, there were minimal treatment effects in the prodromal group, but significant benefits were seen in early manifest HD patients for the HD Cognitive Assessment Battery (HD-CAB) Composite Score across all study timepoints (months 2–17). Benefits were also seen to apathy severity which has been previously correlated with cognitive decline. For patients with TFC 11 at baseline, somewhat more advanced progression of HD, post-hoc analyses suggested benefits for active treatment also on the

Clinical Global Impression of Change score. Finally, imaging data demonstrated significantly reduced caudate atrophy for treatment and a trend in the same direction for ventricular expansion.

'SELECT-HD, an adaptive first-in-human clinical trial to evaluate WVE-003, an investigational allele-selective mHTT-lowering oligonucleotide, in early manifest Huntington's disease' was presented by **Vissia Viglietta** of Wave Life Sciences, USA. Viglietta explained that their dual aim is to preserve the neuroprotective effects of non-mutated wildtype HTT and also reduce toxic, mutant HTT. She noted that wildtype HTT is important in supporting healthy brain function, especially in the context of stress. Wave achieves allele-selectivity by targeting single nucleotide polymorphisms (SNPs) that are associated with the long CAG repeat responsible for the production of toxic, mutant HTT. In a mouse model of HD, potent and durable effects are observed for WVE-003 in the cortex and striatum. Preclinical modelling data has informed the starting dose for human testing in the upcoming Phase 1b/2a SELECT-HD trial. Biomarker and patient identification assays that were developed during the PRECISION-HD clinical trials will be applied again in SELECT-HD. We heard that, excitingly, the first patient has now been dosed and enrolment of the first cohort will be completed as soon as possible.

David Cooper of uniQure, Inc., then presented 'An Update on HD-GeneTRX-1 and HD-GeneTRX-2: Phase 1/2 Clinical Trials of AMT-130 Gene Therapy for Early Stage HD'. Cooper explained that AMT-130 (also called AAV5-miHTT) is a replication-deficient AAV5 that targets toxic huntingtin exon 1 following implantation into the striatum. The ultimate goal, Cooper explained, is to maximise the clinical impact of AMT-130 by focusing neurosurgical delivery to the most relevant brain regions and critically, slow disease progression in patients. Importantly, the CT-AMT-130-01 Phase 1/2 study is the first FDA-approved clinical study for gene therapy in HD. While the primary objective is the evaluation of safety and tolerability, the secondary objective is to test the duration of AMT-130 persistence in the brain. Both a high and low dose is being tested in this randomised, imitation-surgery controlled study of 26 early manifest HD patients with follow-up conducted over 5 years. Despite the pandemic, treatment commenced in the USA in June 2020 and is ongoing, and the planned Phase 1b/2 open-label study in the EU and UK will augment these data.

Irina Antonijevic of Triplet Therapeutics, Inc., presented 'Development of TTX-3360 to Prevent Onset and/or Progression in HD and Other Repeat Expansion Disorders by Halting Somatic Expansion'. Importantly, Triplet's approach aims to stop somatic expansion rather than lower HTT and in doing so, delay/prevent disease onset and halt progression. In addition to general safety considerations, Antonijevic explained the need to identify a clinical candidate with a low propensity to increase neurofilament light protein. Intracerebroventricular injection of the antisense oligonucleotide TTX-3360 in non-human primates has thus far shown a good safety margin, no neurofilament light increase as well as sustained MSH3 lowering in the targeted deep brain areas, including the striatum. Antonijevic further explained that intracerebroventricular rather than intrathecal injection is preferable both for longer-term safety and efficacy reasons. In discussing upcoming trials, Triplet's natural history study, SHIELD HD, will be used to augment the control group and inform the planning of their Phase 1/2a study with TTX-3360, for which CTA/IND submission is on track for mid-2022.

The final speaker in this session was **Michael R. Hayden** of Prilenia Therapeutics with 'PROOF-HD – Update on the Status of the Phase III Clinical Trial of Pridopidine Aiming to Improve Global Function in Early Stage HD'. Hayden explained that pridopidine binds and activates the sigma-1 receptor, which is highly expressed in the brain and plays an important role in the cell's response to stress. In HD, pridopidine activation of the sigma-1 receptor positively influences multiple pathways that lead to neuroprotection. Hayden reminded us of the major burden that decreased functional capacity places on the daily lives of patients and their families. As functional capacity follows a stable decline in early HD, it is noteworthy that in a prior clinical trial, pridopidine maintained functional capacity after 1 year. In addition, neurofilament light levels (a marker of progressing neurodegeneration in

HD) were stabilised by pridopidine. In terms of study progress, as of 9 September 2021, Hayden reported that 570 patients have been screened or reserved for screening in their current Phase 3 study and that completion is on target for October 2021.

The session was concluded with the speakers and taking forward a lively panel discussion focused on what we have learnt in the drug development process in recent times.

Two sessions were then conducted in parallel. The session on multidisciplinary care and treatment was opened (and co-chaired) by **Marleen van Walsem** (of Oslo University Hospital, Norway) with the presentation 'Challenges and Practice-based Approaches in Professional Advanced Care'. Her qualitative research provides important insight into how the challenges facing healthcare professionals in HD affect their care of patients and how various approaches are available to confront these challenges. Fellow co-chair **Ruth Veenhuizen** (of Atlant, Huntington Centre of Expertise in the Netherlands) was next to speak on 'Patients with Huntington's disease living in a nursing home: characteristics, functioning, and gender differences'. We heard how her quantitative research findings emphasise the highly variable and complex care needs of patients with HD, and the need for person-centred, flexible approaches to care and treatment. She was followed by **Manon van Kampen** (also of Atlant) on the topic 'Passivities of Daily Living'. Van Kampen explained how this multidisciplinary approach focuses on stabilisation and dealing with disabilities from which recovery is not possible, with increased attention directed towards the needs of the patient. A case study has provided preliminary positive results for the approach and a further study is in progress looking at the impact in late-stage HD.

The parallel session on neuro-development was chaired by Silvia Gines of the University of Barcelona and Sandrine Humbert. Opening with 'Huntington's Disease Alters Cortical Development in Mice and Humans' was **Monia Barnat** of the Université Grenoble Alpes, France. We heard now HD may affect neurodevelopment and that this has recently been corroborated in humans. She presented data from her laboratory using different mice models that support this view by demonstrating the consequences of HTT mutation/deletion on cortical development, and noted the convergence of these findings with recent human studies. **Ferdinando Squitieri** of IRCCS Casa Sollievo della Sofferenza and Istituto CSS Mendel, Italy, continued on this theme with his presentation 'Pediatric Onset Huntington Disease: Neuro Developmental delay or Early Neurodegeneration?'. Reminding us of the links between neurodegeneration and neurodevelopment, Squitieri shared data supporting his assertion that HD in children, juveniles/young adults and finally adults/late-onset HD importantly differ in terms of impact on the brain as well as expected disease length. The final presentation, 'Specific Developmental Alterations of Striatal Subpopulations in Huntington's Disease', was by **Josep M. Canals** of the University of Barcelona, Spain. He explained the approach in his laboratory of characterising the molecular alterations that occur at embryonic stages and changes in the homeostasis of neuronal progenitor cells during the development of medium spiny neurons. His studies in mice have confirmed specific changes occurring during the embryonic period of development in HD.

The last session of the day was a series of short communications chaired by Ahmad Aziz of the German Center for Neurodegenerative Diseases and Bonn University Hospital, Germany, and Maria Björkqvist of Lund University, Sweden.

First to speak was **Christelle Langley** of the University of Cambridge, UK, with her presentation 'Fronto-Striatal Circuits for Cognitive Flexibility in Far From Onset Huntington's Disease: Evidence from the Young Adult Study'. Cognitive flexibility is vital for adaptive decision making, and Langley noted that performance on measures of cognitive flexibility is particularly sensitive to disruption of the fronto-striatal circuits. Her data with premanifest HD patients and controls confirmed specific impairments in cognitive flexibility in HD, accompanied by an alternative fronto-striatal circuit

associated with attentional set-shifting compared to controls, potentially representing functional reorganisation.

Chiara Casella of Cardiff University, UK, then presented 'Mutation-Related Apparent Myelin, not Axon Density, Drives White Matter Pathology in Premanifest Huntington's Disease: Evidence from In Vivo Ultra-Strong Gradient MRI'. In a comparison of HD patients and controls, she used tractometry to assess tract-specific changes across the callosum, and found significant alterations in callosal apparent myelin. Noting that alterations follow a topologically specific pattern of degeneration, she speculated that the HD mutation leads to excessive myelin production early in disease progression, and this leads to the detrimental effects observed.

Also from Cardiff University was **Duncan McLauchlan** with 'A Different Depression: Antidepressant Efficacy and Cognitive Mechanisms of Mood Disorder in Huntington's Disease'. Depression is common in HD and has major effects on quality of life. In his first study, propensity scoring in the Enroll-HD dataset was used to determine the efficacy of antidepressant classes for depression in HD. Findings showed that SSRIs and NDRI classes outperformed other agents, indicating that antidepressant efficacy differs in HD compared with the general population. In his second study, neuropsychological assessments were used to determine the cognitive mechanisms contributing to depression in HD. Here, he found that motivational anhedonia is the core process underlying depression in HD, and as such, drugs acting to improve this outcome outperform other drug classes.

Anne Rosser of Cardiff University presented 'Clinical Translation of Stem Cell Therapies for Huntington's Disease'. Cell therapy in HD aims to restore structure and function and the value of using donor cells from the foetal striatum is clear. However, human foetal cells are scarce and difficult to work with, meaning that well-powered human studies are unlikely to be possible. Stem cell-derived products, however, show promise, despite the significant clinical translation challenges. Stem Cells for Huntington's Disease and the EHDN Advanced Therapies Working Group were established to create global platforms to combine expertise in addressing these challenges. Their recent work has culminated in a position paper on translating cell therapies for neurodegenerative diseases using HD as a model disorder. She explained that the next steps include creating tasks forces to work on the areas identified in the position paper.

'Triheptanoin is Associated with Clinical Stability and Decreased Caudate Atrophy in HD' was the presentation by **Fanny Mochel** of the Paris Brain Insitute in France. After noting the importance of brain energy deficiency in HD, Mochel explained that triheptanoin is an anaplerotic drug that improves brain energy in HD patients after one month of treatment. She then presented the TRIHEP3 study in early HD patients, which was a larger and longer study of triheptanoin compared to placebo. Findings showed stabilisation at 1 year compared to the assessments at baseline and 6 months in the Unified Huntington's Disease Rating Scale score, as well as improvements relative to placebo. Further analyses showed a decrease in caudate atrophy with treatment. Based on these encouraging data, plans are now underway for a potential Phase 3 study.

The meeting was concluded for the day with a round-up and reflective discussion by Anne Rosser, Jean-Marc Burgunder, Ahmad Aziz and Dina de Sousa.

Saturday 11 September

The final day of the virtual meeting opened with another series of short communications, this time chaired by Kathrin Reetz of RWTH Aachen University in Germany and Jean-Marc Burgunder.

Joseph Hamilton of University College London, UK was first to present with 'FAN1 Controls CAG Repeat Expansion in Huntington's Disease by Dual Functions, MLH1 Retention and Nuclease Activity'.

The importance of the somatic expansion of CAG repeats in HD is well established, and although the endonuclease FAN1 has been found to inhibit this process, how this is achieved has been unclear. Hamilton presented a series of findings illustrating the identification of the mechanistic dual function of FAN1 in CAG repeat stabilisation, and proposed that promotion of specific FAN1 interactions may modify the age of onset in HD and/or the progression of the disease.

Next to speak was **Rafael Alcalá-Vida** of the Centre National de la Recherche Scientifique and Université de Strasbourg in France on 'Striatal Procedural Memory-Induced Transcriptome and Epigenome are Severely Impaired in Huntington's Disease Mice'. The focus of Alcalá-Vida research is transcriptional dysregulation and chromatin alterations and their consequences. Using a mouse model of HD, he has assessed striatal procedural memory across a series of studies. We heard how this work using the Double-H Maze as a paradigm of learning and memory is elucidating the critical role of epigenetic alterations in the cognitive symptoms of HD.

'A New In Vivo and In Vitro Single-Cell Atlas of Developing Medium Spiny Neurons to Guide Future Improvements for Huntington Disease Cell-Replacement Therapies and Disease Modelling' by **Vittoria Bocchi** of the University of Milan and Istituto Nazionale di Genetica Molecolare in Italy was the next presentation. In this work, the human foetal striatum single-cell atlas was used as a reference resulting in numerous findings. Most critically, however, this work in vivo and in vitro single-cell datasets will hopefully act as benchmarks to quantify and refine current stem cell engineering protocols, allowing an improved understanding of HD pathophysiology and an acceleration of the development of therapies.

Alice Migazzi of the University of Trento in Italy was next to present with 'Huntingtin-Mediated Axonal Transport Requires Arginine Methylation by PRMT6'. Neuronal function depends heavily on the ability to transport various molecules along axons, and Migazzi's research has sought to elucidate precisely how HTT mediates axonal transport and why this is disrupted in HD. Presenting a series of findings from in vitro and in vivo studies, Migazzi explained the newly discovered role of the arginine methyltransferase PRMT6 in recovering axonal transport defects and promoting neuronal health.

Lucienne van der Meer of Leiden University Medical Center in the Netherlands took a different perspective in the final presentation, "The 'Hold me Tight' Relationship Program for Couples Facing Huntington's Disease". Noting the impact of HD on families and relationships, van der Meer is investigating how best couples can be helped when facing HD, given the lack of evidence-based interventions in this area. The 'Hold Me Tight' programme is an 8-session intervention that is based on the psychological attachment theory of human relationships, adapted for the HD population. She reported that the programme has been well-received by couples, improved relationship satisfaction and enhanced psychological well-being. She concluded that the intervention may be a useful adjunct in standard care.

Two parallel sessions were next to take place. 'Digital Technologies to Advance Assessment and Care in HD' was chaired by Alzbeta Mühlbäck of the University of Ulm, Germany, and Monica Busse of Cardiff University, UK. **Ralf Reilmann** opened by presenting on the IDEA-FAST consortium, and explained the scientific rationale for the use of quantitative measures in the clinical development process, and then more specifically, the use of the Q-Motor measure to reduce variability and bias in assessment. He then explained the steps being taken towards the use of home-based assessments, such as wearable sensor devices in the OPEN-PRIDE study. The main goal of IDEA-FAST is to identify devices that allow the assessment of fatigue and sleep using a defined selection process and criteria. He concluded that quantitative measures have a high potential for application in clinical research, bringing with them greater sensitivity than clinical scales. Next to speak was **Pearl van Lonkhuizen** of Leiden University Medical Center in the Netherlands, on the development of the European eHealth

Platform for HD patients and their families. Quoting the belief that the knowledge rather than the patient should travel, she explained that the first phase of this work explored the needs and wishes of users of the platform. This formed the basis for the second phase focused on developing and evaluating concepts for the platform. The final concept was described as a 'trusted safety net' for people that encounter HD. The researchers are now working on specifying the platform design and content, and will evaluate this with patients and partners before starting the third phase of the project in which the prototype will be detailed and evaluated. Finally, **Philippa Morgan-Jones** of Cardiff University, UK, provided an overview of the use of Fitbit activity trackers in the European-wide consortium DOMINO-HD, a longitudinal observational study of multi-domain lifestyle and genetic factors in HD. One challenge was accessing Fitbit data, which Morgan-Jones explained was overcome through the development of a bespoke platform and identification of the metrics of interest. She then noted that there are several important considerations involved when using wearable activity trackers in research. These include the issue of whether participant feedback is needed, whether the device is validated, and decisions about what is going to be done with the data once it is collected. As such, we should be aware that embedding activity trackers into clinical studies is a complex process. The speakers and two chairs then reconvened for a stimulating panel discussion on the ethical and practical challenges of using digital technologies in clinical assessment and care.

The second parallel session was on 'Sleep, Circadian Rhythm and Metabolism in HD', chaired by Patrick Weydt and Asa Petersen. The session was opened by **Roger Barker** of the University of Cambridge, UK, on 'Sleep and Metabolism in Huntington Disease'. He explained that anecdotal reports from patients of disturbed sleep-wake activity, and the observed patterns of weight loss had led him to consider these issues in more detail. While his research has not yet provided an account for weight loss, he presented data on sleep problems in premanifest HD, including detailed studies of EEG activity during sleep showing very abnormal activity across many measures. Thus, importantly, sleep presents one of the early abnormalities in HD, and furthermore, these problems coincide with some of the earliest cognitive deficits. Barker concluded with the proposal that problems with sleep may be part of a bigger circadian rhythm problem in HD, which led us on to the presentation by **Charalambos P. Kyriacou** titled 'Clock Genes and Circadian Rhythms'. Kyriacou recapped on the action of clock genes identified in flies and then proceeded to present a series of studies on the molecular clock while explaining their relevance to HD. On the basis of this work, Kyriacou pointed to the utility of the fly as a useful model for sleep/circadian studies in HD, and noted the potential therapeutic avenues arising from such work, not least the promotion of basic sleep hygiene in patients. In summarising his perspectives and wide-ranging findings, Kyriacou concluded by proposing a new model accounting for the potential interactions between sleep, sleep need, the circadian clock and autophagy in HD. The last presentation in this session returned to the issue of metabolism with 'Targeting Cholesterol Metabolism as a Therapy for Huntington Disease' by **Sandrine Betuing** of Sorbonne Université/Institut de Biologie Paris Seine/Neuroscience Paris Seine, France. Cholesterol plays an important role in the central nervous system but in HD, brain cholesterol homeostasis is dysregulated. Betuing is particularly interested in the enzyme CYP46A1 and presented work demonstrating that restoring CYP46A1 activity in the striatum to regulate cholesterol homeostasis has beneficial effects on HD phenotypes in mouse models of the disease. She concluded by presenting a theoretical model of cholesterol metabolism incorporating a discussion of CYP46A1 as a potential therapy in HD. The session was concluded by the chairs with a summary of the key findings arising from the presentions with a specific focus on practical tips to overcome issues such as sleep difficulties in HD.

Plenary Session IV: Upcoming Clinical Trials took a closer look at ongoing and future clinical research and was chaired by Jean-Marc Burgunder and Bernhard Landwehrmeyer.

First to speak was **Catherine Scart-Grès** of SOM Biotech, Spain. Developed in the 1980s, SOM355 is commercialised by Nippon Chemiphar for the treatment of hypertension and has been shown to be safe and well tolerated over more than 30 years of use. SOM Biotech has now identified it to be a potential vesicular monoamine transporter type 2 (VMAT2) inhibitor, supported by their in vitro studies showing inhibitory activity at VMAT2 and in vivo studies showing adequate brain penetration without adverse effects. We heard how a proof of concept study in HD has demonstrated improvement on chorea symptoms with active treatment compared to placebo. C. Scart-Grès explained that the next trial will be an international multicentric double-blind randomised Phase 2b study to assess the efficacy of SOM355 in reducing chorea in two parallel doses compared to placebo, followed by an open-label extension. Currently, site selection is ongoing and the study is due to start by the end of 2021.

Beth Borowsky then presented on behalf of Novartis Pharmaceuticals, Switzerland, on the investigational oral HTT-lowering therapy branaplam. Noting that HTT-lowering therapies are among the most promising in HD, Borowsky added that branaplam will be the first to be given orally to patients. Mechanistically, branaplam decreases expression of HTT mRNA and HTT protein as confirmed in a Phase 1 study. The protocol for a Phase 2b study in early manifest HD patients has now been finalised, with the goal to identify a safe and well-tolerated dose of branaplam that lowers mutant HTT sufficiently to achieve a clinical benefit. Part 1 will be a staggered, dose-finding study and then Part 2 will be an open-label extension of the selected dose. It is planned that 11 countries will participate, and the First Patient First Visit is expected at the end of 2021. Given the advantages of oral administration of HTT-lowering therapies, this is an exciting move forward.

G. Bernhard Landwehrmeyer of Ulm University, Germany, provided an overview of current gene therapeutic efforts. Starting with the 'promise of fixing the root cause of monogenetic disorders', he noted that current in vivo approaches differ in several important respects before summarising the specific development programmes of uniQuare, Spark Therapeutics, Takeda Pharmaceutical Company Ltd and Voyager. Landwehrmeyer then considered the challenges facing gene therapy in HD. In particular, he pointed to the recent FDA focus on the toxicity risks and the further concern that lies with delivery – for example, can the entire human brain be covered? Research is emerging to suggest this will eventually be possible. Looking further to the future, Landwehrmeyer emphasised the utility of capsid engineering to allow precise in vivo targeting of vectors (carriers) in gene therapy.

An update from PTC Therapeutics, Inc., was provided by **Brian Pfister**. PTC is applying splicing technology to treat HD by targeting its root genetic cause. He explained the objective of developing a disease-modifying HTT-lowering small molecule that is orally bioavailable and penetrates the blood-brain barrier, to treat HD as a whole. Turning our attention to the example of the molecule PTC518, he noted that years of research and development have contributed to the achievement of key milestones to date. The Phase 1 study of PTC518 in healthy volunteers consisting of single dose, multiple ascending dose, food effect and cerebrospinal fluid sampling components is currently ongoing. However, the single and ascending dose studies have already confirmed the proof of mechanism through dose-dependent HTT splicing. In summarising the work to date, Pfister reminded us that it meets all the criteria for robust and equitable HTT lowering in vivo. As such, PPTC518 will make the exciting move from Phase 1 to Phase 2 evaluation across multiple countries and centres later in 2021.

Next to speak was EHDN's **Olivia Handley** with an update on the Enroll-HD platform studies. She opened by recapping the platform aims, namely, to enhance the design and expedite the conduct of clinical trials, to improve our understanding of the phenotypic spectrum and disease mechanisms of HD in humans, and to foster good clinical care and improve health outcomes. At the core of the platform is the global, observational, longitudinal study of HD. This is a family study, recruiting gene

positive, gene not known, gene negative individuals, as well as companions/caregivers and community controls. Since 2012, 21 countries have signed up and 26,161 participants have been recruited. Handley continued to note that Enroll-HD releases periodic datasets as well as biosamples, providing an invaluable research resource for the research community. Currently, the Enroll-HD platform is supporting studies looking at brain imaging, health economics, and outcome measures, to cite just a few examples of the input into advancing knowledge of HD.

HDClarity is one of the studies supported by the Enroll-HD platform and was the focus of the presentation that followed by **Ed Wild** of University College London, UK. HDClarity is the largest ever, multi-site, observational cerebral spinal fluid collection initiative, and has been running for four years. Samples can be requested by researchers for further research and analysis and to date, over 600 samples have been collected from more than 500 participants in HDClarity. Globally, there are seven participating nations and 25 clinical sites worldwide. The Enroll-HD Scientific Review Committee decides upon the distribution of samples and data, and 15 requests have been approved to date. These projects have been designed to identify new biomarkers or to research further already identified HD biomarkers. Wild noted that recruitment and collection managed to progress despite the challenges of the pandemic, and the recruitment target has now increased from 1,200 to 2,500 participants as the momentum in HDClarity continues to gather strength.

This session was wrapped up with a panel discussion including the chairs and speakers to address questions arising from the stimulating presentations.

Giorgos Papantoniou (Chair of the Huntington's Disease Association of Cyprus and Board Member of the EU HD Association) and Dina De Sousa chaired the final session of the meeting, which opened with the keynote address by **Cristina Sampaio**, Chief Medical officer at the CHDI Management/CHDI Foundation, USA. Sampaio's presentation 'New Staging System in HD: Extending the Window of Testing and Treatment' provided an important introduction to the HD-ISS – the integrated staging system in HD. As explained by Sampaio, in all clinical research and epidemiology, we need to be able to identify the cases of interest using specific, standardised criteria and be able to define stages of disease. She noted further that precise and accurate classification systems confer many benefits, including the improvement of internal and external validity of research, facilitating communication and contributing to the development of harmonised policies. A need in the HD scientific community was identified for a 'standardised definition of HD that allows for a case definition comprising the totality of the temporal course of disease, i.e., from birth to death'. This led to the establishment of the HD-RSC Regulatory Science Forum Working Group (RSF), which comprises researchers, clinician-scientists and representatives from pharmaceutical and biotech companies. In working to propose an HD research framework that addresses the entire disease continuum, their approach has been one of formal consensus and the use of systematic methodologies for evidence gathering and analysis. A critical outcome of this is the biological research definition of HD, namely, the presence of a CAG expansion in exon 1 of the HTT gene of $\geq$40 CAG or $\geq$36 CAG and the presence of disease-specific biomarker or syndrome. The temporal sequence of HD progression was also defined, from Stage 0 (HD), Stage 1 (biomarkers of pathogenesis), Stage 2 (clinical signs or symptoms) and Stage 3 (functional change). Sampaio noted that although there are different pathways and trajectories within HD, individuals will follow the same temporal stages. Turning then to assessments, Sampaio described the rigorous process of identifying and validating assessments that could be used as landmarks to define entry into these disease stages. Undoubtedly, the future developments and implications of the HD-ISS are considerable, and Sampaio justifiably reminded us of the value this evidence-based staging system will have on advancing therapeutic development and paving the way for trials and treatments earlier in the progression of HD.

As the meeting drew to a close, it was fitting at this point that **Tom Bird** of the University of Washington presented a historical account of his five decades of work in the HD field and

autobiography, 'Can you Help Me?'. He recounted his early-career interactions in his career with an inmate at Walla Walla Penitentiary who had HD, noting the frequency with which HD patients come to the attention of the legal and mental health care system. He noted that lack of judgement and impulsivity, for example, are features of the disease that may increase the risk of not only criminal behaviour in HD but also the risk of harm from others. Bird noted the difficulties for health care systems in caring for individuals, who many years ago, would have been institutionalised. He then turned to the issues surrounding embarrassment, injury (such as through falls) and neglect that affect individuals with HD. He provided the tragic example of a patient who had been neglected and abused in a care home and subsequently died, emphasising the vulnerability of patients without adequate care and support networks. Bird's next anecdote was an account of a girl who developed juvenile HD symptoms aged just ~6 years old, and we heard of the touching and important efforts her elementary school teacher and classmates made in supporting her. Bird then discussed his fascination with similarities between HD and other diseases, such as dementia and bipolar disorder. In summing up, Bird reflected on his experiences with patients and their families, adding how impressed he has been by their compassion, determination and 'gaman', the impressive ability to endure the seemingly unbearable with patience and dignity.

At the close of the virtual meeting, Anne Rosser extended her thanks to all those who had worked endlessly hard to make the conference such a success, the speakers and chairs who had driven the extremely high standard of presentation and discussion, and the meeting sponsors.

EHDN Business Meeting: Update by Anne Rosser

Rosser noted that the EHDN has remained highly active in most areas despite the COVID-19 pandemic, with the Executive Committee (EC) and the Scientific and Bioethics Advisory Committee (SBAC) continuing to meet regularly by Zoom. The main updates and highlights are summarised below.

Endorsement of clinical studies: Since the last plenary meeting, seven major clinical studies have been endorsed and a number of study protocols have been reviewed.

Seed Funds, data mining and sample use: Over the last two years, the SBAC and EC have granted access to ten legacy registry data and samples requests and 16 Seed Funds have been awarded in response to the twice-yearly application rounds for funding.

Working groups (WGs) and task forces (TFs): The majority of WGs and TFs have managed to remain active through Zoom networking with face-to-face meetings largely suspended. Rosser noted that these groups are a testament to the commitment and the generosity of the EHDN membership and that this work is recognised and very much appreciated. The publications by these groups provide one marker of their output.

Think Tank (TT): Key activities of the TT include liaising with WG and TF lead facilitators to help identify potential collaborations and funding opportunities, as well as hold discussions on scientific ideas. The TT also provides a forum for discussion with internal groups such as the Communications Group, as well as internal and external collaborators in identifying important questions for HD research.

Clinical Trial Site Certification Scheme: Managed by the Enroll-HD Clinical Trial Committee, this scheme supports the recording of key information about sites relating to personnel, facilities and

trial populations which can be made available to sponsors preparing to run clinical trials. There are 162 applications in progress, 131 of which are certified.

Constitution amendments and voting outcomes: A summary of changes to the Constitution was presented. Most of these changes were proposed to better align the constitution with current practices or to make semantic edits to improve clarity. Prompted by the COVID-19 pandemic, the provision to extend the terms of the EC due to unseen circumstances was highlighted, and also the proposed increased flexibility in the appointment of individuals to other EHDN committees. At the close of voting, an overwhelming majority of 91.5% of voters agreed with the proposed changes, 6.8% disagreed and 1.7% abstained.

Communication policy: The new EHDN Science Writer, Catherine Deeprose, was introduced and it was noted that the Communications Group is working on a new communication policy as well as conducting surveys with EHDN website users and newsletter readers.

MDS-ES and EHDN Join Online Course Series: Details were provided on this free online course to be run in October 2021 on foundational principles, assessment and management of HD. Course Directors are Michael Orth of Bern University, Switzerland, and EDHN Science Director, and Christos Ganos of the Charité – Universitätsmedizin Berlin and member of the MDS-ES Education Committee.

EHDN 2022 Plenary Meeting in Bologna: It is hoped that the next EHDN Plenary Meeting will be held face-to-face in September 2022. The Programme Committee will be jointly chaired by Patrick Weydt (University Hospital Bonn, Germany, and EHDN EC) and Åsa Petersén (Lund University, Sweden). Elections for the EC will be held and new SBAC members will be appointed at this meeting.