## Short summaries for the posters with presenting author(s):

## Pathogenic mechanisms: A01 – A21

A01

INVESTIGATING THE EFFECT OF DNA MAINTENANCE GENES IN DROSOPHILA MELANOGASTER MODELS OF HUNTINGTON'S DISEASE

*Freja Sadler, UK Dementia Research Institute, Cardiff University*

Pan-neuronal expression of pathological human HTT decreases lifespan and yields a locomotor phenotype in Drosophila models of HD. We showed that knock down of the expression of DNA maintenance genes has an effect on these phenotypes.

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A02

STRIATAL PROCEDURAL MEMORY-INDUCED TRANSCRIPTOME AND EPIGENOME ARE SEVERELY IMPAIRED IN HUNTINGTON'S DISEASE MICE

*Rafael Alcalá-Vida, Laboratoire de Neurosciences Cognitives et Adaptatives (LNCA), University of Strasbourg; CNRS UMR 7364; Strasbourg 67000, France*

We have studied the role of transcriptional and epigenetic alterations in HD striatal-dependent cognitive deficits. Our striatal RNA-seq and ChIP-seq data show strong alterations in R6/1 mice in basal and behaving conditions, and suggest a role for H3K9ac in HD cognitive deficits.

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A03

PRECISE MACHINE-LEARNING SUGGESTS THAT NEURONAL DEATH IN HD IS MAINLY DRIVEN BY THE LOSS OF HOMEOSTATIC RESPONSES

*Lucile Mégret, Sorbonne Université - Institut de Biologie Paris Seine*

Lucile Mégret is assistant professor in the Brain-C lab, a multidisciplinary team that develops precise machine-learning methods to extract biologically precise information from complex HD datasets and to exploit this knowledge for therapeutic purposes.

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A04

CIRCHTT, A CIRCULAR RNA FROM THE HUNTINGTON'S DISEASE GENE LOCUS: FUNCTIONAL CHARACTERIZATION AND POSSIBLE IMPLICATIONS FOR DISEASE MODULATION

*Jessica Döring, CIBIO, University of Trento*

We identified a circular RNA stemming from the HTT locus that is expressed in a CAG repeat dependent manner. It may modulate wt and mut huntingtin translation without affecting the transcription. Our work unveils a new piece of HD biology and identifies a tool to modulate huntingtin expression.

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A05

EFFECT OF SMALL MOLECULE INHIBITORS ON THE AGGREGATION MECHANISM OF MUTANT HUNTINGTIN EXON1

*Greeshama Jain, University of Groningen*

To study the stability and toxicity of the Huntingtin aggregates, we need to examine these disordered deposits at the atomic level. So, we will test to modulate the atomic structure and neurotoxic properties of these Huntingtin Exon1 aggregates by perturbing the aggregation process using small molecule inhibitors.

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A06

TUNING THE STRESS RESPONSE PATHWAY TO RESPOND TO POLYQ AGGREGATION

*Courtney Klaips, UMCG*

Here we describe the identification of factors that enable cells to efficiently sense and respond to pathogenic protein aggregates, such as mutant Huntingtin, via endogenous cellular stress response pathways.

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A07

HUNTINGTIN-DEPENDENT STABILITY OF HAP40 AND DECREASED HAP40 LEVELS IN HUNTINGTON'S DISEASE

*Manuel Seefelder, University Hospital Ulm*

HAP40 interacts abundantly and tightly with HTT. Earlier, we demonstrated evolutionary conservation of their interaction and potential coevolution of HAP40 and HTT. Here, we show the dependency of HAP40 protein levels and stability on HTT levels and reduced HAP40 levels in HD patients and mice.

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A08

SYNAPTIC VESICLE RECYCLING IS DISRUPTED IN A MOUSE MODEL OF HUNTINGTON'S DISEASE

*Karen Smillie, University of Edinburgh*

Presynaptic dysfunction in Huntington's disease may render neurons susceptible to neurodegeneration. This study, therefore investigates presynaptic dysfunction in a mouse model of HD with the aim to better understand the aberrant processes which contribute to synaptic frailty.

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A09

ADAM10 ACTIVITY AT THE HUNTINGTON'S DISEASE PRESYNAPSE

*Chiara Zuccato, University of Milan and Istituto Nazionale di Genetica Molecolare "Romeo ed Enrica Invernizzi"*

Here we present ADAM10 and Piccolo as molecular targets of HTT at the HD presynaptic terminal.

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A10

NAPDH OXIDASES (NOXS) EXOCYTOSIS AND ITS RELEVANCE IN HUNTINGTON'S DISEASE (HD) PATHOLOGY

*Luisana Villegas, University of Copenhagen*

Possible role of NADPH oxidases in the pathogenesis of Huntington's Disease (HD).

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A11

HUNTINGTIN-MEDIATED AXONAL TRANSPORT REQUIRES ARGININE METHYLATION BY PRMT6

*Alice Migazzi, University of Trento*

Migazzi et al. identified arginine methylation as a new post-translational modification in huntingtin (HTT) that modulates its function in axonal transport. In HD models, enhancement of HTT methylation by the arginine methyltransferase PRMT6 rescues axonal transport defects and neuronal health.

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A12

IDENTIFICATION OF THE KEY ROLE OF WHITE MATTER IN THE PATHOGENESIS OF HUNTINGTON'S DISEASE

*Jean-Baptiste Pérot, MIRCen, CEA*

We present a longitudinal MRI study on a mouse model of Huntington's Disease (HD) to measure new biomarkers of its presymptomatic phase. We show altered diffusion and glutamate concentration in the anterior corpus callosum. Our results highlight a vulnerability of the cortico-striatal tracts.

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A13

ABNORMAL SPINAL CORD MYELINATION DUE TO OLIGODENDROCYTE DYSFUNCTION IN A MODEL OF HUNTINGTON DISEASE

*Costanza Ferrari Bardile, University of British Columbia*

The pathology of the spinal cord in Huntington disease (HD) is poorly documented. In particular, it still remains unclear whether the white matter area of the spinal cord is affected. Here we investigate spinal cord pathology in a mouse model of HD and in particular WM and myelination abnormalities.

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A14

RETINAL AND STRIATAL PROFILING OF THE R6/1 MOUSE MODEL OF HUNTINGTON'S DISEASE

*Luis M. Valor, Instituto de Investigación Sanitaria y Biomédica de Alicante (ISABIAL)*

Retina can be useful to monitor the health status of the central nervous system in HD patients using non-invasive techniques. We need to understand first how the molecular alterations linked to the disease correlate between the retina and the most affected brain area, the striatum. To this aim, we examined the popular R6/1 mouse model.

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A15

HYPOTHALAMIC EXPRESSION OF HUNTINGTIN CAUSES DISTINCT METABOLIC CHANGES IN THE R6/2 AND BACHD MOUSE MODELS OF HUNTINGTON'S DISEASE

*Elna Dickson, Lund University*

We have utilized viral-vector based overexpression of huntingtin in hypothalamus in order to study effects on metabolic phenotype and disease features in R6/2 and BACHD mouse models that respectively develop lean- and obese phenotypes.

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A16

UNDERSTANDING THE ASSOCIATION BETWEEN MITOCHONDRIAL DNA COPY NUMBER AND TELOMERE LENGTH IN HUNTINGTON'S DISEASE PATIENTS.

*Sowmya venkatesh, NIMHANS*

We are trying to understand that mitochondrial function and telomere length are known to be compromised in HD by studying the relative mitochondrial DNA copy number and relative telomere length in HD patients compared to controls.

We observed a significant reduction in relative telomere length in HD patients compared to controls. Relative mitochondrial DNA copy number was not significantly different between the groups. Relative mitochondrial DNA copy number showed a significant positive association with relative telomere length in controls but in HD patients.

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A17

TARGETING MITOPHAGY IN HUNTINGTON'S DISEASE PATIENTS' FIBROBLASTS

*Ivan Šonský, Charles University in Prague, Prague, Czech Republic*

Accumulation of dysfunctional mitochondria in neurons is one of hallmarks of Huntington's disease. Moreover, the process responsible for maintaining healthy mitochondrial turnover, mitophagy, is impaired as well. Therefore, we target mitophagy as a possible therapeutic target using a small molecule compound and study its effect in HD firoblasts.

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A18

CAN CUMULATION OF NEURODEGENERATIVE DISORDERS SIGNIFICANTLY PROMOTE MITOCHONDRIAL DYSFUNCTION IN CULTURED SKIN FIBROBLASTS?

*Marie Vanisova, First Faculty of Medicine, Charles University in Prague, and General University Hospital in Prague*

Analysis of mitochondrial impairment level in fibroblasts from the patient with unique combination of late onset HD and fully evolved Multisystem atrophy (MSA) and Alzheimer´s disease (AD).

Results confirmed structural and functional changes of mitochondria were more propagated not only in comparison to controls but also in comparison to 10 HD patients with classical course of HD

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A19

HIGH-RESOLUTION RESPIROMETRY AS A TOOL TO ASSESS SKELETAL MUSCLE MITOCHONDRIAL STATE IN PATIENTS WITH HUNTINGTON'S DISEASE

*Svetlana Kopishinskaia, Kirov Medical University*

This study demonstrates that high-resolution respirometry can be used as a promising tool to assess mitochondrial state in skeletal muscles from patients with Huntington's Disease (HD). Our results show alterations in coupled mitochondrial respiration of skeletal muscle observed in the premanifest stage of HD.

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A20

ASSESSMENT OF MUSCLE REGENERATION IN THE R6/2 MOUSE MODEL OF HUNTINGTON'S DISEASE

*Sanzana Hoque, Lund University*

Skeletal muscle atrophy is one of the hallmarks of Huntington's disease (HD), but it's precise mechanism is not well established yet. In this study I will discuss the muscle regeneration capacity in R6/2 mouse model of HD by using an acute injury model.

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A21

ASSESSMENT OF SATELLITE PROGENITOR CELL DIFFERENTIATION IN HD SKELETAL MUSCLE IN VITRO

*Sanzana Hoque, Lund University*

Abnormal calcium (Ca2+) signalling has been previously linked with Huntington's Disease (HD) neuropathology. In this study our aim is to establish a Ca2+ imaging protocol to assess intracellular Ca2+ dynamics in HD at the same time effect of ghrelin on Ca2+ homeostasis.

## Models for HD: B01 – B04

B01

IN VITRO STUDY OF NEURODEVELOPMENT IN HUNTINGTON'S DISEASE

*Phil Sanders, Laboratory of Stem Cells and Regenerative Medicine, University of Barcelona*

We study how neurodevelopment is affected in Huntington's disease using an in vitro striatal development model combined with transcriptomic analyses. We identified changes in the expression of striatal development genes whose modulation could revert the striatum to a healthy state.

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B02

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

*Vittoria Bocchi, University of Milan and Istituto Nazionale di Genetica Molecolare*

Use of single-cell transcriptomics to measure how well medium spiny projection neurons, derived from human pluripotent stem cells, recapitulate human striatal development in vivo.

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B03

NOVEL HD MOUSE MODELS ENABLING NEW PATHOGENIC MECHANISMS DISCOVERY

*Magdalena Wozna-Wysocka; PhD Agnieszka Fiszer, Institute of Bioorganic Chemistry, Polish Academy of Sciences*

We have generated two new unique mouse models of HD to distinguish between pathogenic roles of HTT transcript and protein. These models allow to study those mechanisms in cell- specific manner. These models have been fully characterized using vast spectrum of behavioral and molecular methods.

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B04

IDENTIFICATION OF THE NEURAL CORRELATES UNDERLYING CONFLICT RESOLUTION IN THE RODENT ANALOGUE OF THE STROOP TASK

*Mariah Lelos, Cardiff University*

The Stroop task is a commonly used task of attention and conflict resolution. Here, the goal was to identify the patterns of neural activation associated with performance on this task, using a rodent model. The results reveal, for the first time, recruitment of dorsomedial striatum during this task, suggesting that impairment may reflect early striatal changes in HD.

## Genetic modifiers: C01 – C07

C01

THE EFFECT OF MISMATCH REPAIR PROTEINS IN A HUNTINGTON'S DISEASE CELLULAR MODEL

*Joseph Stone, Cardiff University*

CRISPR Cas9 gene editing was used to knockout (KO) MLH1 and MSH3 in an induced pluripotent stem cell (iPSC) model of Huntington's disease. MLH1 KO ablates somatic expansion of the expanded HTT CAG repeat in iPSCs when cultured for 59 days.

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C02

FAN1 CONTROLS CAG REPEAT EXPANSION IN HUNTINGTON'S DISEASE BY DUAL FUNCTIONS, MLH1 RETENTION AND NUCLEASE ACTIVITY

*Joseph Hamilton, UCL Institute of Neurology*

FAN1, a DNA repair nuclease, suppresses somatic expansion of the CAG repeat in Huntington's disease, modifying pathogenesis. We show that this mechanism involves sequestration of MLH1 from the mismatch repair pathway and also requires functionality of FAN1's canonical nuclease domain.

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C03

FAN1 PREVENTS CRISPR-CAS9 NICKASE-INDUCED CONTRACTIONS OF CAG/CTG REPEATS

*Laura Heraty, UK Dementia Research Institute, Cardiff University*

We have developed a CRISPR-Cas9 nickase based approach to contract expanded CAG/CTG repeats. This study aimed to determine whether FAN1, a modifier of somatic instability, impacts nickase-induced contractions in HEK293-derived cell lines. In our system FAN1 prevents nickase-induced contractions without impacting expansion events.

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C04

PROTEIN CODING TANDEM REPEAT IN TCERG1 MODIFIES HUNTINGTON'S DISEASE ONSET

*Sergey Lobanov, Cardiff University*

The recent genome-wide association study has implicated a SNP in TCERG1 as a modifier of HD onset. However, the association could be due to other types of variation, such as short tandem repeats. We identified a short tandem repeat in TCERG1 that explains the association with age at onset of HD.

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C05

SAPAP3 SCAFFOLDING PROTEIN AS A REGULATOR OF MITOCHONDRIAL FUNCTION IN HUNTINGTON'S DISEASE

*Patrícia Coelho, CNC - Center for Neuroscience and Cell Biology*

SAPAP3 knockout (postsynaptic protein highly expressed in striatum) is associated with OCD. Preliminary data demonstrated several SAPAP3 mitochondrial interactors in striatum, decreased total, PSD and mitochondrial levels in HD models, suggesting involvement of SAPAP3 in HD pathogenesis. Therefore, here, we hypothesize that striatal dysfunction linked to early mitochondrial deregulation may involve changes in SAPAP3, and potentially contribute to HD-related psychiatric disturbances.

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C06

COMPARISON OF MODELS FOR ESTIMATING AGE AT MOTOR ONSET IN HD

*Peter Holmans, Cardiff University*

The Langbehn formula is commonly used to model the relationship between CAG length and age at motor onset (AMO), although it performs best for CAG between 40 and 55 repeats. We compared its performance to an alternative model proposed by Kaplan. The models had similar performance between 40 and 55 repeats, while the Kaplan model predicted AMO more accurately above 55 repeats. Neither model could predict AMO below 39 repeats

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C07

GENETIC RISK FOR PSYCHIATRIC DISORDERS IS ASSOCIATED WITH PSYCHIATRIC AND COGNITIVE HUNTINGTON'S DISEASE SYMPTOMS

*Branduff McAllister, Cardiff University*

We have previously shown the genetics of neuropsychiatric symptoms are associated with symptoms reported by HD patients. Here we analyse a wide range of motor, cognitive and psychiatric symptoms to identify those most closely associated with polygenic risk for neuropsychiatric disorders.

## Wet biomarkers: D01 – D04

D01

TWO INDEPENDENT VALIDATIONS OF A MUTANT HUNTINGTIN PROTEIN (MHTT) ASSAY TO SUPPORT THE CLINICAL DEVELOPMENT OF MHTT-TARGETING THERAPIES IN HD

*David Hawellek, Biomarker and Translational Technology Group, Roche Pharma Research and Early Development (pRED), F. Hoffmann-La Roche Ltd*

This abstract describes the validation of a bioanalytical method for quantifying relative human CSF mHTT in two independent laboratories, per international guidelines. Quantifying mHTT using a valid, replicable and transferable method supports the clinical development of mHTT-targeting therapies.

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D02

CEREBROSPINAL FLUID AMYLOID BETA AND GLIAL FIBRILLARY ACIDIC PROTEIN CONCENTRATIONS IN HUNTINGTON'S DISEASE

*Sara Korpela, Västerås Central Hospital, Department of Medicine, Neurology*

Biomarkers are needed for assessment of disease progression in HD. We assessed the potential of Aβ42 and GFAP as CSF biomarkers in HD. CSF Aβ42 levels did not correlate with disease stage suggesting no Aβ aggregation in HD. GFAP is a potential biomarker in HD with association to disease stage.

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D03

CIRCULAR RNAS AS POTENTIAL BIOMARKERS IN HUNTINGTON'S DISEASE PATHOGENESIS

*Miguel Pellegrini, NeuroEpigenetics laboratory, Department of Cellular, Computational and Integrative Biology, University of Trento, Trento, Italy*

We characterized circular RNA molecules (circRNA) from blood samples of healthy individuals and Huntington's Disease (HD) patients. RNA sequencing analysis led to the identification of 35 circRNAs that correlate with disease. Among them, 7 circRNAs were revealed to have a CAG repeat size and disease progression-dependent expression. These circular RNA molecules could then function as predictive and prognostic biomarkers for the disease.

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D04

BLOOD GLUCOSE AND INSULIN LEVELS FOLLOWING AN ORAL GLUCOSE CHALLENGE ARE PROMISING BIOMARKERS IN THE ZQ175 KNOCK-IN MOUSE MODEL OF HUNTINGTON'S DISEASE

*An Tanghe, reMYND nv*

Huntington patients suffer from motor as well as non-motor symptoms, including metabolic alterations. When challenged with glucose in an oral glucose tolerance test, zQ175 knock-in mice show prolonged blood glucose levels and lower insulin secretion levels compared to controls. We discuss the potential of these metabolic parameters as surrogate endpoints for assessing the efficacy of Huntington therapies.

## Imaging: E01 – E09

E01

WIDESPREAD LOSS OF PRESYNAPTIC TERMINAL MARKER SV2A IN EARLY HUNTINGTON DISEASE

*Aline Delva, University Hospitals Leuven*

Synaptic damage is thought to play a major role in HD pathophysiology, but in vivo evidence in humans is lacking. In this PET imaging study presynaptic terminal damage and its clinical correlates were assessed in early HD in vivo. Extensive synaptic damage was found and synaptic disconnection may contribute to some of the core clinical symptoms of HD.

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E02

LONGITUDINAL HYBRID PET/MRI IN JUVENILE-ONSET HUNTINGTON DISEASE (JOHD)

*Maria Eugenia Caligiuri[1]; Patrizia Vizza[2], [1] Magna Graecia University of Catanzaro; [2] Mater Domini University Hospital*

Hybrid PET-MRI is an emerging technique that allows multimodal evaluation of brain structure and function. This study evaluates longitudinal PET-MRI in one patient with stage-2 joHD, to assess changes related to disease progression. This approach might be useful to test the efficacy of disease-modifying drugs.

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E03

UNCOVERING THE TEMPORAL SEQUENCE OF REGIONAL BRAIN VOLUME AND NEURAL CONNECTIVITY CHANGES IN HUNTINGTON'S DISEASE

*Alexandra Moura, University College London*

We applied the event-based model, a probabilistic machine learning tool, to cross-sectional magnetic resonance imaging data from both genotype-confirmed Huntington Disease (HD) patients and healthy controls to uncover the most likely temporal sequence of regional brain volume and neural connectivity changes occurring in the HD brain.

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E04

FRONTO-STRIATAL CIRCUITS FOR COGNITIVE FLEXIBILITY IN FAR FROM ONSET HUNTINGTON'S DISEASE: EVIDENCE FROM THE YOUNG ADULT STUDY.

*Christelle Langley, University of Cambridge*

This study examined cognitive flexibility in a far from onset premanifest HD cohort to determine whether an early impairment exists and if so, whether fronto-striatal circuits were associated with this deficit.

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E05

MUTATION-RELATED APPARENT MYELIN, NOT AXON DENSITY, DRIVES WHITE MATTER PATHOLOGY IN PREMANIFEST HUNTINGTON'S DISEASE: EVIDENCE FROM IN VIVO ULTRA-STRONG GRADIENT MRI

*Chiara Casella, King's College London*

I am using knowledge of the typically developing brain, in infancy and throughout childhood, to inform how the brain changes in response to atypical development, especially in the case of epilepsy. In addition, I also use advanced MRI techniques and develop MRI analysis approaches to try and quantify brain changes in response to neurological disease.

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E06

DRUMMING MOTOR SEQUENCE TRAINING INDUCES APPARENT MYELIN REMODELLING IN HUNTINGTON'S DISEASE: A LONGITUDINAL DIFFUSION MRI AND QUANTITATIVE MAGNETIZATION TRANSFER STUDY

*Chiara Casella, King's College London*

I am using knowledge of the typically developing brain, in infancy and throughout childhood, to inform how the brain changes in response to atypical development, especially in the case of epilepsy. In addition, I also use advanced MRI techniques and develop MRI analysis approaches to try and quantify brain changes in response to neurological disease.

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E07

ALTERED IRON AND MYELIN IN PREMANIFEST HUNTINGTON'S DISEASE MORE THAN 20 YEARS BEFORE CLINICAL ONSET: CROSS-SECTIONAL DATA FROM THE HD YOUNG ADULT STUDY

*Nicola Hobbs, UCL Institute of Neurology*

We applied a range of novel MR neuroimaging techniques to a premanifest cohort, approximately 24 years from predicted clinical onset, to characterise some of the earliest neurodegenerative features of premanifest HD, across the whole brain.

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E08

TRACKING THE NEURODEGENERATION PATTERN OF THE ANTERIOR THALAMIC RADIATIONS IN HD: A FOCUS ON BRAIN IRON, WHITE MATTER INTEGRITY AND METABOLITES

*Montserrat Domingo Ayllón, Hospital Universitari Joan XXIII de Tarragona - Institut de Diagnòstic per la Imatge*

The neurodegeneration pattern of the anterior thalamic radiations has uncovered a differential vulnerability between hemispheres, with a gradient from subcortical to deep white matter. Also, it has emphasized different pathogenic mechanisms taking place in HD: iron accumulation and excitotoxicity in premanifest stages and neuronal loss and mitochondrial dysfunction in manifest stages.


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E09

MAGNETIC RESONANCE IMAGING VISUAL ANALYSIS OF NEUROMELANIN AND NIGROSOME-1 FOR THE ASSESSMENT OF STRIATONIGRAL DISFUNCTION IN HUNTINGTON'S DISEASE

*Carla Guerreiro, Centro Hospitalar Lisboa Norte*

This was a retrospective cross-sectional study that aimed to characterize the involvement of the substantia nigra (SN) and the locus coeruleus (LC) in Huntington's Disease (HD) using visual analysis of two recent imaging biomarkers: neuromelanin sensitive MRI and Nigrosome-1, which, to the best of our knowledge, has never been done in previous studies.

Our results support the previous neuropathology findings of involvement of the SN and LC in HD and the possibility of a future clinical applicability of these visual analysis methods for the in vivo evaluation of nigrostriatal degeneration.

## Clinical studies: case reports, oberservational studies and trials: F01 – F54

F01

DEVELOPMENT OF THE HUNTINGTON'S DISEASE INTEGRATED STAGING SYSTEM (HD-ISS)

*Sarah Tabrizi, UCL*

The Huntington's Disease Integrated Staging System (HD-ISS) defines HD for research as the presence of an expanded HTT gene and uses data-driven landmark thresholds to classify individuals into Stages encompassing the full course of HD allowing for clinical trials earlier in disease progression.

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F02

MODELLING HUNTINGTON'S DISEASE PROGRESSION: INTERPRETATION, STAGING AND PROGNOSIS

*Peter Wijeratne, University College London*

We present recent developments in computational modelling of Huntington's disease progression. We demonstrate how disease progression models can be applied to both cross-sectional and longitudinal data to reveal disease insights and clinically useful information, such as patient stage and prognosis.

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F03

FINE-GRAINED PREDICTION OF HUNTINGTON'S DISEASE PROGRESSION USING A STACKED ENSEMBLE APPROACH

*Maitrei Kohli, University College London*

We developed a predictive-classification framework for individual-level prediction of Huntington's disease state using a Stacked ensemble approach. Our model achieved best predictive accuracy for fine-grained classification task & sets the ground for clinically useful future work.

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F04

LINEAR MIXED MODEL FOR THE AGE OF ONSET PREDICTION IN HUNTINGTON DISEASE FROM A PERUVIAN COHORT

*Diana Cubas-Montecino, Instituto Nacional de Ciencias Neurológicas, Lima, Peru*

The variability of the age of onset in Huntington's disease (HD) is not fully explained by a number of CAG repeats in the expanded allele of the HTT gene. We show that including pedigree information to model polygenic effects due to unknown genetic modifiers increases the accuracy of age-of-onset prediction models.

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F05

BIOLOGICAL AND CLINICAL CHARACTERISTICS OF GENE CARRIERS FAR FROM PREDICTED ONSET IN THE HD-YAS STUDY: A CROSS-SECTIONAL ANALYSIS

*Rachael Scahill, UCL Queen Square Institute of Neurology*

In our cohort of premanifest gene carriers ~24 years from expected symptom onset we found no evidence of cognitive or psychiatric impairment. They had smaller putamen volumes than matched controls but there were no differences in other imaging measures. Those closer to symptom onset showed elevated levels of NfL, suggestive of early neuronal damage.

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F06

'WHERE DO WE GO FROM HERE?': A META-SYNTHESIS OF QUALITATIVE LITERATURE EXAMINING THE LIVED EXPERIENCE OF HUNTINGTON'S DISEASE

*Richie Paul Carreon, Liverpool John Moores University*

The systematic method of identifying available literature in HD lived experience has been carried out as part of wider PhD study. By synthesising the sampled studies, this offered a better awareness of the HD lived experiences and identified literature gaps. The insights from the findings have been assimilated in the development of the study design.

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F07

DEMOGRAPHIC CHARACTERISTICS AND HEALTH RESOURCE USE OF THE EUROPEAN PARTICIPANTS FROM THE HUNTINGTON'S DISEASE BURDEN OF ILLNESS STUDY (HDBOI)

*Rosa Willock, HCD Economics*

This piece provides an overview of demographic characteristics and HD-related health resource use of European participants of the HDBOI study. Results presented illustrate differences in health resource use and patient characteristics by disease stage for European participants.

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F08

HUNTINGTON'S DISEASE BURDEN OF ILLNESS (HDBOI): STUDY METHODOLOGY, SAMPLE REPRESENTATIVENESS AND FIELDWORK RISK MITIGATION STRATEGY DURING THE COVID-19 PANDEMIC

*Idaira Rodríguez, HCD Economics*

The HDBOI is a multinational study aiming to quantify the economic and humanistic burden of HD patients by disease stage. Study methodology and attempts to mitigate the impact of COVID-19 on the fieldwork process are described in this piece. The HDBOI sample is representative of the HD population across disease stages and studied countries.

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F09

LATE ONSET HUNTINGTON'S DISEASE PHENOTYPE PROGRESSION. 2 YEARS FOLLOW-UP IN 220 PATIENTS FROM ENROLL-HD PDS4

*Paola Zinzi, Fondazione Policlinico Universitario Agostino Gemelli IRCCS*

This is a retrospective observational study on 220 European HD patients with tardive disease onset ≥ 60 years from Enroll-HD PDS4 with 2 consecutive annual follow-up visits.

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F10

DEVELOPMENT OF ASSESSMENTS FOR LATER STAGE HUNTINGTON'S DISEASE: HD STRUCTURED INTERVIEW OF FUNCTION AND HD CLINICAL STATUS QUESTIONNAIRE.

*Matthew Roché, CHDI Management/CHDI Foundation*

There is a need for validated assessments for patients with later-stage HD. The LSA study aims to provide preliminary clinimetric properties for two such measures: the HD Structured Interview of Function (HD-SIF) and HD Clinical Status Questionnaire (HDCSQ). Both assessments are administered to a Companion Participant either in-person or remotely.

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F11

IMPACT ON THE GRANDPARENTS-GRANDCHILDREN RELATIONSHIP IN HUNTINGTON'S DISEASE

*Laura Armas Junco, Universidad de Burgos*

This research about Huntington's disease (HD) has a double objective: (1) To understand the emotional process of having or being symptomatic of HD, and its effect on the relationship between grandparents and grandchildren (2) To explore the impact of HD on their relationship.

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F12

RESEARCH PARTICIPATION: THE VIEW OF PERSONS AT RISK AND PERSONS WITH PREMANIFEST HUNTINGTON'S DISEASE

*Filipa Júlio, European Huntington Association (EHA)*

The European Huntington Association (EHA) created a survey to determine which factors affect the willingness of persons at risk and with premanifest Huntington's disease (HD) to participate in research. The EHA found that motivation to take part in studies is high, despite limited research experience and literacy, and that it is strongly influenced by HD status.

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F13

SAFETY AND TOLERABILITY OF LUMBAR PUNCTURES (LP) PROCEDURE IN PATIENTS WITH HUNTINGTON'S DISEASE

*Yara Hassan, University College London*

The lumbar puncture (LP) procedure is becoming increasingly popular among patients with Huntington's disease.

Analyzing the safety profile and the tolerability of LP in this specific population will be helpful for the scientists to guide future procedure protocol as well as for providing the patients with thorough information about the procedure.

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F14

COLLABORATING WITH THE COMMUNITY TO CONDUCT CLINICAL TRIALS IN HUNTINGTON'S DISEASE: LESSONS FROM THE TOMINERSEN PHASE III GENERATION HD1 STUDY

*Victoria Liddy, F. Hoffmann-La Roche Ltd*

This abstract showcases how true collaboration between the HD community and Roche resulted in the successful and rapid site activation and recruitment of participants in GENERATION HD1 (NCT03761849), an ongoing Phase III trial of tominersen, across 18 countries.

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F15

VISUAL-COGNITIVE IMPAIRMENT IN ASYMPTOMATIC AND SYMPTOMATIC CARRIERS OF HUNTINGTON´S DISEASE (HD)

*Miriam Turuelo, BioCruces Bizkaia Health Research Institute*

The following abstract portrays the results of a study designed to evaluate the differences in visual cognition performance in HD patients. The main finding lies in the differences between healthy controls and patients in premanifest fases of the disease.

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F16

ETHNOGRAPHY AND SOCIAL COGNITION

*Alex Fisher, BSMHFT and University of Birmingham, UK*

Social cognition is explored in controlled settings. If this translates to concerns with the contextual social functioning of people with HD, there is little 'real life' exploration of this. These abstracts form a summary of an ethnography which is looking to address this. Alex is an Occupational Therapist in a UK HD service and part time PhD student

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F17

AN ETHNOGRAPHIC PROTOCOL FOR EXPLORING SOCIAL FUNCTION DURING A PANDEMIC

*Alex Fisher, BSMHFT and University of Birmingham, UK*

Social cognition is explored in controlled settings. If this translates to concerns with the contextual social functioning of people with HD, there is little 'real life' exploration of this. These abstracts form a summary of an ethnography which is looking to address this. Alex is an Occupational Therapist in a UK HD service and part time PhD student.

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F18

THE ETHICS OF EXPLORING SOCIAL COGNITION IN HD USING ETHNOGRAPHY DURING A PANDEMIC

*Alex Fisher, BSMHFT and University of Birmingham, UK*

Social cognition is explored in controlled settings. If this translates to concerns with the contextual social functioning of people with HD, there is little 'real life' exploration of this. These abstracts form a summary of an ethnography which is looking to address this. Alex is an Occupational Therapist in a UK HD service and part time PhD student.

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F19

COGNITIVE RESERVE: THE LEISURE TIME CONCURS TO THE COGNITION PERFORMANCE AND TO THE INDEPENDENCE OF EARLY HUNTINGTON DISEASE PATIENTS

*Simone Migliore; Eugenia Scaricamazza, IRCCS Casa Sollievo della Sofferenza/CSS-Mendel*

Huntington and Rare Disease Unit at IRCCS Casa Sollievo della Sofferenza/CSS-Mendel and LIRH Foundation take part in clinical therapeutic and oservational trials in Italy. Clinically, we are focused on juvenile onset/pediatric HD and on cognitive and behavioral changes in HD. Cognitive and behavioral changes are challenging in HD. Some of our research lines aim to study and truck cognitive and behavioral changes and their interference with independence, functional capacity and motor impairment in pre- and in manifest HD.

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F20

IS BURNOUT AN EARLY SIGN OF HUNTINGTON'S DISEASE AND MORE PREVALENT THAN IN THE GENERAL POPULATION?

*Kasper van der Zwaan, LUMC*

Burnout is often reported by HD patients. Our study aimed to determine the prevalence of burnout and to correlate it to HD-specific measures. Results showed that burn-out is not more prevalent in HD than in the general population and is related to depressive and anxiety symptoms.

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F21

ON THE ASSOCIATION BETWEEN APATHY AND DEFICITS OF SOCIAL COGNITION AND EXECUTIVE FUNCTIONS IN HUNTINGTON'S DISEASE

*Rebecca K. Hendel, Danish Dementia Research Centre, Rigshospitalet, Copenhagen University Hospital*

This study examined the association between apathy and executive and social cognitive dysfunction, as well as more general variables in Huntington's Disease gene expansion carriers. Apathy were significantly predicted by motor function and depression, but cognitive variables did not predict apathy.

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F22

NOVEL MEASURES OF APATHY IN HUNTINGTON'S DISEASE: CROSS-SECTIONAL AND LONGITUDINAL ANALYSIS

*Emily Hare, Cardiff University*

Apathy is a core symptom of Huntington's Disease (HD) and has been shown to worsen alongside disease progression. Novel tools, that measure apathy in HD, were analysed both cross-sectionally and longitudinally. Findings indicate that a new tool, called the Maze Task, may be sensitive to disease progression across a year.

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F23

IMPULSIVITY AND IRRITABILITY IN HUNTINGTON'S DISEASE: A COMMON FOUNDATION?

*Duncan McLauchlan, Cardiff University*

The links between irritable and impulsive behaviour in HD remain under-explored despite their impact on patients. In this study we recruited HD patients and controls who performed a battery of cognitive assessments measuring mechanisms contributing to irritable and impulsive behaviour in HD.

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F24

UNSUPERVISED CLUSTERING REVEALS LONGITUDINAL PSYCHIATRIC SIGNATURES IN HD

*Estela Camara, Cognition and Brain Plasticity Unit [Bellvitge Biomedical Research Institute – IDIBELL]*

The present study strives to discern longitudinal psychiatric signatures that may inform patterns of HD progression. By employing unsupervised clustering of weighted PBA-s scores using the Disease Trajectories analysis, we identify two psychiatric profiles defined by non-depressive and non-irritable temporal signatures, respectively.

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F25

THE CLINICAL, IMAGING AND BIOLOGICAL FEATURES OF PSYCHOSIS IN HAN CHINESE PATIENTS WITH HUNTINGTON'S DISEASE

*Xiao-Yan Li, Zhejiang University*

The imaging and biological features of psychosis in HD

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F26

IDENTICAL TWINS .. ARE THEY IDENTICAL?

*Muthukumaran Thangaramanujam, Trinity College Dublin*

Two female monozygotic twins with HD were born 6 weeks premature and raised in the same environment. We will report on motor, neuropsychological and psychiatric manifestations along with MRI findings. A detailed comparison of motor, cognitive, and behavioural profile is currently in progress.

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F27

CLINICAL PRESENTATIONS IN PATIENT WITH 34 CAG-REPEATS (CASE REPORT)

*Diana Khasanova, Center for Movement Disorders*

We represent a case report of clinical manifestation in patient with intermediate allele length of Htt gene. The patient M., 47 years old, with predominantly psycho-emotional disturbances, has 34 CAG-repeats. No family history was observed. This patient was recommended to have a genetic counselling for the family and follow-up.

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F28

NOVEL MUTATIONS AND FINDINGS IN A COHORT OF MCLEOD NEUROACANTHOCYTOSIS, AN X-LINKED HD PHENOCOPY

*Kevin Peikert, University Medical Center Rostock*

Our case series represents the second largest cohort so far of the hereditary hyperkinetic syndrome of McLeod neuroacanthocytosis: novel mutations and manifestations are described.

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F29

DOMINO-HD: A 12-MONTH OBSERVATIONAL COHORT STUDY OF LIFESTYLE FACTORS IN PEOPLE WITH HUNTINGTON'S DISEASE

*Cheney Drew, Cardiff University*

DOMINO-HD will collect information on lifestyle (physical activity, sleep and nutrition) across 12 months. This will be linked with functional and clinical outcomes collected in Enroll-HD, alongside genetic data, to examine the causal effect of lifestyle and genetic factors on HD progression.

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F30

Q-MOTOR ASSESSMENTS IN THE BIDIRECT COHORT STUDY: FEASIBILITY, NORMATIVE DATA AND DEMOGRAPHIC EFFECTS

*Robin Schubert, George Huntington Institute*

Applying Q-Motor assessments in a large cohort study, normative data for finger tapping and grasping & lifting tasks of the Q-Motor battery were generated, and effects of age, sex and other potentially mediating variables were explored. The data provides hints for further enhancement of future analyses.

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F31

EXAMINING THE EFFECT OF EXERCISE ON THE PROGRESSION AND SEVERITY OF HUNTINGTON'S DISEASE USING DIFFERENT COVARIATE BALANCING METHODS AND SIMULATED DATA DERIVED FROM THE PACE-HD STUDY

*Andreas Markoulidakis, Cardiff University*

We compare the performance of a number of commonly used estimation methods on a synthetic data set based on the Physical Activity and Exercise Outcomes in Huntington Disease (PACE-HD) study, which explored whether enhanced physical activity affects the progression and severity of the disease. We provide general guidelines for the choice of method for estimation of PS and balancing weights, interpretation, and sensitivity analysis of results.

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F32

EXPLORING THE FEASIBILITY OF A NOVEL AND EFFICIENT TRIAL DESIGN FOR THE EVALUATION OF LONG-TERM PHYSICAL ACTIVITY AND EXERCISE OUTCOMES IN PEOPLE WITH HUNTINGTON'S DISEASE.

*Monica Busse, Cardiff University*

Novel trial designs which capitalize on linkage with existing cohort studies for example Enroll-HD are useful to facilitate evaluation of physical activity life-style interventions in Huntington's Disease.

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F33

PERCEPTIONS, MOTIVATORS AND BARRIERS TO THE ACCEPTANCE OF WEARABLE ACTIVITY TRACKERS IN PEOPLE WITH HUNTINGTON'S DISEASE

*Philippa Morgan-Jones, Cardiff University*

This study used focus groups and a questionnaire to explore how the Huntington's disease community view wearable activity trackers. Whilst acceptable for monitoring and management of lifestyle behaviours, device design/functionality must be considered to promote acceptance in this clinical cohort.

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F34

REMOTE MONITORING OF SPEECH IN HD USING MOBILE DEVICES

*Vitória Fahed, University College Dublin*

Mobile technology has potential for monitoring speech, an important marker in Huntington's disease (HD). This study compared acoustic voice features using mobile devices and gold standard microphones, in control and HD participants, validating the accuracy of mobile technology for speech analysis.

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F35

SLEEP MONITORING IN HUNTINGTON'S DISEASE USING FITBIT COMPARED TO POLYSOMNOGRAPHY

*Emer Doheny, University College Dublin*

Sleep is affected by Huntington's disease (HD). Fitbit Charge 4 monitors sleep, but it is not yet validated in HD. Preliminary data from the DOMINO-HD study are reported, comparing Fitbit sleep data to the gold standard, polysomnography, and monitoring sleep for 7 nights at home in HD participants.

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F36

DXA, BIA, ANTHROPOMETRY AND SKIN FOLDS METHODOLOGY IN BODY COMPOSITION

*Jéssica J. Rivadeneyra-Posadas, Unidad de Investigación, Hospital Universitario de Burgos, Spain*

We evaluated and compared body composition using DXA, BIA, anthropometry and skinfolds in patients with Huntington's disease (HD). The result of this ongoing pilot study will provide the accuracy of anthropometric and skin folds measures to estimate the body composition in patients with HD.

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F37

USE OF CERVICAL AUSCULTATION FOR SWALLOWING ANALYSIS IN HUNTINGTON'S DISEASE

*Angela Nuzzi*

This study proposes the use of cervical auscultation and acoustic analysis as an additional and non-invasive tool for the evaluation of swallowing in HD patients.

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F38

SKILL-BASED DYSPHAGIA TRAINING AS AN INTERVENTION FOR INDIVIDUALS WITH HUNTINGTON'S DISEASE

*Emma Burnip, University of Canterbury*

Impaired swallowing is common in HD; however, intervention options aimed to maintain or improve swallowing are limited. This is the first research to use instrumental swallowing outcomes to evaluate the feasibility and effectiveness of a novel skill-based swallowing therapy for individuals with HD.

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F39

DESIGN OF AN ADAPTIVE RANDOMIZED CONTROLLED PHASE 1B/2A TRIAL OF WVE-003 IN PARTICIPANTS WITH HUNTINGTON'S DISEASE

*Danlin Xu, Wave Life Sciences*

Wave has initiated SELECT-HD, an adaptive randomized controlled phase 1b/2a trial of WVE-003, in participants with Huntington's disease. WVE-003 an investigational stereopure oligonucleotide designed to selectively reduce the expression of mHTT mRNA while preserving wtHTT mRNA, and it contains Wave's new PN chemistry, which has been shown to improve the pharmacological profile of oligonucleotides in preclinical studies.

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F40

PROOF-OF-CONCEPT STUDY TESTING SOM3355, A VMAT2 INHIBITOR FOR THE TREATMENT OF CHOREA IN HUNTINGTON'S DISEASE

*Aileen Ferré, SOM Innovation Biotech SA*

SOM Biotech discovered that SOM3355 (bevantolol hydrochloride) has VMAT2 inhibitor activity and could be repositioned for the treatment of chorea in Huntington's disease. A proof-of-concept study was conducted to confirm that SOM3355 effectively reduces Huntington's chorea and has a good safety profile.

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F41

THE PROOF-HD PHASE 3 STUDY: PRIDOPIDINE'S OUTCOME ON FUNCTION IN HUNTINGTON DISEASE (PROOF)

*Michael R. Hayden, Prilenia Neurotherapeutics*

PROOF-HD is a phase 3 clinical trial actively enrolling at 60 sites, including 30 sites in Europe and 30 in North America. PROOF will evaluate the effect of pridopidine on functional decline in early HD as measured by TFC. As of July 4, 2021 235 participants have been randomized (49% of total), and there have been no dropouts from the trial.

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F42

EXPOSURE RESPONSE ANALYSIS (PKPD) PREDICTS OPTIMAL EXPOSURE OF PRIDOPIDINE FOR CLINICAL EFFICACY OF FUNCTIONAL CAPACITY

*Michal Geva, Prilenia Neurotherapeutics*

Pridopidine is a safe and well-tolerated oral drug candidate currently being evaluated in the Ph3 PROOF-HD trial. PROOF assesses the effect of pridopidine on TFC in early-stage HD patients. Analysis of plasma exposure and TFC from PRIDE-HD demonstrates that a 45 mg bid dose of pridopidine correlates to optimal exposure for clinical efficacy.

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F43

PRIDOPIDINE MAINTENANCE OF TOTAL FUNCTIONAL CAPACITY (TFC) IS ASSOCIATED WITH STABILIZATION OF PLASMA NEUROFILAMENT LIGHT (NFL) LEVELS

*Michal Geva, Prilenia Neurotherapeutics*

Plasma NFL levels are a promising biomarker for assessment of disease progression and treatment efficacy. Data from the Ph2 PRIDE-HD trial show that pridopidine 45 mg bid has a stabilizing effect on NFL levels, associated with the clinical finding of maintenance of functional capacity.

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F44

HUNTINGTON'S DISEASE PATIENTS AND FAMILIES FACING COVID-19 EMERGENCY IN ITALY

*Marcella Solito, Fondazione Policlinico Universitario Agostino Gemelli IRCCS*

A telephone survey investigated how Italian HD patients and families followed at Policlinico Gemelli neurologic outpatient clinic in Rome coped with the COVID-19 emergency and social restrictions during the first pandemic wave.

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F45

IMPACT OF COVID-19 PANDEMIC IN PATIENTS WITH HUNTINGTON DIESEASE

*Chiara Pane, University "Federico II", Naples, Italy*

The existence of a close relationship between Covid-19 and neurological and psychiatric disorders brings up some fundamental questions. First, whether HD patients have increased morbidity and mortality related to Covid-19 infection. Second, whether and in what way Covid-19 pandemic may have modified the clinical course of the pre-existing neurological disease. In HD patients, the pandemic has had direct implications on the infection itself and indirect consequences resulting from restrictive measures.

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F46

THE EUROPEAN HUNTINGTON'S DISEASE NETWORK

*Jenny Townhill, EHDN*

The European Huntington's Disease Network (EHDN) is a non-profit research network with the mission of advancing research, facilitating conduct of clinical trials, and improving clinical care in HD. EHDN forms a platform for clinicians, scientists, academics, patients, and family members to work together to achieve these goals.

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F47

THE EUROPEAN HUNTINGTON'S DISEASE NETWORK (EHDN) SCIENTIFIC SUPPORT

*Christine Capper-Loup, EHDN*

The European Huntington's Disease Network (EHDN) has developed several strategies to advance research : a seed fund program, the Registry dataset (RDS), the Think Tank and support from a Grants and collaborations manager.

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F48

ENROLL-HD STUDY STATUS

*Selene Capodarca, EHDN*

Enroll-HD is a clinical research platform that includes an observational study of Huntington Disease (HD). Eligible participants include individuals who are gene expansion carriers, individuals with unknown genotype and controls. Data are collected annually on on motor, cognitive and behavioral symptoms, releasing coded data to researchers periodically.

Enroll-HD provides high quality clinical data and biological samples. As a research platform, Enroll-HD brings together a novel set of tools for HD clinical research that is easily available for researchers.

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F49

ENROLL-HD CLINICAL TRIAL COMMITTEE

*Jenny Townhill, EHDN/Enroll-HD*

The Enroll-HD Clinical Trial Committee (CTC) provides recommendations and guidance to clinical trial sponsors for clinical development and/or review of trial protocols for operational support using Enroll-HD resources.

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F50

ENROLL-HD PLATFORM SUPPORT FOR INDUSTRY AND ACADEMIC SPONSORS

*Jenny Townhill, EHDN/Enroll-HD*

Enroll-HD is a global research platform with the infrastructure to support clinical trials and studies in Huntington's disease (HD). The Enroll-HD platform makes these resources and support available to the HD research community.

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F51

ENROLL-HD PLATFORM DATA RESOURCES

*Mette Gilling Nielsen, EHDN*

Enroll-HD is a clinical research platform that includes at its core a global observational study of Huntington's Disease (HD) families who are followed annually. Enroll-HD provides high quality coded clinical data and biosamples to qualified researchers via a straightforward request process (https://enroll-hd.org/for-researchers/).

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F52

ENROLL-HD PLATFORM BIOSAMPLE RESOURCES

*Mette Gilling Nielsen, EHDN*

Enroll-HD is a clinical research platform that includes at its core a global observational study of Huntington's Disease (HD) families who are followed annually. Enroll-HD provides high quality coded clinical data and biosamples to qualified researchers via a straightforward request process (https://enroll-hd.org/for-researchers/).

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F53

INTRODUCING JOIN-HD: THE JUVENILE ONSET INITIATIVE FOR HUNTINGTON'S DISEASE

*Rebecca Mason, Huntington's Disease Youth Organization*

JOIN-HD is a patient registry launched by HDYO in 2021 for young people who have Juvenile onset Huntington's Disease and their caregivers. The aims of JOIN-HD include to identify JoHD cases and map their locations globally, to support research in this patient population, and to identify unmet needs to improve advocacy, care and support.

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F54

"SPAZIO HUNTINGTON – A PLACE FOR CHILDREN": AN ITALIAN OBSERVATIONAL, MULTICENTRE, PROGRAM TO DETECT PEDIATRIC HUNTINGTON DISEASE CASES

*Federica Graziola, Bambino Gesù Children Hospital*

Pediatric Huntington Disease (PHD) is the rarest HD variant. Strategies are needed to recruit PHD cases in clinical trials according to recent European Medicine Recommendations. Spazio Huntington is a LIRH Foundation program to meet HD families with at risk minors in a nonmedical environment.

## Genetic testing and counselling: G01 – G03

G01

MOLECULAR TESTING FOR HUNTINGTON DISEASE AND THE RISK OF DISCLOSURE OF UNSOLICITED PRE-SYMPTOMATIC STATUS: A RECURRING THEME

*Elaine Cristina Miglorini, Hospital de Clínicas de Porto Alegre*

Molecular diagnosis of Huntington's Disease can bring challenges, as when the molecular diagnosis of a symptomatic person can reveal the pre-symptomatic status of others. We report here how we handled the detection of a homozygous status in a molecular diagnosis that preceded genetic counseling.

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G02

THE EXPERIENCE OF LIVING IN THE PRE-MANIFEST STAGE OF HUNTINGTON'S DISEASE: AN INTERPRETATIVE PHENOMENOLOGICAL ANALYSIS

*Gina Wieringa, Lancaster University*

This paper explores the lived experience of individuals in the pre-manifest stage of HD i.e. they have tested positive for the gene expansion but have not yet received a diagnosis. The paper suggests that, whilst the majority cope well in this period, those who are struggling may benefit from psychological support to help manage their anxieties.

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G03

THE HOLD ME TIGHT RELATIONSHIP PROGRAM FOR COUPLES FACING HUNTINGTON'S DISEASE

*Lucienne van der Meer, Leiden University Medical Center*

Strenghtening the emotional connection between spouses may be seen as an investment in a couple's capacity to face HD together, after a positive predictive test result. In this study, we investigated whether the Hold me Tight relationship program, which aims to enhance a couple's emotional bond by targeting attachment needs, contributes to relationship satisfaction, well being, and resilience of presymptomatic HD-carriers and their partners. This program could become a standardized procedure in regular care for couples facing HD.

## Clinical care and clinical services: H01 – H14

H01

DISEASE BURDEN IN PATIENTS WITH HUNTINGTON'S DISEASE FROM A NATIONWIDE SWEDISH REGISTRY COMPARED WITH THE GENERAL POPULATION (2002–2019)

*Hannah Furby, F. Hoffmann-La Roche Products Ltd*

This abstract describes findings from a large cohort study using the Swedish national registries. The incidence of clinical events in patients newly diagnosed with HD were compared with the general population, to help better understand the clinical burden of disease in a routine healthcare setting.

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H02

'THERE IS THIS BIG GAP': THE UNMET NEEDS OF PEOPLE WITH ADVANCED HD, FAMILIES AND CAREGIVERS.

*Richie Paul Carreon, Liverpool John Moores University*

The participatory group exercise is part of a longitudinal PhD research which explores the illness experience of people with HD, their families and caregivers in different disease stages. The findings contributed to the overall project by giving voice to people with advanced HD, where there is limited research on their subjective experience, problems and needs.

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H03

EXPERIENCES OF OUTPATIENTS WITH HUNTINGTON'S DISEASE WITH CASE MANAGEMENT; A QUALITATIVE STUDY

*Cindy Kruijthof, Atlant, Huntington Centre of Expertise, Apeldoorn, the Netherlands*

We studied the experiences and meanings of outpatients with Huntington's disease with the care, guidance and support provided by a case manager. To enable participants to recount their experiences semi-structured interviews were conducted during 2020-2021.

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H04

MAPPING HD SERVICES IN THE UK – A PARTNERSHIP APPROACH

*Wendy Kane, F. Hoffmann-La Roche Products Ltd*

The United Kingdom Huntington's Disease Network, Huntington's Disease Association, Scottish Huntington's Association, and Roche Products Ltd. are collaborating to map the UK HD services capturing how they are delivered and resourced at a local and national level. This will provide evidence to support dialogue with payers/decision-makers to help secure resourcing and funding for HD patients.

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H05

A JOINT INITIATIVE FOR IMPROVED CARE OF HUNTINGTON'S DISEASE PATIENTS IN GERMANY

*Michaela Winkelmann, Deutsche Huntington-Hilfe e.V.*

Jointly defined activities aim to provide a comprehensive multidisciplinary treatment concept covering all HD patients' stages. Therefore, different stakeholders collaborate: patients, families, patient organization, various medical and therapeutic specialties as well as researchers.

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H06

CHALLENGES AND OPPORTUNITIES OF HUNTINGTON'S DISEASE IN EGYPT: A QUALITATIVE STUDY

*Shaimaa El-Jaafary, Faculty of Medicine, Cairo University*

The current study is of a qualitative nature, where young neurologists were interviewed in a semi-structured manner with open ended questions to explore the difficulties they face while dealing with cases of Huntington's disease in Egypt. Our results showed that delayed diagnosis is common due to lack of knowledge and training among neurologists, lack of awareness among patients as well.

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H07

THE IMPACT OF A HIGH CARE UNIT FOR PATIENTS WITH HUNTINGTON'S DISEASE FROM A MULTI-PERSPECTIVE VIEW; AN EXPLORATORY STUDY.

*Loes van Dusseldorp, Atlant, Huntington Centre of Expertise*

We studied the impact of a newly constructed high care unit in a skilled nursing facility for five patients with Huntington's Disease showing complex behavior. The experiences of the patients, family caregivers and nursing staff is mapped with qualitative and quantitative research methods.

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H08

MULTIDISCIPLINARY TREATMENT AND CARE WORKING GROUP - OCCUPATIONAL THERAPY

*Kirsty Page, Hamberley Care Homes*

Every Huntington patient must receive comparable, high-quality occupational therapy. The aim of the MDT treatment and care working group is to connect all occupational therapists working with HD.

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H09

BEST PRACTICE OCCUPATIONAL THERAPY FOR PEOPLE WITH HD

*Alex Fisher, BSMHFT and University of Birmingham, UK*

Specialist Occupational Therapists working with people with HD, involved in the original production of the Best Practice Guidelines for OT for people with HD. Through EHDN collaboration, they are now in the process of updating the Guidelines to reflect this ethos and to reflect worldwide best practice.

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H10

APPLICABILITY AND EFFECTS ON INITIATIVE OF SOCIAL ROBOT TESSA IN PATIENTS WITH HUNTINGTON`S DISEASE – A MULTIPLE CASE STUDY

*Yvonne Zwaagstra, Atlant, Huntington Centre of Expertise*

In this multiple case study two patients with Huntington's Disease residing in a skilled nursing facility were reminded by Tessa of activities and chores. Patients' behavior was monitored and patients, family caregivers and nursing staff were interviewed.

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H11

IMPLEMENTING PHYSIOTHERAPY HUNTINGTON'S DISEASE GUIDELINES IN CLINICAL PRACTICE: A GLOBAL SURVEY

*Una Jones, Cardiff University*

The Physiotherapy Working group carried out a survey to identify barriers and facilitators to implementation of recently published guidelines. Our workstreams will use the findings to develop resources to support physiotherapists in HD clinics, residential care facilities and the community.

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H12

PSYCHOLOGICAL INTERVENTIONS FOR PEOPLE WITH HUNTINGTON'S DISEASE: A CALL TO ARMS

*Nicolò Zarotti, Division of Health Research, Faculty of Health and Medicine, Lancaster University*

The present study represents the first review of psychological interventions for individuals with Huntington's disease available to date. It aims to act as a call to arms for HD researchers worldwide to help shed light on the most effective way to translate psychological theory into practice for the benefit of people with HD.

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H13

ADVANCE EUTHANASIA DIRECTIVES IN HUNTINGTON'S DISEASE: A PATIENTS' PERSPECTIVE

*Marina Ekkel, Amsterdam UMC*

For patients with HD in the Netherlands, one way of dealing with their poor prognosis is by drafting up an advance euthanasia directive (AED). In this qualitative longitudinal study we aim to gain insight into patients' motives for drafting up an AED and to explore the expectations patients have of their AED.

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H14

END-OF-LIFE CONVERSTATIONS WITH PATIENTS WITH HUNTINGTON'S DISEASE

*Linda Schippers, Atlant, Huntington Centre of Expertise*

A qualitative study using semi structured interviews with nursing home care provider, HD patients and family caregivers with end-of-life conversations.

## Experimental therapeutics – preclinical: I01 – I13

I01

ORALLY BIOAVAILABLE SMALL MOLECULE SPLICING MODIFIERS WITH SYSTEMIC AND EVEN HTT-LOWERING ACTIVITY IN VITRO AND IN VIVO

*Anuradha Bhattacharyya, PTC Therapeutics, Inc.*

This describes the discovery of a class of small molecule splicing modifiers synthesised to promote selective splicing and reduction in huntingtin mRNA and protein levels in cells and animal models, which could represent a non-invasive effective treatment for patients with Huntington's disease.

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I02

A CAG REPEAT-TARGETING ARTIFICIAL miRNA LOWERS THE MUTANT HUNTINGTIN LEVEL IN THE YAC128 MODEL OF HUNTINGTON'S DISEASE

*Marta Olejniczak, Institute of Bioorganic Chemistry, PAS*

We confirmed that vector-based RNAi molecules targeting CAG tracts can be used to lower the mutant huntingtin level in vivo in an allele-selective manner. AAV5-based amiRNA molecule was effective, selective and well-tolerated up to four months post injection. This strategy could make an original and valuable contribution to currently used therapeutic approaches for HD.

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I03

CPEB ALTERATION AND ABERRANT TRANSCRIPTOME-POLYADENYLATION UNVEIL A TREATABLE VITAMIN B1 DEFICIENCY IN HUNTINGTON'S DISEASE

*Sara Pico, Centro de Biologia Molecular ''Severo Ochoa'' (CBMSO) CSIC/UAM*

Here we find altered CPEBs and transcriptome-polyadenilation in HD, affecting SLC19A3 thiamine transporter (mutated in biotin+thiamine responsive basal ganglia disease) and causing thiamine deficit in HD patients. Biotin+thiamine in HD mice attenuated their phenotypes, unveiling an easy to implement therapy for HD.

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I04

REDUCTION OF GLUTAMATE DEHYDROGENASE INCREASES AUTOPHAGY AND AMELIORATE MOTILITY AND SURVIVAL IN A DROSOPHILA MODEL FOR HUNTINGTON'S DISEASE

*Paola Bellosta, University of Trento*

Our work investigates how reducing Glutamate Dehydrogenase (GDH) can modulate autophagy, fundamental for protein aggregates clearance, to identify potential GDH inhibitors. The beneficial effect of GDH downregulation is exerted through the reduction of amino acids, that contributes to the inactivation of TOR pathway, to induce autophagy.

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I05

INCREASING BRAIN PALMITOYLATION RESCUES BEHAVIOR AND NEUROPATHOLOGY IN HUNTINGTON DISEASE MICE

*Laura Auboyer, GRENOBLE INSTITUT NEUROSCIENCES (GIN)*

We hypothesized that improving vesicular transport of BDNF in Huntington Disease could slow or prevent disease progression. We found that increasing brain palmitoylation restores axonal vesicle transport, synapse homeostasis, and survival signaling of neurons in a HD cortico-striatal network-on-a-chip and reverses neuropathology, locomotor deficits, and anxio-depressive behaviors in HD knock-in mice.

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I06

SREBP2 DELIVERY TO STRIATAL ASTROCYTES NORMALIZES TRANSCRIPTION OF CHOLESTEROL BIOSYNTHESIS GENES AND AMELIORATES PATHOLOGICAL FEATURES IN HUNTINGTON'S DISEASE

*Giulia Birolini, University of Milan and INGM*

SREBP2 gene therapy targeting striatal astrocytes normalized the transcription of key cholesterol biosynthesis genes in the R6/2 mouse model, resulting in restoration of synaptic, molecular, and neuropathological defects and attenuation of behavioral deficits.

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I07

A NEW GENERATION OF BRAIN-TARGETED NANOPARTICLES FOR CHOLESTEROL DELIVERY IN HUNTINGTON'S DISEASE: KINETICS, DRUG RELEASE AND BEHAVIORAL EFFECTS IN MOUSE MODELS

*Marta Valenza, University of Milan*

Here we describe a new generation of brain-permeable nanoparticles (NPs) allowing to deliver optimal doses of cholesterol to the Huntington's disease brain after systemic injections. We will show data regarding NPs distribution, kinetics, drug release, long-term behavioral benefits and safety in Huntington mouse models.

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I08

LXR SIGNALING IN THE STRIATUM AND NEUROPROTECTION IN HUNTINGTON'S DISEASE

*Coline Mounier, Sorbonne Université - Institut de Biologie Paris Seine - Neuroscience Paris Seine*

Cholesterol metabolism is altered in HD and restoration of the neuronal enzyme for cholesterol degradation (CYP46A1) is neuroprotective. Since 24S-OHC binds to Liver X Receptors (LXR), we hypothesize that CYP46A1 neuroprotection is mediated by the LXR. Cell survival and clearance of HTT aggregates in HD neurons are improved after LXR activation.

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I09

IN VIVO MTHTT PROTEIN REDUCTION IN THE CNS AND PERIPHERY BY PASSIVE IMMUNIZATION WITH THE MONOCLONAL ANTIBODY C6-17

*Stefan Bartl, Affiris AG*

AFFiRiS AG is developing an immunotherapy targeting an exposed region of the HTT protein. In preclinical in vivo prove of concept experiments we treated YAC128 animals with our lead monoclonal antibody C6-17 and we could demonstrate a reduction of mutated huntingtin protein in CNS and in peripheral tissues. The mAB C6-17 treated YAC128 animals showed benefits in body weight and motor behaviors and we could observe a delay in the HD disease progression. Our findings support the suitability of an antibody treatment approach in Huntington's disease and our in vivo data could set the ground for a new HD treatment regime based on a therapeutic antibody molecule.

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I10

ACUTE INNATE IMMUNE RESPONSES TO SIMULATED TRANSPLANTATION SURGERY IN TWO HD MOUSE MODELS

*Feras Sharouf, Cardiff University*

Simulated cell transplantation surgery produced an amplified pro-inflammatory response in two HD mouse models. The inflammatory reaction to surgical trauma post-CRT is likely to contribute to neural graft site hostility. Simultaneous modulation of these pro-inflammatory pathways during graft delivery may improve graft survival in CRT.

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I11

PHARMACOLOGIC INHIBITION OF THE CLASSICAL COMPLEMENT PATHWAY ENHANCES NEURONAL FUNCTION AND HD R6/2 MOUSE SURVIVAL

*Alessia Tassoni, Annexon Biosciences*

The role of the classical pathway in HD is unclear. Using the R6/2 mouse model, we found positive correlation of plasma C1q with the neurodegenerative biomarker NFL in the CSF. Inhibition of C1q resulted in normalized complement activity, reduced CSF NFL levels, improved motor behavior and survival. A Phase 2 study of anti-C1q in HD patients is ongoing.

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I12

DECIPHERING THE NEUROPROTECTIVE ROLE OF SIGMA1 RECEPTOR, AN IMPORTANT FUNCTION TO OVERCOME THE SYMPTOMS OF NEURODEGENERATIVE DISORDERS.

*Veronica Morea; Andrea Ilari, CNR (italian national research council)*

The sigma-1 receptor is expressed in the central nervous system and has neuroprotective activity in neurodegenerative diseases. By integrating computational and experimental methods, we have identified six known drugs able to improve growth of fibroblasts from Huntington's Disease patients.

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I13

PRIDOPIDINE RESTORES MITOCHONDRIAL FUNCTION AND DECREASES ER STRESS WHICH IS MEDIATED THROUGH THE S1R

*Michal Geva, Prilenia Neurotherapeutics*

Pridopidine is a safe and well tolerated drug in clinical development, currently being evaluated in the actively enrolling PROOF-HD trial. Pridopidine selectively binds and activates the sigma-1 receptor. Activation of the S1R rescues mitochondrial function, which is impaired in HD, and ameliorates ER stress in HD models.

## Clinical therapeutics: J01 – J05

J01

TRIHEPTANOIN IS ASSOCIATED WITH CLINICAL STABILITY AND DECREASED CAUDATE ATROPHY IN HUNTINGTON DISEASE

*Fanny Mochel, Paris Brain Institute*

Recently, the HD community has been very affected by the failure of gene therapies. Instead, here we provide evidence that a metabolic drug targeting the Krebs cycle can both stabilize motor scores but also reduce by half the rate of caudate atrophy, the core region affected in HD.

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J02

TRIDENT: INVESTIGATING THE SAFETY ANF FEASIBILITY OF FETAL CELL TRANSPLANTS IN HUNTINGTONS DISEASE

*Cheney Drew, Cardiff University*

TRIDENT is designed to assess the safety and feasibility of cell replacement therapy in HD. Information collected in this open label trial will also provide much needed information on trial design and allow the development of surgical pipelines for future stem cell trials.

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J03

CLINICAL TRANSLATION OF STEM CELL THERAPIES FOR HUNTINGTON'S DISEASE (HD)

*Anne Rosser, Cardiff University*

We set out the challenges associated with the clinical translation of cell therapy in Huntington's disease (HD), and suggests potential strategies to address these challenges. We propose that solving these challenges in HD would provide a road map for many other neurological conditions.

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J04

EFFICACY AND SAFETY OF TIAPRIDE FOR CHOREA TREATMENT IN HUNTINGTON'S DISEASE: A SYSTEMATIC REVIEW

*Stephanie Feleus, Leiden University Medical Center*

As an MD doing research I focus on the potential of personalized medicine in Huntington's Disease. Can we tailor prescriptions to individual patients' needs by selecting the most optimal drug, both in efficacy and side effect profile, for the individual patient?

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J05

A DIFFERENT DEPRESSION: ANTIDEPRESSANT EFFICACY AND COGNITIVE MECHANISMS OF MOOD DISORDER IN HUNTINGTON'S DISEASE

*Duncan McLauchlan, Cardiff University*

Despite the high prevalence of depression and impact on quality of life, the best treatment and underlying mechanisms in HD remain obscure. We used propensity scoring to assess antidepressant efficacy in the ENROLL-HD dataset, and cognitive assessment to delineate mechanisms of depression in HD.