HDBUZZ

EuroBuzz 2014: day one

Highlights from the opening day of the 2014 European Huntington's Disease network in Barcelona, Spain

By **Professor Ed Wild**   September 19, 2014   Edited by **Dr Jeff Carroll**

Join Jeff and Ed as we tweet live from the 2014 European Huntington's Disease Network meeting in Barcelona! Exciting science ahead!

Prof Bernhard Landwehrmeyer opens the 2014 European Huntington's Disease Network meeting in Barcelona

EHDN is a huge network of scientists, clinicians and HD family members across Europe. 2014 is EHDN's 10th Anniversary!

Letitia Toledo-Sherman of CHDI Foundation described the development of CHDI's KMO inhibitor drug CHDI246

The day starts with a lecture from **Prof Sarah Tabrizi**, who reminds us that we have to understand HD in humans, not just flies and mice

Observational clinical trials like PREDICT-HD, TRACK-HD and ENROLL-HD help us understand how symptoms progress in people with HD

Tabrizi: the goal is to intervene early to prevent Huntington's completely. "I hope to achieve this in my professional lifetime"

Observational studies have revealed that shrinkage in very specific brain regions predicts when people will have HD symptoms

Tabrizi: But other changes in HD mutation carriers, including high levels of apathy, also predict onset of symptoms

Tabrizi: HD mutation carriers, even before they have symptoms, have difficulty recognizing negative facial emotions

Tabrizi: We shouldn't ignore symptoms like apathy and difficulty in emotional recognition, because they can cause major problems

Tabrizi: A study called TRACK-ON was designed to study how parts of the brain communicate with one another in the face of HD

Tabrizi: The 'wiring diagram' of vulnerable brain regions in HD is altered in ways that might help explain patients symptoms

Tabrizi: Using fancy math, researchers examined TRACK-ON brain imaging data and show that the HD brain has reduced connections

Tabrizi: New data suggests that when one part of the brain becomes sick in HD, other regions increase their activity to compensate

Tabrizi: A major remaining question is why some HD patients have fast and some have slow progression

Prof Roger Barker from Cambridge University presenting a roundup of animal models used in HD

Barker: animal models are useful but we must remember they're not humand when we interpret what they tell us

Barker: If you take one message from my talk, it's "animals cannot talk!" So they can't describe their symptoms, like HD patients

Barker: to show signs like HD, animal models have very long CAG repeat' counts, some much bigger than we see in real patients

Barker has created a virtual reality swimming pool to recreate in patients a widely used mouse test

Barker: HD is a disease of people, but going between animal models and people can help us best understand HD

Bernhard Landwehrmeyer again, giving an update on the Enroll-HD study http://enroll-hd.org

Landwehrmeyer: ENROLL-HD was developed because 'we need speed'.

BL: enroll is a world wide study with big ambitions, aiming to study 25,000 individuals!

BL: why do some people experience HD symptoms early, and some late? What factors can explain this?

BL: a multi-year study of more than 4000 volunteers suggests a new gene that could modify the age of onset of HD

BL: these results reveal why we need huge members of volunteers for HD observational studies like ENROLL

BL: enroll-HD has 102 active sites around the world, with more than 3000 participants

BL: you do not need to have a predictive test for HD to be involved in ENROLL-HD - anyone can participate

BL: hopefully the large group of patients in the ENROLL-HD study can help fill up drug studies quickly with the right participants

Excitement for next session on 'modifiers' of HD. Genetic Modifiers international collaboration has made a big breakthrough

First **Jan Frich** from Oslo is talking about environmental modifiers of HD

Frich: an environmental modifier is anything a person can do, or encounter, that alters how HD affects them

Exercise, smoking, diet, pollution, occupation are examples of potential 'environmental modifiers'

Frich has conducted a study of 1 year intensive programmed activity as a way of improving symptoms in HD

Message: physical activity is helpful for many aspects of Huntington's disease

Jong-Min Lee from Massachusetts General Hospital is presenting the genetic modifiers work on behalf of international group

Genetic differences between people can affect when HD symptoms begin. We call these 'genetic modifiers'.

The biggest 'genetic modifier' is the CAG count in the HD gene itself. But differences in other genes might affect HD as well

If we can find out what those genes are, they might tell us where to focus our drug development efforts

> **"Tabrizi: The goal is to intervene early to prevent Huntington's completely. I hope to achieve this in my professional lifetime "**

Advances in genetic technology let us look for genetic differences in thousands of people to see what changes speed or slow HD

It's thanks to efforts like EHDN's Registry study that we have enough samples and data to do these huge, important studies

A study this large takes years of hard work - the study discussed here began in 2008, and looked at 8 million genetic differences!

Interestingly, the researchers have found modifiers that are associated with having HD symptoms both later and earlier

When you test 8 million genetic variants in more than 4000 people, the math gets pretty complicated!

All the information generated in the huge modifier study will be freely available to researchers around the world

Leslie Jones of Cardiff University presenting exciting genetic modifier data

Jones describes the team's efforts to understand how the mapped genetic changes actually change how genes function

The new genetic results suggest that something may be going wrong with the DNA proofreading that cells have to do to stay healthy

This is exciting because earlier work, in mice, suggested this DNA proofreading process is important in HD

Ed: The next science session is on 'kynurenine mono-oxygenase', or KMO.

Ed: KMO is a molecular machine that determines the balance of harmful and helpful chemicals in the brain.

Ed: KMO has been shown to be involved in HD in experiments in yeast, flies and mice.

Ed: blocking the activity of KMO should protect HD brains against some damage

Ed: You can read about KMO and some previous success with a KMO-inhibiting drug here

Ed: **Laci Mrzljak** of CHDI Foundation is presenting the latest on CHDI's efforts to develop their KMO inhibitor drug 'CHDI246'

Mrzljak: treating mice with CHDI246 helps the connections between brain cells to keep working properly

Mrzljak: CHDI246 treatment also improves brain activation when you do MRI scans of the HD mice

Letitia Toledo-Sherman, a 'drug designer' at CHDI, takes up the KMO story

LTS: CHDI has developed new methods for measuring the KMO-related chemicals in human patient spinal fluid

Ed: CHDI's Chief Medical Officer **Christina Sampaio** is now talking about how we can get CHDI246 into human trials

Sampaio: To get CHDI246 into clinical trials we need biomarkers - ways of measuring whether the drug is working.

Sampaio: CHDI is setting up a big project to collect spinal fluid, to measure the balance of protective and harmful chemicals...

Sampaio: ... the CHDI cerebrospinal fluid project will be led by a plucky young HD researcher called Dr Ed Wild

Sampaio: CHDI has detailed plans for getting CHDI246 into human trials and showing whether it works

Alexandra Durr from Paris: Between 1992-2013, 1,705 predictive tests for HD have been conducted at at Pitié-Salpêtrière Hospital in Paris

Durr: Only 5-25% of persons at risk for HD undergo predictive testing

Durr: Of people requesting predictive testing for HD, 63% complete the process and actually receive their result

Durr:Since 2000 there's been no obvious increase in people requesting predictive testing at her center, despite more info available

Durr: The average age of people requesting predictive testing is about 35, and rarely from very young

Durr: about 70-80% of patients who received predictive testing results say they pay more attention to possible symptoms of HD

Durr: We should take the opportunity to try and run pre-symptomatic trials in HD, targeted at preventing onset of symptoms

Elizabeth McCusker considers whether diagnostic criteria in HD should be changed

McCusker: There's no formal means of defining onset of HD, but rather clinical practice that has developed over years

McCusker: The diagnosis of HD is made in a complex environment, with possible family, social and other consequences for patients

McCusker: From the point of view of research, the formal diagnosis of HD may be coming too late

McCusker: Does diagnosis of HD help patients? There are ways that we can see at least

some patients benefit from a clear diagnosis

Jong-Min Lee presented exciting news about genetic differences linked to earlier or later than expected onset of HD. These help us direct our drug development efforts.

McCusker: All the HD mutation carriers that have been studied pre-symptomatically are from the rare 5-20% of patients who are tested

McCusker: The issues around what constitutes a diagnosis of HD are complex and somewhat unique to each patient's situation

David Craufurd addresses the EHDN on the question of whether HD patients, or pre-symptomatic mutation carriers, should have checkups

Craufurd: Behavioral symptoms are often more distressing than motor and cognitive ones for HD families

Craufurd: Symptomatic treatments for HD have improved dramatically over the last few decades

Craufurd: HD symptoms are a "moving target", because the symptoms in a given individual change throughout the disease

Crufurd: Treating HD can be difficult, in part because patients can be unaware of their own symptoms or apathetic

Craufurd: We should have a program for HD patients that helps ensure they receive necessary treatments for their symptoms

Craufurd: Should HD mutation carriers regularly see medical professionals?

Craufurd: Some symptoms, like irritability and depression, seem to occur a long time before formal diagnosis of HD

Craufurd: There could be down-sides, as well as up-sides, to pre-symptomatic HD mutation carriers regularly attending HD clinics

Carufurd: Some people 'cope by denial', avoiding thinking about HD, and those people may have difficulty \ being in an HD clinic

Craufurd, on balance, thinks that it is beneficial for HD mutation carriers, as well as HD patients, to attend clinics

The final session of the day is focused on the development of 'biomarkers' for HD research

Biomarkers, measurable characteristics that can be quantified in people, are things like like brain imaging, or blood markers

We'd like to have things that are readily measurable in people that allow us to track the progression of HD more reliably

After years of work, studies like TRACK and PREDICT have provided a large number of potential biomarkers for HD

Blair Leavitt discusses how the findings of TRACK and PREDICT are already informing the design of new drug trials

Leavitt: if we follow HD patients for as long as 2 years, there are clear changes that can help inform clinical trials

Leavitt is interested in a technique called magnetic resonance spectroscopy, which measures the levels of specific brain chemicals

Leavitt's team is developing these techniques to look at chemicals in HD patient brains

Specific brain chemicals are increased in the brains of HD patients over time, while others decrease

Some of these changes are even observed in the brains of HD mutation carriers that do not yet have disease

Leavitt's team has also looked at the levels of specific chemicals in the blood that suggest increased inflammation in HD

Leavitt:proposed biomarkers should be measured by more than one lab, to ensure that they're reproducible before being used in trials

Finally, **Beth Borowsky**, of the CHDI foundation, outlines the challenges of using biomarkers in clinical trials

BB: The point of biomarkers is to provide information that is useful in the clinic - either to tell you about HD or a drug effect

BB: Some biomarkers show how HD progress over time

BB: Other biomarkers let you measure the effect of a drug - for example, does your drug get into the right part of the brain?

BB: Drug development is a very long, and very expensive, process, even after all the basic lab work is complete

BB: Every trial ends in one of 3 ways - positive, negative or inconclusive. How can we use biomarkers to prevent inconclusive ones?

BB: We have a huge number of tools in our toolkit right now, thanks to years of study of HD patients. Which ones are most useful?

BB: In other diseases, things that were thought to be biomarkers turned out not to work in clinical trials- we have to be careful

BB: Until we have more clinical trials, we won't know which proposed HD biomarkers actually tell us about the progress of HD

BB: Validating biomarkers is a kind of chicken and egg problem - we can't prove they work until we have drugs that work!

BB: New trials, and upcoming trials, should include exploration of biomarkers as part of their design

BB: Trials of gene silencing which rely on invasive delivery, require good markers to prove that the drugs got where they need to go

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GLOSSARY

CSF A clear fluid produced by the brain, which surrounds and supports the brain and spinal cord.

magnetic resonance A technique using powerful magnetic fields to produce detailed images of the brain in living humans and animals

gene silencing An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein

observational A study in which measurements are made in human volunteers but no experimental drug or treatment is given

inflammation Activation of the immune system, thought to be involved in the HD disease process

CAG repeat The stretch of DNA at the beginning of the HD gene, which contains the sequence CAG repeated many times, and is abnormally long in people who will develop HD

kynurenine a chemical similar to kynurenic acid (Kyna)

KMO kynurenine mono-oxygenase, an enzyme that controls the balance of harmful and protective chemicals resulting from the breakdown of proteins

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