EuroBuzz 2014: day three

Our third and final report on the 2014 European Huntington's Disease Network meeting in Barcelona

By Dr Ed Wild on September 21, 2014

Edited by Dr Jeff Carroll

Our final report from the European HD Network meeting. For the first time, video of many presentations, including our 'EuroBuzz' sessions will be made available online shortly.

08:09 - This mornings EHDN session focuses on one of the most exciting therapeutic options of all - Huntingtin lowering

08:10 - **Leslie Thompson** is interested in how small changes to the huntingtin protein itself control it's turnover. If we can understand how cells normally get rid of huntingtin, maybe we can increase the process with drugs. Thompson's team is exploring a key pathway that cells use to get rid of huntingtin called "sumo-ylation" (really!). Another way to benefit cells with the HD mutation is to help them make proteins more carefully. Cells make proteins to do most of their work, which have to fold into complex shapes, this process can sometimes go wrong. A normal part of the cell protein-folding machinery is called TRIC. Giving cells more TRIC protects them from the HD mutation. Thompson is now exploring different ways to get TRIC into the brain, to understand whether this could be a therapeutic option for HD.

Leslie Thompson of UC Irvine was among today's presenters. Her team studies the mutant huntingtin protein and ways to reduce the harm it causes

08:27 - **Doug Macdonald** of the CHDI foundation has been working for a long time on Huntingtin lowering therapeutics. Huntingtin lowering is one of the most exciting potential therapies for HD. The mutant HD gene gets used by the cell to make a copy we call a "message RNA", which gets turned into a protein. Confused? Surprisingly, there are now therapies that can attack each of these levels - gene, message and protein, to try and get rid of it. So which approach will work best to reduce the symptoms of HD? CHDI is, with other investigators, trying a number of approaches. One issue with all these approaches is how will we know if we've reduced huntingtin levels? Amazing new approaches allow researchers to count individual copies of the huntingtin protein. Because they're so sensitive, these techniques let scientists measure huntingtin in cerebrospinal fluid, which bathes the brain. If we can get drugs into the brain to lower HTT, maybe we'll be

able to ensure it's working by collecting spinal fluid. Donating spinal fluid is not trivial, but it's a lot easier than donating your brain! CHDI is working to develop high tech measures of brain function that work in HD mice, in hopes they'll also work in people.

08:51 - **Jang-Ho Cha**, of Merck and the HDSA, addresses the conference on the challenge of clinical trials in HD. "Our finish line: Treatments for HD. What are we going to require to get to this point?" Without a path through clinical trials, we won't get effective treatments. There's two kinds of research we need to get to clinical trials - "clinical" work in people, and "pre-clinical" work in the lab. Along the way, there'll be impossible seeming gaps, but if we're clever we'll get across. Once we figure out how to solve impossible seeming problems for one trial, the solutions will help speed future ones. The first phase of testing a drug is a 'phase 1' trial. These trials are just to establish a drug is safe and well-tolerated. Biomarkers, measurable traits that can be measured in people, help keep HD drug developers 'on the trail'. Drug development for multiple sclerosis was accelerated by the development of MRI-based biomarkers. This rapid speeding of trials in MS has led to 14 treatments for this previously untreatable disease. What is 'phase 2' study? A study designed to provide some "proof of concept" that a drug works. We have to think differently about drugs designed to improve HD symptoms and those we think might actually prevent the disease. Better ways of quantifying HD symptoms will lead to smaller, faster and cheaper trials. A 'phase 3' trial is designed to provide 'pivotal' evidence that a drug works, and can lead to its approval. "No patients, no trials". An engaged and informed HD community is required to complete the clinical trials we need.

10:10 - **Prof Landwehrmeyer**'s thoughts on coping with disappointment and frustration, quoting Churchill - "The route to success is to go from failure to failure with undiminished enthusiasm"

10:22 - Landwehrmeyer tells us: We've been saying "The drugs are coming" for years - it's finally happening

> "We're on the verge of having treatments that really might work – Jang-Ho Cha"

The authors have no conflicts of interest to declare. For more information about our disclosure policy see our FAQ...

Glossary

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

huntingtin protein The protein produced by the HD gene.

multiple sclerosis a disease of the brain and spinal cord, in which episodes of inflammation cause damage. Unlike Huntington's disease, MS isn't genetically inherited.

therapeutics treatments

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

HTT one abbreviation for the gene that causes Huntington's disease. The same gene is also called HD and IT-15

RNA the chemical, similar to DNA, that makes up the 'message' molecules that cells use as

working copies of genes, when manufacturing proteins.