EuroBuzz 2014 Video, day one

Video of our first live session at the European Huntington's Disease Network Meeting.

By Professor Ed Wild | **October 10, 2014** | **Edited by Dr Jeff Carroll**

We present the video of Ed and Jeff's review of first day's science at the European HD Network meeting in Barcelona.

ANNOUNCER: Ladies and gentlemen, welcome to EuroBuzz. Please welcome your hosts Ed Wild and Jeff Carroll. [Applause]

JEFF: This is my good side.

ED: Good evening. Are we standing the right way round? No, we stand the other way around, don't we?

JEFF: That's better.

ED: Europe, America, like a World map. That's how you know who's who because there's no other way. So, good evening. My name is Ed Wild. I'm a Huntington's disease researcher and neurologist from London.

JEFF: My name is Jeff Carroll. I am a Huntington's researcher as well but also a Huntington's disease family member. You're here us tonight for two reasons really. One of which is that there are several hundred family members in the audience, which is wonderful, and while they heard all the words from the scientists' mouths today, they might not have understood every single one of them per se, and also because we're going to try to bring the excitement

of what we saw today to a broader Huntington's community audience who weren't able to make it to Barcelona via video that's being taken. So thank you for participating in that.

ED: And this is all part of our broader effort to make Huntington's disease research news, and the excitement that rightly accompanies it, accessible to the entire global HD community. So our HDBuzz project aims to bring research news in plain language to anybody who's interesting in HD.

JEFF: And speaking of HDBuzz, we wanted to take a chance while we were in Spain to thank the hard work of our Spanish and other European language translators who have dedicated really countless hours to making sure that Huntington's disease research news on HDBuzz is available not just to English speakers who, we realise, not everyone in the world speaks English, much to my dismay and so families across Europe and in fact, across the world, are able to do that and so, if we could just take a minute. I know there're a lot of translators here. Translators, if you ever translated an HDBuzz story could you please stand up?

ED: Or make a noise of some kind in your native language. [Applause]

JEFF: And could you join me in a round of applause. Thank you very much. [Applause]

JEFF: Thank you.

ED: I, for one, am very glad that, as a result of the events over night we don't have to set up a new Scottish language version of HDBuzz [crowd reacts]

ED: Phew, okay. So I'm not getting back into the UK. So, what we're here to do is give… We have a fairly brief session today and a slightly longer session tomorrow and what we want to do is give you some brief messages [laughter]

ED: some of the themes that have struck us as exciting throughout the day. I would be remiss if I didn't point out that obviously the most exciting talk of the day was from my boss, Professor Sarah Tabrizi. [Laughter]

ED: The author has no conflicts of interest to declare. [Laughter]

ED: Sarah gave a talk about the natural history of HD, in other words, what we know about HD and how it affects humans so not exactly a small topic to cover. One of the things that she said though, struck me, struck a chord with me and really resonated with how I few HD, she said that she hoped that and was optimistic that Huntington's disease would be turned into a treatable or even preventable disease within her professional lifetime and I feel exactly the same way. In fact, Jeff allows me to go slightly further with that thought. When I talk to patients and families, I say that HD is the most curable incurable brain disease. What I mean by that is that unlike other brain diseases like Alzheimer's or Parkinson's, we know exactly what causes HD in every single person who has it. It's the mutant Huntington gene. Everyone with that mutation will get HD unless we can do something about it. Now that's

obviously bad news for the people who have that mutation, but it's great news for figuring out how to develop treatment because we know exactly what we need to do in order to prevent HD. We need to stop that gene from having it's bad effect. So we have this huge head-start on other tough brain diseases and that's a real asset. I think that's one of many reasons why I and, I assume everyone else in this room, is optimistic that we can develop effective treatments for HD. Speaking about this also gives me the chance to remind us of Sarah's slide which she presented. It's very much been the talk of the conference. This is a map of the connected brain areas in HD and it gives me the opportunity to say what everyone is thinking which is that we all admire Sarah Tabrizi's balls. [Laughter]

ED: Jeff.

JEFF: Moving right along. [Laughter]

JEFF: I would say that another theme from this meeting so far is the real matriation of technology. So this was a field that was carried along for a long time by individual researchers, individual clinicians figuring things out on their own, working in their own labs and these networks, that have been established recently and are forming and really maturing, have been incredible to see the progress of. And not just the sophistication of the clinical networks that exist to bring together data on Huntington's patients from around the world, like ENROLL which was discussed by Bernhard Landwehrmeyer which now has over a hundred sites across the world and thousands of patients enrolled, but also the matriation of technology. So rather than individual researchers working in their lab to analyse one DNA sequence at a time, we've heard the results of studies where literally millions of sequences of DNA are analysed on a single chip. So there's the coming together on the one hand of the clinical networks being very mature and very well developed and also the hardware, the technology, the computers, the MRI scanners that are being used in really novel and exciting ways.

JEFF: The final thing I wanted to highlight as one of the themes of the day has been - it came home to me during a session this afternoon about KMO inhibitor drugs. Now these are basically drugs that are being worked on by CHDI Foundation, among others, and the aim of these drugs is to attempt to restore the balance of helpful and harmful chemicals in the brain. The progress is... the work is going really well but what struck me was how the make up of the people who are contributing to meetings like this has changed over the past 10 years or so. What we hear now is that, as many more contributions from people who are experts at designing drugs, tweaking molecules, making a drug hit a particular target and then taking those drugs forward, through the process of testing in models, model systems and then into clinical trials, I think that's a real asset to this community and it's something that's become much more of a theme over the past few years and I think that's really going to be helpful when it comes to taking these drugs to patients and making the difference that we all want to make. So that was a really encouraging session. So the thing we wanted to focus on though, for the majority of our time remaining, was a specific finding which had us both pretty excited and we think is worth drawing specific attention to for the people who

are watching online as well, and this was from the genetic modifier session this morning. So, Jeff, what is a 'genetic modifier'?

JEFF: So in the context of Huntington's disease, we know that every patient with Huntington's disease fundamentally has the same mutation. It was mapped in '93 and we've known since then, with certainty, what causes, genetically what causes Huntington's disease in every person. But, as HD family members will know, there's quite a lot of variation in when people experience HD symptoms. And for a given severity of mutation you can predict roughly when someone will get symptoms but some people will, in fact, have symptoms earlier and some will have symptoms later. And if you look really hard at families, which researchers in the room have done, you realise that that variability and how soon you experience symptoms, for a given mutation, is itself heritable. So to a biologist, a geneticist, when something is heritable it means it's likely genetic so there are genetic differences in people that determine whether they have a relatively early or a relatively late on-set of Huntington's disease. So that's what we're searching for. Our so-called 'genetic modifiers' of when someone would get Huntington's disease. So what was discussed today in a session was the results of something called a GWA study so Ed, what is a GWAS?

ED: So yeah, a GWA stands for a Genome-wide Association study and essentially this involves two very large numbers. The first is a large number of patients who donate their blood and the DNA is extracted from it and then it's all collected together in one place and the study that was presented today by Leslie Jones and Jong-Min-Lee was an international collaboration involving DNA from over 4,000 people. The second big number is the number of differences that are looked for between the DNA of all of these people and state of the art genetic technology now enables us to look for millions of these differences all in one experiment. And in this experiment they'll take over eight million spelling differences in the DNA of these subjects. So that's a Genome-wide Association study. The power of it comes from the number of genes that are looked at and the number of patients and the combination of the two enables the important stuff to rise above the stuff that's just sort of noise in the genetic data. So what, what did they find?

JEFF: Well I think, exciting for everyone in the room, they found what we call "hits." They found they results. They found places that, with great mathematical certainty, we can say there are sequences here that are associated with if you have one version of this sequence, you may have an earlier or a later on-set of disease. And, in fact, they found more than location that looks likely to contribute. Interestingly to me, they found genetic variations that both make you have an earlier, as well as other variants, that make you have an earlier, on-set of disease. So this is really informative for future studies and is a result of years of hard work and lots of money. We don't know yet exactly what those changes mean but there were some tentative discussion this morning and some early-days data that suggests that part of the process that might be going wrong - the implication from these changes - is that it might be the really important process of repairing DNA which every cell has to do to stay healthy; and other mouse data that already existed had suggested this process might

go wrong in Huntington's and so this is a really nice confirmation of that hypothesis. So that's really good basic science but, Ed, maybe you can describe to people why should we care? How does this actually inform developing therapies?

ED: Yeah, I mean, it's an important point because fundamentally we can't change peoples' DNA. So we're talking about people who have genes in their bodies, which make it likely that they'll get earlier or later on-set than expected of Huntington's disease. We can't, unfortunately yet, edit peoples' DNA although that is actually something that's being worked on. The immediate importance of these findings though is that it's real data from thousands of patients that tells us that these are real life things that change how Huntington's behaves in real patients. The whole experiment the prominent geneticist, Jim Gusella says, the whole experiment is contained in that DNA molecule and Mother Nature has done the experiment for us. So the importance of these findings is that it tells us that these are really important, real life, changes and, essentially, if it's the DNA repair system that's affected by these genetic differences then lots of attention then needs to be focused on figuring out how those differences make, how those differences alter the on-set of HD and then directing drug development efforts towards that to see if we can, hopefully, reproduce with a pill some of the helpful changes that DNA differences are making or block some of the harmful effects of those differences. So it's a really important step on the road and the next steps are no less important but it's really cool because this is work that's been in progress since 2008, and it was entirely possible that it would come up with nothing, but, in fact, it's come up with some really useful leads.

JEFF: That's exciting. So this wouldn't be an HDBuzz thing if we didn't give you something totally trivial to go along with your, you know, healthy dose of science. So we've done a little Barcelona quiz so that you guys can leave with something useless. Okay, so you can just yell out. We don't have time do to anything fancy. Who knows who's in this famous Barcelona statue? Just holler.

AUDIENCE: Christopher Columbus.

JEFF: Columbus.

ED: Did someone say Al Gore? [Laughter]

JEFF: Okay, what do you think he's pointing at?

AUDIENCE: America. Majorca.

ED: Someone said Majorca. Most people said America.

JEFF: In fact, he's pointing in the opposite direction of America for reasons that no one understands apparently. So we don't know if it's just bad geography on behalf of the sculptor or whatever. Make up your own story. But there's your fun Barcelona fact for the day. [Clapping]

ED: A round of applause for Christopher Columbus, there. [Laughter and applause]

ED: He has a lot of places named after him already. He doesn't need our applause. So that's it from us for tonight. Tomorrow night, as I said, we'll have a slightly longer session and we have a kind of fun treat planned for you all. The... one thing that we've been asked to point out is that there's going to be Tapas. The guided poster tour starts at 6:30. The streaming of "Alive and Well" the film starring, oh, not starring Jeff Carroll. [Laughter]

ED: The film that features Michael Hayden among other people, that's being screened in this room and another documentary "Do You Really Want To Know?" which, unfortunately, does contain Jeff Carroll, that's being screened one floor down in the auditorium downstairs. So that's it from us. I will say Hasta La Vista, baby! And we'll see you tomorrow. [Applause]

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

GLOSSARY

genome the name given to all the genes that contain the complete instructions for making a person or other organism

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

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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