EuroBuzz 2014 Video, day two

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

By Dr Jeff Carroll on October 10, 2014
Edited by Dr Ed Wild

Ed and Jeff present the second day's science at the EHDN meeting in Barcelona. Features a clinical trials roundup, an exclusive interview with Prof Sarah Tabrizi about the first trial of a huntingtin lowering 'gene silencing' drug, and a surprise for EHDN president Prof Bernhard Landwehrmeyer.

PRESENTER: Ladies and gentlemen, please welcome your hosts for the second and final instalment of Eurobuzz: Dr Jeff Carroll and and Dr Ed Wild [Applause]

ED: Good evening. Thank you and welcome once again – and thank you to the introducer guy; I think he's awesome [Laughter]

ED: I just love his voice. He's got a real talent. I must find out who he is. I'm going to stop that because of the risk of epilepsy [Laughter]

ED: Welcome back. My name is Ed and this is, as I say, as the introducer said, the second and final night that we'll be presenting our digests of the science that has been presented here, for the benefit of everyone in the audience and everyone watching at home on the internet via HD Buzz.

JEFF: Hi, everybody. My name is Jeff Carroll. Some of you may not know we've been tweeting live throughout all the sessions. I'm sorry to tell you now, after you missed the chance to hang out by the pool and keep up with what was going on, but you can follow us tomorrow if you like

at HD Buzz feed. We're also at the end of each day posting a digest, so if you see something and think, "That's cool, I want to tell my family about it," yesterday's stories are already up on HDBuzz.net and tonight's will be done by the time you all finish drinking yourselves silly at what sounds like a lot of drinking events [Laughter]

ED: As those of you in the auditorium will have just heard, this is the 10th anniversary of the European Huntington's Disease Network, but for the benefit of the people who are not physically here but are watching at home, we thought it would be cool to explore some of the things that that means. Ten years of anything is a pretty good achievement, I guess, but what's so special about this network? What's the point of a network? What is the Euro HD network? Put simply, as simple as it needs to be for me to understand it, it's a network of professionals linked to family members, whose aim – whose shared aim – is to try and improve the lives of people living with and living at risk of Huntington's disease. The professional side is clinicians, so that's people involved in patient care – doctors, nurses, physiotherapists, genetic counsellors and lots of other health professionals. There are also scientists, so people who work in labs and in other scientific settings doing research but who don't necessarily interact directly with patients. That's the core of the network, but it's also closely linked to the patient organisations from across Europe. It's not just European either; the network has links with other networks across the world, like the Huntington Study Group and various new networks, like the South American and the Chinese networks – and there are honorary members, so a lot of people who contribute to meetings like this aren't necessarily from Europe, but they have stuff that Europeans need to hear about and there are a lot of collaborations, both within and beyond Europe. What has been achieved in 10 years? That sounds awesome, but what has actually happened? Jamie Levey very kindly supplied me with some numbers. We like numbers. There are over 2,000 members, over 2,000 professionals involved in HD care and research in Europe, and that includes the honorary members as well. In 20 countries the Euro HD Network has established 159 study sites. Many of those are multidisciplinary clinics that care directly for patients, and the contributions of Euro HD Network have been crucial for the setting up of those clinics, so that's a direct contribution to the care of HD patients and family members now – in addition, of course, to the fact that those are now 159 places where people can go to to take part in HD research, which is awesome. There's a seed funding scheme. This is a way that the Euro HD Network strategically donates money, in the form of funding, to scientists who want to do research that other people wouldn't fund. HD is a relatively rare condition, but a small amount of money to generate what we call 'pilot data' enables people to then set up a bigger project that, because the principle has been shown to work, can then get funding from a bigger organisation. That sounds cool, but what has that achieved? Sixty peer-reviewed publications have come from that seed funding scheme alone. The intangibles there are that the scheme… I know for a fact, as an outgoing member of the Scientific and Bioethics Advisory Committee, that that scheme has brought in researchers from other fields who would otherwise not be involved in Huntington's disease. Then the families do their work because once you meet HD family members, it's very difficult to leave HD research. Bringing in researchers from outside the field to take part in research that's funded by Euro HD has made a big difference and has brought into the field lots

of prominent researchers who would otherwise not be here. What about drug trials? Eight clinical trials have been supported by the Euro HD infrastructure and expertise – and as we're about to hear, there are more on the way. It's an extremely exciting time. How many people have been touched by the Euro HD Network? It's very difficult to say, but if we look just at recruitment into the clinical studies that EHDN has conducted, over 13,000 family members have contributed to those research projects – principally REGISTRY and ENROLL-HD. Again, many more will continue to contribute to the research in the future. Also on the research side, over 10,000 biological samples have been collected from HD family members, and those are really critical to our research efforts. As I say, there are intangibles, so the influence of the network stretches far beyond these numbers. You just have to take it from me, I guess, that networks like this and similar networks, the global HD research community is one of the biggest assets that we have. Through working together and sharing our information and our expertise freely, it dramatically accelerates the research that's so crucial to families.

JEFF: The point of all of this research, obviously, is to develop treatments that make a difference in the lives of Huntington's disease patients. Those of us that are from HD families or speak often with HD families and interact with them in their care will be familiar with the refrain of "What's taking so long?" – the disappointment that often comes along with how tedious and slow the development of a drug can be. So, Ed and I, each day at this conference, wanted to try to find a highlight. Today's highlight was really obvious and I hope everyone will agree with me that hearing about not one, not two, not three, not for, but five new clinical trials happening, or just starting, was certainly the highlight of the day.

ED: Yes, so we're just going to briefly mention them for the benefit of anyone who wasn't in that session. The first trial that we want to mention is supported by Teva Pharmaceuticals and it concerns a drug called pridopidine, also known as Huntexil, and for those with long memories also formerly known as ACR16. This is a drug which has been tested in two clinical trials already: the HART study and the MermaiHD study. In each of those trials, there was a suggestion that the drug was helpful for the movement problems of people with Huntington's disease. However, those trials were not conclusive on their own enough to get the drug licensed and so the Pride-HD study, which is already enrolling and is going to ramp up very rapidly across the world, in fact, is going to involve larger numbers of people and higher doses of the drug, to establish whether this drug can obtain a role in the movement problems of people with HD.

JEFF: Ralf Reilmann joined us to talk about another new trial, also run in conjunction with the support of Teva Pharmaceuticals, designed to test whether a drug called Laquinimod might be useful in Huntington's disease. This is a drug that has already been tested in patients with multiple sclerosis, so we have a lot more history about the drug's safety and potential adverse effects that might have happened and didn't from those trials, so that's really good news for moving quickly into trials with Huntington's. This trial is not yet recruiting but will be soon to see whether this drug, which is designed to block a process called 'inflammation', which is sort of the body's self defence system – and we know that this defence system is sort of amped up in the

brains of Huntington's disease patients; that has been seen – and so the question is whether this drug can dampen that down and therefore improve the symptoms of Huntington's disease. We don't know that yet, but we soon will, thanks to the trial Legato-HD.

ED: The third study we wanted to mention was a trial of deep brain stimulation, or DBS. This involves drilling tiny holes in the scull of people.

JEFF: Just tiny ones.

ED: Just miniscule holes in the head, and inserting tiny electrodes very carefully into the brain and then delivering tiny quantities of electricity to the brain [Laughter]

JEFF: It all sounds very safe.

ED: It is safe, and we know this because it's actually reasonably widely used already in the field of Parkinson's disease, which is another movement disorder problem that causes brain degeneration and movement problems, and it's a treatment that's increasingly being applied to other disease areas as well. A Euro HD-funded and supported trial, a small-scale trial, has already shown some potential for this treatment for the movement problems that are seen in Huntington's disease, particularly the chorea, the unwanted movements. Again, getting a radical treatment like this demonstrated to be safe is a big task and so it was very gratifying today to hear about the progress of this multicentre DBS trial – again supported by Euro HD – which aims to look into this question more definitively and will also, hopefully, give us an idea of which patients stand to benefit the most from this treatment.

JEFF: Cristina Sampaio, the Chief Clinical Officer of the CHDI Foundation, joined us to talk about not one but several trials being planned or started to test drugs that block a little brain machine called phosphodiesterase 10, or PDE10. The details are a bit complex, even for neuroscientists, but the net effect of these drugs – at least in mice, where it has been looked at in great detail – is that communication between brain cells, which we know breaks down in the brains of people who have Huntington's disease, seems to be helped. There are two pharmaceutical companies, Omeros and Pfizer, who have drugs that block this PDE10 machine and that will be tested in Huntington's disease patients to see if this is beneficial, so there are not one but several trials starting or happening to test PDE 10 inhibitors in Huntington's patients.

ED: The final trial that we wanted to cover we were actually going to make the subject of a special interview, because I think it's a trial that has been long-awaited and it's a trial that deals really with Huntington's – aims to deal with Huntington's disease – in a very fundamental way, because it's aiming to treat the known cause of the problem, which is the Huntington's disease gene and the mutant protein. I won't go into detail, because I want the person we're going to interview to go into it. The technique is known as 'huntingtin lowering', sometimes referred to as 'gene silencing', but we're kind of moving towards calling it 'huntingtin lowering' because it's slightly more precise. She's my boss, so I'm going to keep completely silent.

JEFF: Yes, right.

ED: If you can imagine such a thing [Laughter]

ED: You may see my head explode or my ears bleeding because I want to speak but will try not to. Please welcome my boss and Huntington's disease researcher from University College London, Professor Sarah Tabrizi [Applause]

SARAH: I think I have to start by saying that no-one can be your boss, Ed [Laughter]

SARAH: You're unbossable, but in a good way.

JEFF: Thank you, Sarah. This is super cool news, but we haven't shared any details with the folks at home, so what is this trial, this first trial of huntingtin lowering, what is it structured to do?

SARAH: This is a first-into-human study of a molecule or a drug therapy that is looking to try and lower huntingtin. It's a DNA-like molecule that binds to the huntingtin message and lowers then the huntingtin protein.

JEFF: Okay, so we have the huntingtin gene that everyone has a mutated copy who will develop Huntington's disease, there's this intermediate message step, and then there's the huntingtin protein, which we think is the bad guy. This drug blocks that middle step, the message.

SARAH: It does.

JEFF: Okay, and so what are the drugs called, what type of drugs are they?

SARAH: It's an antisense oligonucleotide.

JEFF: Antisense oligonucleotide.

SARAH: ASO, and the name of the drug is ASO Huntingtin Rx.

JEFF: Snappy [Laughter]

SARAH: One of the reasons we wanted to discuss this with you is that unlike some of the other drugs that are being tested, which are more traditional molecules you take as a pill, those of us who study these things know that ASOs, as these large DNA molecules, are a little more difficult to get where they need to be, so what's the plan for delivery?

SARAH: This drug is going to be delivered via lumbar puncture. This is what we call 'intrathecal' delivery and so it's a lumbar puncture into the lower spinal cord.

JEFF: That sounds like a big deal.

SARAH: Actually, it's not into the lower spinal cord; it's into the lower lumbar region.

JEFF: Just where there's fluid space.

SARAH: Where the lumbar spinal cord ends, where there's a fluid space, yes.

JEFF: Okay, so even if there's no spinal cord there, that still seems like kind of a big deal. Is this a routine procedure or something we should be worried about?

SARAH: This is very commonly used in oncology – in cancer therapy – so, for over 20 years they've been giving, via a lumbar puncture, what's called 'intrathecal' delivery of agents to treat cancer. In oncology intrathecal delivery is routine and there are many years of established guidelines for intrathecal delivery of substances. It's also used commonly and many of you who've had children have had an epidural, and an epidural is a delivery of anaesthetic into the lumbar region to numb the area. In anaesthetics, in pain relief, and in many other neurological diseases, and in oncology, it's a very common form of administration, so many years of experience with this form of administration.

JEFF: So, childbirth, or cancer, or other diseases like that? [Laughter]

ED: You're in so much trouble with your wife.

JEFF: I'm not the physician of the team, so I'm approximating – are treated acutely. You get a tumour, you try to get better; you have a baby, you stop, hopefully. What about Huntington's as a chronic disease, are we going to have to get lumbar punctures every day? What's going to happen?

SARAH: It's a good question. The way that ASO works is that it lasts for about four months. Its onset to lower huntingtin is about four to six weeks and then it lasts for about four months, and at the moment the delivery is going to be every month. It's a single dose at monthly intervals and it's just purely looking at safety. The interval at the moment is once per month and it may be that that interview changes, but it's only a rare dosing.

JEFF: Right, it's not constant.

SARAH: Not every day.

JEFF: You said, "This is a safety trial first and foremost." Obviously, with something this experimental, that's important, but what would be the next steps if this first trial is successful?

SARAH: I want and it's important to emphasise this: that this trial is about safety. It's a first-into-human safety study and many different steps are being taken to ensure that this is a very safe study and we're going to look at safety and tolerability. We're going to be looking at some potential measures or endpoints, and we know from animal model work that switching off or lowering huntingtin for a period of time is highly beneficial. So, if this study we show that is safe and tolerated, then the next phase will be to go into what's called a phase II and then a phase III, which is to look at how effective this drug is at treating Huntington's disease. Then, when we know if that works, then in the future, as in my talk yesterday, in the future, if it reaches phase II and phase III, then it might be that we're able to then give it to people who carry the gene but who are completely well.

JEFF: Try to do disease prevention.

SARAH: This is the beginning of a path along that way. The study Roche is partnering with Isis to take it forward, if it's promising, and safe, and tolerated to a phase II and a phase III.

JEFF: That's great. Thank you very much, Sarah, for joining us [Applause]

ED: I nearly did stay quiet. If you want to find out more about huntingtin lowering or huntingtin gene silencing, we've written tons of articles about it because we've thought it's cool for quite a while. The best place to start is article number 23 on HD Buzz, so check that out if you are interested. We're nearly done, but we've discussed that this is the 10th anniversary of Euro HD Network and the people who are watching at home won't know that Barnard Landwehrmeyer, Professor Landwehrmeyer, esteemed senior neurologist and extremely respected clinician and HD researcher, is stepping down as the head of the Euro HD Network, after 10 years. It was his idea and he's been very much the driving force behind this remarkable network for these 10 years, and so we wanted to pay our own personal Eurobuzz/HD Buzz/Jeff and Ed tribute to Bernard – in the only way we know how, which is through humiliation [Laughter]

ED: Please welcome him to the stage, Professor Bernard Landwehrmeyer [Applause and laughter]

ED: So, Bernie – you don't mind if I call you Bernie – I want to give you a big hug now.

BERNHARD: Aw, so sweet.

ED: Because I love you dearly and because I won't want to hug you in a moment [Laughter]

ED: Yes, we've got time. In 2006, I had a phone call to my mobile from an unknown number in Germany and a man said, "My name is Bernhard Landwehrmeyer and I want to invite you to a workshop about biomarkers for Huntington's disease." I think it was like my second week in the – no, it was 2005 – my second week in the job and I said, "That sounds good. I'd like to go to Paris, but I don't know who you are." Story of my scientific career [Laughter]

ED: So, I phoned Sarah Tabrizi and said, "A man called Bernhard just rang me and said do I want to go to Paris with him. Do you think it's okay?" [Laughter]

ED: She said, "That's Professor Landwehrmeyer. He's very senior and very important, and of course you must go to…" Oh, I'm doing the voice [Laughter and applause]

ED: "Of course you must go." Anyway, that was the start of a beautiful friendship, which is about to end [Laughter]

ED: Bernhard, I want to ask you if you are familiar with the phrase 'Ice Bucket Challenge' [Laughter]

ED: We're not going to make Bernhard do the Ice Bucket Challenge; it's much worse than that [Laughter] Let me show you a video and then you'll know what I'm talking about. There we go. I forgot to do the Bernard slide. Okay, so the Ice Bucket Challenge, this is Donatella Versace experiencing the Ice Bucket Challenge, raising awareness for ALS, or motor neurone disease.

JEFF: Why did you pick this video, Ed? [Laughter]

ED: I don't know; it's just the first one that came to mind. There we go. People get a bucket of water tipped over their heads, and it raises awareness and funds, and it has been hugely successful in doing that. There's a movement in the Huntington's disease community some of you may have heard of called the 'Pie in the Face Challenge' [Laughter]

ED: Give us a cheer if you've done the Pie in the Face Challenge. [Cheering]

ED: Yay. It began in the US and it's certainly gathering momentum. The HDYO folks have been doing it on Facebook and we don't like to be left behind. This is Matt Ellison receiving, for some reason, two pies in the face.

JEFF: From, it must be said, his brand-new wife. I don't know what that means [Laughter]

ED: There we go, that's the sort of thing that happens and the hashtag 'pieinthefaceforHD' is how you track this thing online. I won't so much ask you whether you want to do it as sort of instruct you to stand there, while my accomplice, Dr Yury Seliverstov from Moscow, presents today's 'Barcelona Fact of the Day' [Laughter]

ED: This is the Hesperia Hotel's finest Crema Catalana, which is as close as it gets to a pie in these parts. You have the choice; we're going to de-mic you and then you have the choice of whether you wish you go au naturel or whether you want a towel over your shoulders [Laughter]

ED: I'm going to give the honour to my esteemed friend and colleague, Dr Jeffrey Carroll.

JEFF: Me?

ED: Yes [Laughter]

JEFF: Hang on; this is going to be good.

ED: Because I still need to be able to work in Europe after this [Laughter]

ED: I'm going to step down. We're going to probably endanger the lives of the flamenco dancers who are to follow.

JEFF: There's really no pretty way to do this, Bernard.

ED: Yes, that's the idea. You might have to… If you want to come and video it, run to the front now with your smartphones.

JEFF: There we go. I think the only way is… Wait, wait, wait.

ED: Wait, wait, wait, wait; not yet, not yet, not yet, not yet, not yet.

JEFF: Does anyone want to come video?

ED: [Applause]

ED: Keep clapping, keep clapping and we'll do a countdown. Are we ready?

JEFF: What? You're going to count down?

ED: Ten, nine, eight, seven, six, five, four, three, two, one, pie in the face [Laughter and applause]

JEFF: Get that man a towel.

ED: Come here. Mm, it's delicious; I recommend it. At this point, Jeff thinks we're done.

ED: At this point Jeff thinks we're done, but I've done the challenge, and Barnard's done the challenge, and there's someone else on the stage who has not yet done the challenge – and Yuri brought a spare pie and you've taken your jacket off. May I suggest that you take your microphone off?

JEFF: No, I don't think I will; I think I'll keep it on.

ED: Well then, you have to pay for the microphone because this is not optional.

JEFF: Oh, God.

ED: Would you like to do it, Bernhard?

BERNHARD: Go ahead.

ED: I'll do it – a long time in the desire. Are you ready?

JEFF: No.

ED: I think we need another countdown from ten: ten, nine, eight, seven, six, five, four, three, two, one, pie in the face [Laughter and applause]

ED: Mm, it really is lovely. Well, there we go.

JEFF: That was much more involved.

ED: That, ladies and gentlemen, is how Huntington's disease research works [Laughter]

ED: I think we're probably done here. We'll help clean up the stage. You guys have a great evening. We've been Jeff and Ed. We love Professor Landwehrmeyer, we love Euro HD, and thank you. Goodnight [Applause]

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

Glossary

ASOs A type of gene silencing treatment in which specially designed DNA molecules are used to switch off a gene

deep brain stimulation direct stimulation of the brain using electrical impulses through tiny wires.
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.
Phosphodiesterase a protein that breaks down cyclic-AMP and cyclic-GMP
gene silencing An approach to treating HD that uses targeted molecules to tell cells not to produce the harmful huntingtin protein
inflammation Activation of the immune system, thought to be involved in the HD disease process
phase III The phase in the development of a new treatment where clinical trials are conducted using many patients, to determine whether the treatment is effective
chorea Involuntary, irregular 'fidgety' movements that are common in HD
PDE10 a brain protein that may be a good drug target and biomarker in Huntington's disease. PDE10 is found almost exclusively in parts of the brain where brain cells die in HD.
