Ed

Prof Ed Wild on Huntington’s disease – from genetics to clinical trials

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SPEAKERS

Steve Flemming, Selina Wray, Ed Wild

Steve Flemming 00:01
Hello, and welcome to brain stories. I'm Steve Fleming, and I'm here with my co host, Selena Ray.

Selina Wray 00:08
On brain stories, we aim to provide a behind the scenes profile of the latest and greatest work in neuroscience, highlighting the stories and the scientists who are making this field tech.

Steve Flemming 00:20
We don't just ask about the science, we ask how the scientists got to where they are today, and where they think their field is going in the future.

Selina Wray 00:28
Today, we are joined by Ed Wilde who is a Professor of Neurology at UCL Associate Director of the UCL Huntington's Disease centre, and a consultant neurologist at the National Hospital for neurology

what we're trying to change. So we're basically the the big picture is that ultimately, we want to develop treatments to slow or reverse or even prevent the onset of Huntington's disease in people who have had a positive genetic test. And we do that in a number of ways. And obviously, that's not, that's not something that one person can accomplish. So my bit of training to sort of build bricks in this wall towards or this road towards a cure is to work on biomarkers. So these are kind of measurements that

and one of them in a cage and give them chocolate every day for 10 or 20 years. So the progression of

Selina Wray 30:45
So there are some kind of silver linings potentially, I heard, come in sorry, I don't know.

Ed Wild 30:52
It's a good, but if I may say so. It's, you know, seven years since we gave that first dose of Tommy, nurse, and of course, the nothing stands still. And you know, the great thing about science is that it never stops. It's cumulative. We learn from failures, and we learn from successes, and everything moves us closer. As long as people aren't faking data, everything moves us closer towards our goal. And so in the meantime, several other techniques have been developed and honed and finessed and are now actually in human trials. So two big examples. Number one is gene therapies for Huntington's disease. So gene therapy is a distinct thing where you add an extra gene to a person that is actually an active gene, right. So it's, it's active, and it's producing protein, or producing a gene product. So, you know, it's been a big couple of years for unhealthy viruses. But we can actually take a healthy virus called AAV, or harmless virus called AV scoop out this content, replace it with something else that we've or other drug company, unico has designed. And then in a very long, but very carefully worked out brain operation, we can inject this virus genetically modified virus into the part of the brain that's affected by HD, that then gives the cells the neurons a set of instructions, that turns them into a factory for making a molecule that switches off the Huntington gene. And the good thing about these viruses is that the way they inject their contents into the neuron should be lifelong, the effects should be lifelong. So it's kind of a one off treatment, a one shot treatment, that's that's hard when you first do it, but then you don't have to do anything after that the patient is says is essentially self treating inside the brain. So that trial started in I think, 2019, with very, very small numbers. And it's been slowly, slowly, slowly ramping up. And it's still ongoing. And the good thing about that is that, you know, the, the more people we add to that trial, the more data we have, because everyone who first started getting treated in 2019 is still active in the trial, because the drug, the gene therapy never stops. So we're very optimistic that that is something that will also produce a degree of Huntingtin, lowering that might be helpful. And then the other big thing is the advent of oral Huntingtin, lowering drugs. And so this is basically trying to accomplish the same thing that the injected drug did back in 2015. But in the form of a pill. And, you know, if you told me in 2015, when I was sat there with my needle waiting to stop the first patient in the back, that in seven years, we'd have a pill to do the same thing. You know, I don't I don't know for sure, I probably would have said, well, let's do this for now. And we'll see what happens. But, you know, certainly if I had a choice back then of an injection or a pill, I probably would have gone for the pill, we have to explore all avenues. And we don't yet know what the potential benefits and disadvantages of these pills might be. One big issue is that being a pill, they're probably slightly less specific to the Huntingtin gene. So they can't they can't be made of DNA or RNA. So they have to kind of use other little genetic quirks of the Huntington gene. And that might make them a bit less specific. And the other thing is, we have no idea what the effects might be of switching off the Huntington gene outside the brain, so Huntington in the body. Most people don't really have physical bodily symptoms of HD beyond weight loss. But we don't know what happens if you actually, you know, cause people's bodies to
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sense, using their brains to try and figure out the problem. And, you know, making potentially small iterative c

and one of the people I've been sucking up to happen to be on the panel. I don't know whether it helped or not, but it was certainly nice to see when I got into this very intimidating room and, and I long story short, I got the job. And during that nine month clinical attachment, that's when I met Sarah to breezy in a general neurology clinic, and we kind of really clicked with each other. Personality wise. Someone took me aside, actually one of one of Sarah's friends and colleagues, now Professor Simon Mead, who's a prion disease researcher, he took me aside and said, I heard you might be thinking of getting a job with Sarah Tabrizi. And I said, Yeah, and he said, Well, I just want you to know, she's going places. And that was what he said, you know, you should do whatever is right for you. But Sarah Tabrizi is going places. And that really stuck with me, as you can tell. I mean, am I like 15, more or more years later, and I still remember it. And it's absolutely true. She and she really, she has been an incredibly kind of generous mentor in that she's often passed to me opportunities, you know, talks and collaborations and projects that she could easily have taken on herself. But but it's the selflessness alongside the surpassing accomplishment and intelligence of search breezy, that is really what what, what constitutes the ideal mentor, slash, friend, and colleague.

Selina Wray 52:56
And I, you know, I feel I'm lucky enough to know both you and Sarah read. And actually, when we were discussing, who should we invite as a guest on the podcast we did at one point, think about inviting you both on together as kind of a little double act. But then I thought, No, this is, you know, a bad idea because it would be a five hour long episode.

Ed Wild 53:17
Neither of you would get a word in. Exactly. I'm not even sure there is a microphone on Earth captured that podcast.

Selina Wray 53:24
I was lucky enough to be its own little miniseries. So maybe we need to do one or two.

Steve Flemming 53:30
Yeah, we could do a spin off. Tune in.

Selina Wray 53:38
Yeah, you heard it here first coming to UCL podcast soon. So Ed, I mean, thank you so much for being so generous with your time and sharing your story states honestly be such a fascinating discussion. And I think we could go on, but we should bring things to an end. So I thought, first of all, can we just thank you for joining us? And can we wrap up by picking up on something you said earlier, which is you mentioned you had an interesting fact about sea urchins. And I don't want to leave our listeners in suspense. So can you can we close by you telling us about sea urchins and the relevance to Huntington's

Ed Wild 54:12
always happy to talk about sea urchins? I've gone veggie though, so I can't eat them anymore as part of a Japanese meal. But anyway, so there's this amazing scientist called Elena Cattaneo in Italy, and she spends a lot of her time studying the evolutionary biology of the Huntington gene. And what's

remarkable is that if you look at slime mould, okay, so this is a story about sea urchins that begins with slime mould. dictyostelium, right is the first is the most primordial organism that has a Huntingtin gene. And it's also one of the first organisms that's capable of forming multicellular structures rather than existing as a single cell. So there may be a clue there as to how Huntington is doing what it does, but that the slime mould, Huntington has no CAG at the beginning of it on Like the gene that we talked about earlier, to find the CAG. Back looking back and evolutionary time, you have to start with sea urchins. Okay, so sea urchins are one of the earliest creatures that still exists that has any kind of nervous system. And clearly it's rather rudimentary. So sea urchins do have a nervous system, but the organisms just before them in evolution don't have a nervous system. And amazingly, that coincides with two cagrs, appearing at the beginning of the Huntington gene. So the sea urchin is the first organism in evolutionary biology that has CGS in Huntington gene. And it's also one of the first that has a nervous system, which probably tells you something about how important that Huntington protein is for the nervous system. And then as evolution proceeds, the number of CAG slowly, slowly, slowly creeps up. So like, you know, dogs, I think, have six or eight ckgs. Lower primates, like chimps have, like 10 to 12. And then humans have typically 15 to 20. And then Huntington's disease happens when you have 40, or more. So really, the disease we're studying is a case of a gene trying to get bigger over evolutionary time, and succeeding and in the process, enabling humans to develop this state of the art luxury nervous system that we are blessed with. But the downside is that this tendency of the gene to expand can also happen from one generation to the next. And when that happens, it becomes too much of a good thing. And that's when we start to see Huntington's disease. So big thanks to sea urchins for being that critical piece in the millennia old history of the Huntington gene.

Steve Flemming 56:40
Okay, well, well, CH ins to the Pope. We have covered a lot of ground today. Well, thank you so much and wild for coming on Grey's stories, and we wish you all the very best of luck with the ongoing clinical trials for Huntington's disease. We'd like to thank Matt Wakelin, Maya Sapir and Travis mark for their roles in taking Bray stories from an idea to a fully fledged podcast. We thank Patrick Robinson and UCL digital education for editing and mixing. Please follow us on Twitter at UCL brain stories for updates and information about forthcoming episodes, and we'll see you next time.