

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 and neurosurgery. And EDS research is focused on Huntington's Disease, which we will hear a lot more about in the duration of the podcast. Welcome, Edie. And thanks for joining us today.

00:50

Hi, thanks for having me.

Selina Wray 00:52

So maybe we can just start by hearing kind of, in your own words, in a in a kind of a very brief summary of what your research focuses on.

Ed Wild 01:00

Yeah. So as you said, I study Huntington's disease, mostly. And I've been doing that since about 2005. So Huntington's Disease is a progressive neuro genetic condition, and it's incurable, which is kind of

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 tell us something about what's happening in the brain or body of a person. And so we're looking for things like biomarkers that can predict the onset of Huntington's disease, or can tell us whether someone's HD is progressing quickly or slowly, or whether a treatment that we are testing is working or doing harm or not doing anything. So that's kind of that's kind of my research in a nutshell.

Steve Flemming 02:16

Fantastic. And wondering, just for our audience, whether you could just give us a brief overview of what we know already about the mechanisms behind Huntington's disease, what it is and how it's caused.

Ed Wild 02:27

Yeah, so actually, I've kind of previously described Huntington's disease as the most curable, incurable brain disease. And I think what what distinguishes it from any of the other neurodegenerative diseases like Alzheimer's or Parkinson's is that every case of Huntington's disease has a known cause. And that causes the same in everybody who gets the disease or everyone who's going to get the disease. It was one of the first diseases for which the causative gene was discovered. And that happened in 1993. So, oh, gosh, it's the 30th anniversary. So we've had 30 years of studying this gene and the protein product of the gene, which is called hunting tin, with a ti n at the end. And so you know, that that, we have a really solid starting point for understanding the biology of the disease. Now, unfortunately, that with that very simple starting point, the gene, the RNA, the protein, everything suddenly then gets very complicated and a little bit like all of the other neurodegenerative diseases in that this rogue protein. Although we know exactly what the protein is, that causes the disease, this rogue protein then basically messes up more or less everything in neurons and other brain cells, you know, other microglia, and oligodendrocytes, and so on. So it things find out very rapidly from a simple cause to hundreds of derangements. And so the, I guess what we've been doing for 30 years, what the field has been doing is figuring out which of these arrangements are the most important, and of the important ones, which are the most treatable and druggable. And in at the same time, you know, we've been focusing on this very pinpoint cause of the disease, to try and develop targeted treatments that will engage directly with this very upstream gene, RNA protein bit of the disease, which, you know, if we can find something that works there, it should be relatively clean, and it should be something that would work for everyone, regardless of the kind of balance of the other stuff that's going wrong in their neurons. So in terms of the biology, essentially, the the mutant gene produces a mutant protein, that protein is toxic to cells, and the most visible manifestation of that is that it produces aggregates, little blobs, clumps of protein, and again, this is, you know, strongly echoes what we see in many other neurodegenerative diseases. And like with the other diseases, those those blobs are visible, but it's not clear whether they are are harmful or whether they might be a kind of protective mechanism, you know, hiding more toxic proteins away from the rest of the cell. But one way or another, many things go wrong, the cells start to malfunction, they lose control of their ability to fix themselves, and eventually they give up the ghost and die. And that's what produces the symptoms of HD. And we can see it happening quite clearly on brain scans, MRI scans, for instance, 20 or 25 years before expected onset of the disease, you can see

very subtle shrinkage of parts of the brain called the basal ganglia, the caudate and putamen, which are really important for the control of movement. So and we see that before the development of symptoms later on the symptoms develop. So patients develop involuntary movements, and a form of progressive dementia and behavioural change. So in terms of developing, trying to develop treatments, that's kind of the big picture. Lots of things are being worked on to, to kind of correct some of the more subtle, or the more pathway like derangement, so individual mechanisms that were wrong in cells, but a big focus for me and my colleagues is these kind of targeted genetic treatments or treating the sort of genetic pathways that lead to the disease.

Steve Flemming 06:14

And I mean, be fantastic to Dotto more about the treatments. Later, and I was just wanted to get a sense of the cohorts of people you're studying here, because it feels like such a unique disease in that because it is so strongly genetically linked, you can look much further ahead of time of when symptoms occur. So I'm just wondering, at the moment, if people are getting screened, essentially from childhood? And if they know that they might be at risk for the disease, do they know very early in life? And is it at that point when they start enrolling in in your studies?

Ed Wild 06:53

That's a you might think there's a simple answer, but it's actually very complicated. The so the age of onset of symptoms of ADHD, people can become sick. Anytime from early childhood, you know, two or three years of age into old age, late 90s. And we've seen patients at both ends of that spectrum, most people, the vast majority of people who are going to develop HD do so between the ages of about 30 and 50. So it's in most cases, it's a sort of mid adult life onset condition. And so what that generates is a situation in which many people, the majority of people know that they're at risk of this condition, because of an affected parent. But at the time that they become aware of this knowledge, you know, in their teens, or 20s, or whatever, they, they also have a good reason to expect that they may have several decades of healthy life ahead of them, during which their brain will actually function indistinguishably from someone with no problems, no, no disease. So the genetic test is, in most cases is something that predicts the future. But it does so in a slightly unhelpful way. In other words, it tells you that you will get Huntington's disease at some point, but it doesn't really give you some information about when that's going to happen, not accurately enough to make very precise plans about your life. So in Canada as a consequence of that, and also as a consequence of a lot of the genetic discrimination that exists, and the fact that there is no, currently no treatment to slow the disease. The majority of people who know that risk of HD currently aren't tested. So it's in the UK, it's only about 20% of people who are at risk who have actually had a predictive genetic test. I think this is probably changing very slowly, as as a sense emerges that we you know, that we're making solid progress towards treatments, but those figures are still about accurate. So the short answer to your question is no, we don't we don't generally do predictive tests on anyone under the age of 18. Because it is, you know, it is really, the person's right to make an informed decision as an adult to about whether they wish to get tested and whether they wish to have this knowledge about the future or whether they would rather carry on not knowing and living at risk. When we test children. It's usually because of a clinical change in the child that is suspicious of childhood onset Huntington's disease, things like going off the rails at school or, you know, developing neurological signs or symptoms, that's when we would generally test a child. In the future. If we have a really good treatment, I could easily see us testing, you

know, neonates in you know, on a on a after shortly after birth, in order to give them the treatment, whatever it is, but we're not in that position. Yet. However, we do have large cohorts of very enthusiastic people of all ages. including children, lots of young adults and older adults as well, who either take part in research without having been tested simply on the basis of their at risk status, or are, have had a positive genetic test, and then use that information as part of a decision to take part in research. And those cohorts, particularly of the young adults, who are enrolled in research studies to understand the natural history of the disease and develop to develop biomarkers have have really been instrumental in the progress that we've made towards treatments, because it's really only, you know, the, the unique property of this disease is that we do have this genetic test that will predict exactly who's going to get the disease. And actually, increasingly, we, we think of everyone with that mutation as having Huntington's disease, even if they haven't developed symptoms yet. But what they have is a form of Huntington's disease that maybe confined to cells or, or to, you know, changes on neuro imaging or biomarkers. And that understanding has come from studying people who are young, or far from clinical onset to help understand the very early subtle changes that the disease starts to cause.

Selina Wray 11:10

And so I think it's such a beautiful summary that you're giving us something quite complicated before we maybe talk a little bit about the trials, because I really do want to give you kind of space to talk about those. I just wanted to pick up on something you mentioned, where the test can tell you that you will get Huntington's but it can't tell you when. And so it's not as simple as looking at the age that somebody's parents or other family members develop symptoms. Can you elaborate on kind of that? That area a little bit?

Ed Wild 11:40

Yeah, it's it's super interesting, because HD, like I said, it was one of the first genes for a brain disease that was discovered back in the early 90s. But what was what's special about this particular mutation is that it's not a point mutation. So it's not a single letter substitution, or insertion or deletion, it is a triplet repeat expansion. So the base sequence CAG, in the DNA exists repeated several times in every human being. And there's an interesting side story there if you want to talk about sea urchins. But in humans, we all have two copies of the Huntingtin gene, containing, you know, somewhere between 10 and 20, CAG years. And that's, that's a normal, healthy number. And each of those cagrs is an instruction to add a glutamine residue, amino acid to the Huntington protein when it's being made. So an over evolutionary time, the number of CA G's tends to grow. And there's some suggestion that more CAG makes the cells better at to metabolising, which is probably why this phenomenon exists. In people with Huntington's disease, or people who are going to get Huntington's disease, they generally have 40, or more CAG is, so they have a big expansion in the number of CAG is outside the normal range. And one of the earliest observations, once a gene had been discovered was that more CAG is correlated really well with earlier onset of the disease. So you know, 42, or 44. CAG, is this sort of very common number for an expansion carrier. And those are the people who tend to get the disease between 30 and 50 years. But if you have 70, or 80, CAG, is that is a strong predictor of juvenile or even childhood onset Huntington's disease. And it's a really strong correlation, when you look at 1000s of patients. And there CAG is in the age of onset, however, in that 40 to 50 CAG range, the correlation is there, but the there's a lot of variability. So it's very clear that the CAG is a very important contributor to the age of onset. But but, you know, we've, we've absolutely seen people with the same CAG count

the number of stages, get the disease at 20 years of age, or 80 years of age, there's that much variation, which is why for most people, we're happy to tell them the number of CPGs, and many people are interested. But the next thing we need to say is, this is your cog count, but it's actually not that helpful. Because you might get Huntington's disease in your 20s or 30s. Or you if you're lucky, you might be 70 or 80. And actually, one of the big things that's changed over the past few years is thanks to 10s of 1000s of people giving blood samples over the past couple of decades through the enrol HD study. We have enough DNA samples now to conduct really well powered genome wide association studies. So that's where we, we look for things other than that CAG repeat count, that predict the age of onset or the rate of progression of Huntington's disease. And with that, 10s of 1000s of samples, you start to get really strong signals of genes other than the HD gene, which are influencing the age have onset of Huntington's disease. And so a big discovery in the past few years has been that there are genes whose job is making the machinery that repairs DNA. And tiny changes in those genes can have a big impact on the age of onset of Huntington's disease. And it's something to do with the way that the DNA is repaired in our neurons. If if you have an unfavourable set of little genetic differences, you can actually end up with a DNA repair machinery that repairs the DNA not so well. And in the process of trying to repair it, it actually adds extra cagrs. And as we know more cagrs creates a more toxic protein. So we've got this really interesting mechanism where these DNA repair proteins are now a big focus of the disease and these and the genes that encode them. Because this whole DNA repair machinery turns out to be really important for keeping the CAG in your brain the same size as it was when you were born. And you know, we're hoping that we might be able to actually, therapeutically stop the CAG, from growing, that's called somatic expansion. And if we can do that, we might be able to slow the progression of HD. So that's another kind of really strong genetic lead. But I guess that's the answer to why the age of onset thing is interesting. But like everything in HD, it starts off with a simple concept. And then it immediately gets more complicated. But that's life.

Steve Flemming 16:26

And other other factors outside of the do us study that also predicts age of onset. So I'm thinking if it you mentioned their DNA repair and not allowing the CAG repeats to get too long. So I'm thinking if there are other factors that have been looked at in terms of environmental factors, or is there anything beyond that, that has has been discovered?

Ed Wild 16:50

That's a huge question. And I think the answer is definitely yes, there are definitely things other than genes, things in the environment, and by which we mean, you know, life stuff, right. So diet, exercise, medications, other diseases, you know, what, what colour jumper you whatever that can, that can influence the progression of HD, it's very easy to identify things that can speed up the progression of HD, okay, so, you know, people who have multiple head injuries, people who generally look after their brains poorly, people who abuse alcohol, or are at high risk of cardiovascular disease will tend to have rates of progression of HD that are faster. What we don't have is strong evidence of anything that was in the in the life, stuff that people can do that will slow the progression of HD. And it's not for want of trying, right, but like I say, we have these 10s of 1000s of patients in in cohorts. And we, we study them every year. So we ask them about lifestyle, and medications and so on. And then we follow them prospectively. But the trouble is that, you know, humans are not like mice, it's you can't, you know, get 100 Humans and 100 other humans and put one of them in a cage and give them cheese every day

and one of them in a cage and give them chocolate every day for 10 or 20 years. So the progression of HD is really slow. And the data around lifestyle are so noisy, because there are so many differences from one person to another in terms of what they do in their lives, that it's we just don't yet have the statistical power to be able to confidently say this is good, and this is bad. So unfortunately, the the best advice we can give here is the really boring stuff that comes from other fields. It is exercise is good. Look after your blood vessels, you know, get your blood pressure checked, get your cholesterol checked. Yeah,

Steve Flemming 18:49

don't do that don't do the bad stuff.

Ed Wild 18:51

Yeah, exactly. Probably don't smoke, although we're like, we're not 100% sure about that. But it's it seems bad. And it's definitely bad for blood vessels. And it seems to make sense that healthy blood vessels equals healthy brain. But again, you know, we just don't have the data specific to Huntington's disease to be able to say, you know, this is the advice. So it's something that's being worked on. There's an interesting story, though, that does come from mice, which is this thing about environmental enrichment. And it sounds very posh. But actually what was what the experiment was, was that they took some mice with the HDX mutation, and they they left half of them in cages with sawdust, and half of them they gave them the cardboard in a bit of a toilet roll. And that was the environmental enrichment. And the difference in terms of the onset of the disease symptoms and the rate of progression. The mice that had the cardboard toilet roll tube to play with was as strong as any medication that had been tested in the mice. And so from that it hasn't been replicated in humans because it's very difficult to do but from that, it's really, you know, we have really strong reason to believe that environmental enrichment in other words, having a varied intellectually and physically fulfilling life is probably one of the best ways to safeguard your brain against whatever might be about to happen to it. But in particular, people with ADHD mutation can protect their themselves in that way. This is not me advising everyone to invest in a giant cylinder of cardboard and spend half their time running through it in their living rooms.

Steve Flemming 20:28

If only adults, if only adults, were please so easily my one year old is certainly happy with a cardboard.

Selina Wray 20:37

So I wonder if we could maybe now and ask you to talk a little bit about treatments and the trials that have happened because I know, this is something you've been really deeply involved in. And I know, it's also something that's been a bit of a emotional roller coaster, I think in in some ways, so maybe we can get you to kind of elaborate on that a

Ed Wild 20:57

little. Yeah, roller coaster is right. It's been, it's been a very interesting decade, for treatments in Huntington's disease. So until about 2015, the things that we had tested in HD, because we hadn't figured out mechanisms. And we hadn't, we didn't have great drugs for addressing the known cause of HD. So what we were testing was basically stuff that we thought might be broadly good and healthy for

brain cells. And that was a bunch of stuff that has largely been tested and other diseases, things like creatine coenzyme, Q minocycline, you know, various kind of potentially neuro protective substances. And unfortunately, none of it worked. And that's fine. And that's good to know. But since the late 90s, there's been a huge amount of progress in the field of the targeted therapeutic modulation of DNA and RNA. So in other words, things like RNA interference, where basically, instead of trying to change someone's DNA, we kind of monkey around with the protein manufacturing pipeline at the level of the RNA. So the DNA is a template for the RNA, the RNA is kind of a working copy of the DNA. And actually, the RNA just floats around freely in the cell and is relatively easy to interact with. And in fact, you can make a drug molecule out of DNA or RNA. And that drug molecule because of the way that DNA pairs up one base to another, it's relatively easy now, with advances in chemistry and technology, and so on to make a drug as a DNA RNA that will interact very specifically with the RNA of the gene that you want to interact with, and not other genes. And therefore, you can actually make a kind of custom volume control for any gene, you can turn it up or turn it down, depending on how you approach the the problem. So for us in Huntington's disease, this is where our genetic advantage really gives us a head start, because we know exactly what we need to do, right? This mutant gene is producing a toxic protein. So if we tell ourselves to make less of that protein, all being well, we have every right to expect that that will work, not only to slow the progression of the disease, but also potentially to prevent it. And so that's what we did. And the first of these Huntingtin, lowering drugs that we tested, now goes by the name of Tommy nurse, and at the time, it was called HTT RX. And after at least 10 years of preclinical development by a company called Ioannis pharmaceuticals, we were able to set up the first clinical trial of that drug, and actually by a quirk of destiny, I guess I ended up being the person who gave the first dose of that drug back in September 2015, to a patient that I had known for 10 years. And honestly, she's the Neil Armstrong of Huntington's disease, or maybe the Yuri Gagarin of Huntington's Disease extraordinary. It was the first time this drug has been given to a human being. And what's more, because of the structure of this drug, it's made from genetically so chemically modified DNA, it has to be injected directly into the spine in a lumbar puncture procedure. So we stick a tiny needle into the spine, and inject the drug into that and from there, it spreads up into the brain. We've never done that before with a drug. So it was a kind of the start of a very emotional roller coaster. It went in fine and nothing bad happened. And we we then enrolled i 46 patients in that very first trial. And the main outcome of that trial was safety. In other words, was this drug safe? If we gave four doses a month up. The second thing we were looking for was in the spinal fluid, could we measure the level of the Huntington protein, the mutant Huntingtin protein? And could we show that we had actually successfully told the brain to produce less of that protein. And it took two years and three months, and six days for that result to come through. And but in December 2017, we were able to show that not only had we done it, lowered the protein, but we'd also done it in a, in a way that dramatically exceeded our best hopes for the drug. And it was also what we call dose dependent lowering. In other words, the bigger the dose of drug that was given, the bigger the reduction in Huntington protein. And so this is exactly what we wanted, it was this kind of volume control concept, where we have this really like custom tailorable, degree of Huntington lowering. So that was, you know, kind of big news. We were the lead story on the BBC News at 10, and so on. And it was definitely even now, we look back on it. And we still agree that Well, I think, personally and many other people agreed that it was the it was the best piece of research news, we've had Huntington's disease, certainly since the discovery of the gene in 93. This is where the story gets a little bit sad. So we started a face that we went straight into a phase three trial enrolling 800 people. And at that point, the drug programme had been taken over by Roche

pharmaceuticals. And so we started enrolling into this trial called Generation HD one. And then COVID happened and the Huntington's disease community really came into its own, because in the middle of the very first COVID, lockdown, we still managed to get this 800 person trial fully recruited in record time. And we managed to get the whole trial run, even though there were kind of rolling lock downs all around the world. So we've got fully recruited. But then in March of 2021, the data safety committee that had been looking at the data all along, basically issued a report saying that having looked at the trajectories of the people who were taking the drug, it was clear that they weren't the Detroit was not going to meet its endpoint. And in fact, there was a sign that the people who were on the more frequent doses of drug every eight weeks, were actually doing a bit worse than the people who were on placebo. So the trial was immediately halted. And this happened during what in the UK was another big COVID lockdown, which meant that all we could do was phone our patients and tell them, we couldn't even see them in person. Nor could we even meet with each other as researchers and sort of commiserate in person give each other hugs it were a very huggy community. You know, we've all kind of got skin in the game at this point in terms of our personal, you know, commitment to the field, and we all have friends with HDX, and so on. So it was it was absolutely heartbreaking. Since then, we have been, you know, waiting for the dust to fall, waiting for the data has come out from the trial waiting for the follow up data from the people who had been on drug and things are kind of looking much more optimistic. Now, I think we have a good working hypothesis for what happened, and there's a strong consensus that basically, the number of milligrammes of dose Sorry, the number of milligrammes of drug given was 120, which is a big dose of this particular class of ASO drugs made from DNA, that high dose of DNA injected into the spine appears to trigger something like an inflammatory reaction in the brain. And we see that in the spinal fluid in terms of white cells and protein being released into the spinal fluid. And later on, we see an increase in this protein called neurofilament, which is a marker of neuronal injury and the neurofilament level actually went up in the first six months of treatment. But then, and this is one of the kind of biggest mysteries in the field. Even though people carried on getting the drug, the neuro filament levels started to fall, suggesting that something was improving, but it was improving from a level that was higher than we started with. So needless to say, we then stepped back and said, Well, that might be promising. But like, Wouldn't it be good if the neurofilament never went up in the first place? In other words, if we could start from zero and go down, that would be a sign that we'd actually done something to protect neurons. And so we looked back at the whole data set in a post hoc analysis. And the hypothesis was if people are younger, and with smaller CAG, repeat length, so in other words, they're expected to progress more slowly, their brains might be more resilient, and they might be people who were able to sort of do reasonably well in spite of this early inflammatory response to the drug. And indeed, that's what we saw. And and those that subgroup of people seemed to be on their way to to actually achieving benefit from the drug and we don't, you know, there's no clinical claim Names made from this particular trial. It's a, it's an after the event analysis, it's like, you know, you you do something cool with a pool table and then say I meant to do that the only really counts if you say it in advance, right? So, but it's something that generates a hypothesis. And that hypothesis has now been turned into a design for a new trial of Terminus and where we're testing lower doses and slightly further apart at the beginning of the trial, with the expectation that we will avoid this inflammatory thing and hopefully tap directly into potential benefits from the drug. And that trial actually started enrolling in the USA yesterday, by coincidence, January the 11th, at the time of recording, so that's pretty exciting.

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, unigo 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 produce less Huntington than they normally would. So very exciting times multiple different approaches being tried. And you know, we're not going to stop until we have one thing that works for everybody.

Steve Flemming 34:49

I mean, it's such an amazing story and such an exciting field with obviously huge relevance to people's lives to be working in AI I'm just wondering, from the what the response was amongst the hunting community amongst the 800 people enrolled in that trial when the data safety board made that ruling. And I could imagine people, I guess, having their own emotional rollercoaster surrounding that.

Ed Wild 35:19

Yeah, I mean, I think universally, the reaction was heartbreak, from people in the trial scientists and clinicians involved in the trial and also the whole field, but even if they had no involvement in the trial, because really everyone's in it for the same thing. And even if they're working on their own treatments, they everyone just wants something that works. That heartbreak, then I think, quite rapidly evolved into a sense of enthusiasm for finding out what went wrong. And I've not spoken to anyone who was in that trial, who regrets being in it. And even the people who themselves would acknowledge that they progressed more rapidly than they would have liked. They most of our patients have multiple family members affected by HD, many of them have kids or nieces or nephews who are at risk, and they're all doing it for someone else. And across the board, the reaction was basically, well, I went into this trial, knowing that there might be some risk, this drug is still the drug, the only drug we have that's actually engaged meaningfully with the cause of HD, therefore, it was the right thing to do the trial, knowing what we know, now we might do it differently. And, you know, as a person in the trial, my my contribution, even though it may have left me worse off or didn't help me. My contribution is exactly what it was supposed to be, which is adding to knowledge it obviously, not everyone ends up rapidly being that kind of sanguine, but like I say, I've spoken to lots of people at our site, and others who were involved in that trial. And they're all really glad that they were they they were in it, because they all know a that there was risk, but also be that we, as long as we learn as much as possible, then the trial was worth was worth doing. Absolutely.

Selina Wray 37:13

And I think I think for listeners who maybe aren't familiar with this area, it's also worth saying how you've not only learnt more about how to do Huntington's Disease tap trials, it tells us what we should be doing in other neurodegenerative diseases as well, we're really learning a huge amount about what we might do in outsiders or what we might do in Parkinson's based on what we've, we've kind of the information we've got from this amazing community. And I think, as you said, the community is really at the centre of what you do, and we work extremely closely with them. And I wonder if you might elaborate a little bit on your experience of being part of this patient. Family, clinician scientists community, and I'm particularly interested, for listeners can't see this, but I did recording in his office and over his right shoulder is a framed photo of him meeting the Pope. And I wonder if we, we might talk a bit about how that happened.

Ed Wild 38:11

Yeah, sure. That's such a really good example of how these things kind of come together when everyone pulls in the same direction. I mean, the thing that's clear about HDX, like people, people who have a terrible disease, brain disease will tend to find other people and will form a community so that there are strong communities. For for people with all sorts of brain diseases, I think genetic diseases tend to create a particularly interconnected kind of community because like I say, people are maybe at risk themselves, and want to do what they can to protect their own brain. But they're also, you know,

thinking about the next generation and other family members. And so, you know, the gene for HD was, was actually discovered by a consortium that was put together by one family, the Wechsler family from the US that put together this big consortium of scientists that then discovered the gene. And that's how we've done everything. Everything that we've done in HD has been as a result of really close collaboration between network scientists and researchers, plus network patients and families and actually, increasingly, the people the scientists working on HD are many of them are HD family members themselves, some have tested positive, negative or not tested, but they you know, they're, they've, they're, you know, they really got skin in the game. And so as a, you know, I joined the community in 2005. And I was a young child looking boy, basically, in my mid 20s. And I kind of joined the field because I met Sarah Tabrizi, who is the director of the UCLA HD centre and my sort of friend and mentor, and I met her and she said, Well, I've got this research post and that you might be interested in? Why don't you come to an HD clinic. So I went to one HD clinic and was immediately kind of struck by this sense of community and working together and, and being there for these people who wanted to do whatever they could. But we, they just needed some help from people like me. So then, as you as you sort of get more and more involved in the community, you meet lots of patients in the clinic, but also you meet patients and families at the, at the conferences and things like that. And many scientists who, like I say, have HD in their family. And you know, you look back and you find that actually, this has become really personal. And this has become, well, let me put it this way. This is this quest to find meaningful treatments for this disease has given my life a meaning that it didn't have before, that I'm not sure I could have got any other way. Maybe that's not true. I guess I'll never know. But anyway, we are where we are. And this is now my life's work. So the nature of this interconnected community is that it tends from time to time, it will sort of throw up someone with a particular skill set, who has a personal connection. And one such person is a friend of mine called Charles Sabae, in who used to be an NBC News correspondent, he was a war correspondent. So his face was quite well known, particularly in the US. And about was 22,007, I first met him when he gave her incredible introductory speech at a conference. That was for scientists, but he got this really moving account of his own journey of discovering that he was at risk, and then testing positive for HD. So Charles is always looking for ways to increase awareness. And when Pope Francis was first elected, he made a public announcement that a big focus of his papacy was going to be illness and genetic disease and removing the stigma of genetic disease, because he's a Franciscan. And St. Francis was big into healing, as I understand it. So with it, so Charles got together with colleagues who look after patients in South America where there's a lot more HD than there is in Europe. And they wrote to the Pope's office and said, Would you be willing to have an audience with one Huntington's disease patient, because if we could take a photo of you, and Huntington's patient from Venezuela, that would make a huge impact in terms of the awareness of the disease, and would probably directly lead to improvements in the health of the patients in Venezuela, knowing that the Pope has, you know, caring for patients as a priority. And the pope amazingly wrote back saying, I will not meet with one patient from Venezuela, I will meet 350 people in a formal audience, in the audience hall in the Vatican, and so in, in 2017, in the summer of 2017, of patients and family members, in fact, it was 1000s, gathered in the Vatican. And as a Huntington's Disease researcher, and Doctor, I was incredibly privileged to be invited to be part of that audience. And we were expecting him to give a talk, meet a couple of patients on the front row of the audience and go back into his chambers. He gave this speech in which he said that genetic stigma is wrong. It's not a sin to have a genetic disease. It's not unclean, we must embrace patients with diseases, we must work together. And it must be a focus of all healthcare organisations, including the

Catholic Church, to, to work to reduce the stigma and improve the lives of people with all incurable diseases. And then he stepped off the stage and spent an hour and a half, embracing all of the people in front of the audience, like I say, about 350 people. And there were people sort of throwing themselves at his feet and, you know, trying to kiss his ring. And without exception, he sort of lifted them up and embraced them standing because he just really doesn't want you know, he wants to meet people as equals. Extraordinary. And to see Charles Sabae, my old friend on stage, addressing the Pope, talking about the plight of his family describing how his brother had died in a nursing home having been an extremely high achieving lawyer. I think it's the most moving thing I've ever seen. And I'm not, you know, I'm not an overly sentimental person, but goodness me what an incredible occasion and really, just one example of the ways in which this community always comes together and always surpasses expectations of what a group of human beings living with such a terrible condition can be expected to deliver.

Steve Flemming 44:47

So you can fantastic story and really uplifting as well. And you already mentioned briefly at the start of that story about how you started getting in This field. And you mentioned, working with serendipity at the start of your career here, I'm just wondering whether we can take it a bit earlier than that. Because on this podcast, we also like to hear how the people doing the scientists doing the science got into what they're interested in now. So could you give us a bit of background? Like, what were your steps from studying medicine to then getting into research on on this topic?

Ed Wild 45:28

Well, so when I was at medical school, I guess I was just a very kind of cautious person, I was really interested in surgery. And I used to love going to theatre and getting covered in blood and all that stuff. And being asked to stitch stitch the abdomen up afterwards, and so but then,

Steve Flemming 45:53

did you do your medicine, medical training in London was

Ed Wild 45:58

one of those people, but I was my, just in my defence, my background was, was quite, quite different from sort of stereotypical Amish background, I grew up in a tiny village in the north and single parent family. And, you know, I was I went to a private school, but on a kind of scholarship from the government. And so, for me, the choice of medicine was part partly motivated by financial security, because I'd seen both my parents go through some very difficult financial times in the 80s, and 90s. So Cambridge, let me in. And I just loved it, love the science, love the medicine. You know, it's hard, but it was really fulfilling, got to the clinical side, and like I say, really enjoyed the surgery. But I had a slightly dodgy shoulder. And it was just, it just made me aware that if I became a surgeon, I'd be perpetually reliant on my hands. So if my hands for any reason, like if I lost a finger in a railway accident or something, or whatever, it, you can't do the job anymore. So I thought, well, to be a surgeon, you've got to have a good brain and good hands to be a physician, you only need a good brain, right? You could do it, most of it sitting down and someone else, someone else can examine the patient for you. So that was part of it. But actually, the reality is that when I actually started working on the wards, it was the, it was the physicians that were really doing the things that I had wanted to do, which is in a more general

sense, using their brains to try and figure out the problem. And, you know, making potentially small iterative changes in the lives of people that would and thinking very holistically about the, you know, the patient's home circumstances. And so not that surgeons don't do that. But I think even surgeons would agree, physicians do it more. And so that's what sort of pushed me towards medicine rather than surgery. Then after my first year, in, in the hospitals in the UK, I just wanted a big change. So I moved to New Zealand for a year with my partner, we lived in Wellington, and it was the most wonderful time strongly recommend living in New Zealand. And randomly I was allocated to a job working with neurologists. And it was, it was on my list of things I might be interested in, but I hadn't really settled on anything. And then day one on the wards doing neurology absolutely loved it. It's just a real, you know, kind of Sherlock Holmes kind of specialty, where you really, there's not many symptoms, and signs that a patient can have, right, the you know, blurred vision, headache, weakness, tingling, numbness, there's not that many, it wouldn't take me long to list all of the possible symptoms. But the thing is that combinations that people come in with, and the order and the the way that they affect them is always different. And so even the most kind of mundane sort of headache story will always have to it something unique, and something to get your teeth into. And so that, you know, that's it's that kind of Sherlock Holmes, thrill of the chase thing. And you're also he has a bit of a stereotype for being this specialty of medicine that just documents decline. And you know, from time to time, we'll give a short course of steroids. But actually, during the course of my career, it has completely transformed into something that is actually one of the most active in terms of the development of new treatments. If you look at things like multiple sclerosis, spinal muscular atrophy, these are things that were completely untreatable when I started or the treatments we had were, you know, a bit rubbish. And now that you're diagnosed with MS, and the first thing is, well, which of these 10 Amazing drugs we put you on that will suit you best? Because we know they're all really good at preventing the disease from progressing. So that's, you know, hopefully a trend that will continue. Yeah, so that was really for clinical.

Steve Flemming 49:47

And then and then from there, did you have to and what was the journey from there to Queen Square and meeting Sarah?

Ed Wild 49:56

Yeah, so a guy called Lindsey Haas, who's now no longer with us. sat me down and said we want you to be a neurologist. We think you're good but we want you to go back to go back to London go to Queens square get yourself trained up. Never heard of Queen Square. No reason anyone listening should have heard of it unless they're already interested in neurology but basically Queen Square is kind of a it's a place obviously. But it's also a kind of a metaphor for neurology in the UK basically and I hope that doesn't offend anyone any neurologists who work outside Queen Square but basically it squares the place in the UK complaints directly. It I mean, it is kind of used interchangeably for it's certainly outside the UK, it's, you know, go to Queens square is something that people say when when they what they mean is go and do something with it as intensely neurological. So, I got back to London and spent a year at the Whittington in an archway North London. And while I was there, it happened that the three neurologists who work at the Whittington also had attachments in Queens square. So I basically spent all of my free time sucking up to these neurologists sitting in on their clinics, asking them question after question, probably being super annoying, but in the process, kind of, they told me how to get a neurology job in Queens square, the National Hospital for neurology, neurosurgery. So I applied

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 Sarah 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 cags. 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.