The Synthetic Biology Podcast

Episode 1: Tilo Kunath

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00:03 Stevie: Welcome to the Synthetic Biology Podcast brought to you by the UK Centre for Mammalian Synthetic Biology at the University of Edinburgh.

00:12 Stevie: In this episode, I talk to Tilo Kunath, a reader in Regenerative Neurobiology at the Institute for Stem Cell Research. Tilo tells us about his work on Parkinson's Disease, a progressive neurological condition, and how synthetic biology is helping us to understand and treat this disease.

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00:33 Tilo: A lot of people know someone with Parkinson's, it causes problems with movement, tremors, difficulties with balance but you can also have problems with things like constipation and sleeping problems. So, it's quite a complicated condition. It usually affects people that are a bit older – over 60 or 65 – but not always. It's not really known what causes Parkinson's. An often-central theme for a lot of these Parkinsonian conditions is the aggregation of a small protein called alpha-synuclein. So, we use a term sometimes to describe these conditions as synucleinopathies because this is being aggregated in different types of neurons and in different places in different people. But in some rare cases it is actually caused by a genetic mutation. Almost ten years ago now, we obtained a skin sample from a family in Iowa that had three copies of this gene, alpha-synuclein, this gene that makes this protein. So, this is a genetic condition that has been inherited in this family since the 1800s. 50% of the family members get Parkinson's and, in this case, we do know the cause – it's essentially their genetics. So, we make stem cells from this patient and these stem cells will have this Parkinson's causing mutation and we use skills that we know from developmental biology to make neurons from these stem cells. So now we have neurons with the same genetics as this patient that we can use to study Parkinson's. We try to study what's wrong with these neurons, can we use drugs to help these neurons behave better? So we have essentially created a model of this person's brain – or at least the neurons in their brain – from a skin sample from them. This is a type of technology called Induced Pluripotent Stem Cell technology or IPS cells. This is what the lab started out doing 10 years ago, this is how I got my first foray into Parkinson's disease.

02:35 Stevie: So how exactly do you use stem cell technology in your lab?

02:40 Tilo: We will push the stem cells halfway to making neurons, we call them neural progenitors, so it doesn't quite look like a neuron yet but it's on the route, then transplant them into an animal like a rat. What happens if you transplant good progenitors then they continue on the route to making neurons in the brain of the rat and then they make these neurons, instead of in a dish, in the brain. So this is the type of work that many groups are doing for what's called cell therapy for Parkinson's. So Parkinson's patients lose their dopaminergic neurons, this is what causes their symptoms so this type of experiment is to

replace these neurons surgically. The other area is that we do make the fully-fledged neurons in culture and then we try to look at the aggregation of this protein, alpha-synuclein: How does it aggregate? Where does it aggregate first? Can we measure the aggregation in a very quantitative way? Can we see how it affects the neurons, the energy usage, the signalling of neurons to neurons – synaptic signalling? But also to see if any drugs can reduce the aggregation in the neurons. So this is the disease modelling part of the lab. If we can measure the aggregation of synuclein in human neurons and get really nice quantitative images of these aggregates and then we can introduce a series of drugs, maybe a small collection or a drug library and we can find drugs that reduce these aggregates that can then be used for reducing aggregates in people. I think they are incredibly useful for drug testing and drug screening.

04:17 Stevie: Ok yeah, so when you are talking about cell therapy, what does that actually look like in practice?

04:25 Tilo: So the process would be you take your IPS cells, you put them through this recipe to precursors and then you lift them of the plate and give them to a neurosurgeon and they place them into a part of the brain called the striatum which is where the dopaminergic neurons innervate or interact and this is where the dopamine is need. What's asked of these cells is that they need to survive the surgery and then they need to continue maturing into neurons. That can take time – it has to mature and it has to interact with the host brain and then start making dopamine.

05:00 Stevie: Cell therapy involves putting some new neurons into a patient but are these new neurons susceptible to Parkinson's disease as well?

05:14 Tilo: The answer is absolutely yes. There are a couple of solutions to this creeping in of disease in the graft. We have published some work on how if you knockout the alpha-synuclein gene that the ability of Parkinson's to invade a graft will likely be very low or nil. So this is one possibility to engineer the cells to make them what we call disease-resistant. Some of the work that we are doing now is about what alpha-synuclein is meant to do. This a gene, a protein that everyone has and its certainly not meant to cause Parkinson's, it's not why this gene exists. We've knocked it out of course to make these disease resistant cells, that was our aim, but we are starting to get some insight into what this protein actually does – why does it exist in animals? We have evidence now that it might be important in protecting neurons from viruses. This is very timely finding now with all of this COVID-19, but the neurons that we have knocked out alpha-synuclein in are very susceptible to viral infection. This is something that we didn't expect because we couldn't see anything wrong with the neurons, they made neurons fine without alpha-synuclein, the only thing that we showed was that they don't get Parkinson's, which is a good thing. But they are very susceptible to virus infection which is a bad thing. Maybe getting a handle now on what this protein does – it maybe a protein that protects neurons from viruses when we are young and that's it's job in youth. As we age, it may then start taking on properties that are not positive such as causing Parkinson's disease. So that's an area that we are quite excited about now in the lab – that alpha-synuclein, this Parkinson's gene as we know it – it's original function may be to actually protect us from viruses.

07:03 Stevie: That's really interesting. I look forward to hearing more about that in future. One thing that I was interested in as well is … we have talked about this in relation to your work in the lab, but you are also very involved with charities and you spend time talking to people that actually have Parkinson's disease or family members and those close to people that have Parkinson's disease and I just wonder how that started and how it influences your work?

07:33 Tilo: My involvement with people with Parkinson's happened very organically. As part of my initial funding was from Parkinson's UK, I hosted some lab visits. But then I met this extraordinary individual, Ken Bowler, he was a physics professor at Edinburgh University and on retirement he was diagnosed with Parkinson's. Ken and I became good friends, and we hosted a number of events in our institute explaining research to people with Parkinson's and invited speakers from all throughout Scotland to talk about their research. He started up something called the Edinburgh Parkinson's Lecture which is this huge event that happens once a year. I should also mention Tom Issacs who I didn't meet until much later into my Parkinson's research, but he is an outstanding advocate for Parkinson's research. He started the Cure Parkinson's Trust and he very sadly died a few years ago. There is an award given out for researchers that interact with the patient community called the Tom Issacs Award and it's something that I won last year to my big surprise but that's definitely the most treasured award that I have won in my life. Tom Issacs has been an amazing individual as well.

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08:52 Stevie: Thank you so much to Tilo for telling us all about his work. Be sure to tune in to future episodes of The Synthetic Biology Podcast.

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