Interview Transcript - Dr Andy Tee

Hello, I'm Dr Sharon Ann Holgate, and I'm here at the Institute of Medical Genetics at the University of Cardiff today to talk to Dr Andy Tee who's doing research on BHD Syndrome, which is being funded by the Myrovlytis Trust.

It was through my work with John Blenis working at Harvard on tuberous sclerosis complex that really almost carved my career as such, looking at and piecing together elements of how tuberous sclerosis works. And it's through that that led me on to BHD, because they're so similar that it makes perfect sense for my lab to be trying to understand how BHD works, because we uncovered how TSC worked which then led to clinical trials and other work. Actually, Medical Genetics here at Cardiff are pushing forward, but not just Cardiff, there's lots of other trials within the world- the American groups are doing similar things, but it's almost like a collective research drive in the TS community to push these clinical trials along with the basic research as well. But this is what we want to try to do with BHD.

What BHD research are you currently doing, and how far are you from anything that would get to a point of needing a clinical trial for that?

Well I think we've made progress. We've only been working on BHD for about a year and a half now, but we're taking all the strengths to what we've learnt to do with TS and applying it to BHD. Much of what we're doing with BHD is looking at cell lines. So we have cell lines which are representative of the disease, and we're trying to understand the basic mechanics of what one cell line where they have a mutation in BHD- so this is what causes the disease- how that is different to a normal cell line, because we need to understand what BHD is doing. BHD is a gene that creates a protein within the cell that has a function- we need to know that. We're at the stage with our research, coming back to your question, where we're starting to understand what the function is, but it looks like a very complicated, interesting protein, and it seems to be doing a lot of things. One task which will be the main hurdle just now is to understand what its direct function is, because when it's lost it must do something, but the cell copes or adapts to not having BHD there anymore, so so many things change in the cell, so we're trying to understand what BHD directly affects, as well as other things- because this all leads to cancer progression.

So new experimental work that you're carrying out, are you using classic techniques or are you using any next generation technologies at all?

We're using a mixture, I mean the classical techniques work, so why break them, and these are techniques which I learnt when I was in Dundee, when I was working in Professor John Blenis' lab, but you have to also look at newer technologies, newer ways of pushing research on, and so one of the elements is to use next generation sequencing. So James Colley, at Medical Genetics, he's pushing that element forward. This is where you're able to deep sequence entire genomes a hundred-fold, a hundred times over, so in theory what you could do is you can take a BHD patient tumour sample, purify the DNA (their genome), and sequence the entirety, and the power of that is phenomenal. One element is like ok, so we have a technology to do sequences. However, we need the bioinformatics, so these are people to crunch the sheer volumes of data, and for people to analyse that to say- ok, yes, within that tumour cell, you'll be getting mutations, not only in BHD, but other genes involved in cancer progression as well. So when you get to that stage, we can start to understand why in some BHD patients, they end up with renal kidney cancer, while in some other BHD patients they don't, because I think it's a systematic series of genetic errors, and we're in a very strong position to actually look at that.

A lot of our work, actually we have a paper which we're submitting, shows that HIF protein is involved in BHD as well. But as with all research, it's just really important to understand that this is work based on a collaborative affair, but it will be interesting to see other research labs, when they look at this, they can also see similar findings to ourselves.

HIF is this hypoxia inducible factor, so it's a protein in the cell which under oxygen starved conditions- we breathe oxygen all the time, and the reason being is that it feeds all of our cells in our body oxygen, because all of our cells need oxygen to make energy. If we stop breathing, we'll just pass away- what happens is that if there's an area within your body where it becomes oxygen starved, HIF turns up, and it encourages blood vessels to grow towards that place of starved oxygen. So it's a way for your body to maintain itself. In the context of cancer, what happens is that you have a small bundle of cells which grow out, and in the centre of this bundle of cells, the cells are oxygen starved, so HIF gets turned on, and this encourages blood vessels to grow/integrate into the heart of the tumour, and then the tumour grows even larger, and a lot of renal cell carcinomas/kidney cancer –

VHL, BHD, TSC, all seem to involve HIF, hypoxia inducible factor- and work which we are doing just now is indicating that BHD is involved in HIF.

Going back to tuberous sclerosis complex, it was not just the work that I carried out in John Blenis' lab, but it was a whole collective – lots of other labs did similar things – and it's the combination of everyone's research that strengthens the research, if that makes sense. So again, this is why collaboration is good as well.

So what's the ultimate aim of your work?

I think, if you go back to tuberous sclerosis complex, 10 years ago, we just uncovered the gene to what caused the disease, and it's taken 10 years of time to uncover the function and where in the cell it works/it ticks, and why a cell without that gene, why it's prone to causing cancer. And then, using that basic information, formulating therapies, which- and there's a whole series of clinical trials, some which are finished, and some which are being initiated, and they're all looking quite hopeful. But there isn't a cure for tuberous sclerosis yet, we're just able to reduce the effects or the size of the tumours just now, so further trials are needed to be done, further basic research is needing to be done. So if you take that timeline and apply it to BHD, we only uncovered the BHD gene expressed Folliculin- the protein- in 2002, but if you take a 10 year timeline from that, you can see already we're behind in comparison to the TS research community. But that's because there's less people working on it, I think. So hopefully with the papers which are coming out, the Myrovlytis Trust, our funding will inspire other research groups to take notice- "ok BHD, it seems to be really important here, it's involved in a cell signalling pathway, a mechanism in the cell which we're very interested in, so we'll start to look at that", and I think that's needed in order to speed up the research for BHD. But we need to know how BHD works, we need to know how it ticks in the cells, and that's really the main hurdle just now. But we can learn a lot from all these other inherited disorders because they're highly overlapping and these clinical trials in TSC, they may be applicable for BHD patients as well.

How do you think the BHD research field is going to look in 5 to 10 years' time? What do you think we might know by then?

Well, I think it's all dependent on the quality of the papers which we're getting now, and so just by speaking to people like Professor John Blenis, I asked him if he'd heard of BHD

and he said no. And there's another rising star called Brendan Manning- I asked him if he knew about BHD and he said no. So I think it's just getting knowledge out to these researchers, the people who have been in the field for a very long time, to try to get their interest up as well would be quite important. So it's all dependent on the quality of science, and if it integrates with their area of expertise, and to sort of inspire them to maybe look at BHD, I think that's it.

Well thanks ever so much for talking to me Andy and best of luck for your research in the future.

Thank you.