Interview Transcript – Dr Arnim Pause

I'm Jill Woodward, I'm at the Third BHD Symposium, joining me is Dr Arnim Pause, who leads the research group at McGill University. Dr Pause, can you talk about the research that you presented here at the Symposium?

Yeah so, at this Symposium we had three talks. The most exciting one I find was that we made a model of the BHD disease in a model organism which is a little worm that lives in the earth, it's called *C. elegans*. And this worm is used frequently in research to find out how certain disease genes work. Because it is much easier to work with this worm than to work with patients or with mice or other complicated organisms. So we use this worm to study the function of the BHD gene or protein. And we got some interesting results, in that a worm that's devoid of this gene or protein lives twice as long as a normal worm. So getting rid of this gene in this worm, and maybe also in mice or humans, prolongs life. Now what does it have to do with the disease, you will ask. I don't really know; I can't tell you that. This is just the first step into further understanding what this protein is doing in the cell. What we know is that it's involved, through the work in the worm, we found that it's involved in a process called autophagy which is complicated work which basically means self-eating. It's a recycling programme that each cell in the body has. And when you starve a cell, or starve an organism so that you limit the food intake, this programme is turned on and basically recycles all the useless contents of the cell and makes energy out of it—makes food for the cell. So it's a survival programme. And this programme, this autophagy programme, is continuously turned on when the BHD gene is not present in the cell. And that means that these cells are under a kind of starvation mode, although they are not starved. So the cells think, or the organism thinks, that there's limited food and that there is an energy problem. So they are basically in the state of somebody who would run for half an hour, or somebody who would cycle for an hour. That kind of state, where you lose weight, you basically use all the energy resources you have in your body. This also is very beneficial for you. It's been shown many times that people who exercise are usually healthier than people who don't—and the idea or the theory behind this is that when you exercise or when you don't each much you starve yourself, not not eating anything like anorexia, but maybe eat less than you'd usually like to eat, that turns on this autophagy programme which in turn is very beneficial for health. So people who eat very little would live much longer than people who eat a lot. So when you knock out the BHD gene you're always in that state. So why do you get sick? That is probably something that is a

long term accident. So in general it is probably good to lose this gene for you. I mean it's crazy, but that's what we see. But the disease that you get, that probably is a long term accident in the sense that you accumulate other mutations that predispose you to tumours.

What are some challenges that you've faced in your research?

In the beginning when the gene was cloned—that was many years ago—it wasn't really clear where to start. It wasn't clear what this gene or this protein was doing. And that's what I'm interested in. There was no clue. So what you do is you try all kinds of different approaches. Random. You just try whatever you can try, and that's usually not a very smart, straightforward approach. But this is what we do. So that takes a lot of time, until you find something that's reproducible, that gives you some kind of hint where you can dig deeper. In the beginning it was like years of fishing. Two or three years, we got really no interesting results. There you're sometimes close to giving up and thinking maybe I should work on something else.

Can you talk about your future plans for this research project?

Right now we basically discovered what happens when you take this gene or protein out of the cell or out of the organism. And we got very interesting correlations; they call it phenotypes. I don't know what a good lay term for that: observations, let's call it observations. The surprising thing was that, especially in the worms, but also in the mice, they actually are not very sick. So it's not like they die very early or something like that, so it's a pretty mild phenotype. But the next step will be to understand on a molecular level what the *Folliculin* gene or protein is doing in the cell and why do we get those phenotypes or observations, why do we see those things. So that's the next step. What we also are interested in is what does this gene or protein do in the cell, in the normal cell that's not mutated. Why is this gene here? Why is it conserved from worms to flies to mice to humans? Must be a very important gene for something. My guess is that it's important in energy regulation. It's important for the regulation of energy metabolism, or energy maintenance in the cell. And when you take it out, this regulation is no longer functioning. So the cell is in a state where it thinks it has no food, and so if you want to survive, if you don't have a lot of food around it's probably not a good state to be in. But in our case when we have too much food around, it's probably a good state.

Why is rare disease research important?

You write research grants to get money for this and the first sentence is always 'ah this is so rare, why would you work on that?' And you have to justify it. And there's a very easy justification in that, yes it is rare, but once you understand it and fully discover the pathway that it's involved in, which not only involves let's say the Folliculin protein but it involves maybe ten or twenty other players in the cell, what usually happens is that you will later find that this pathway is a very important pathway for cancer and it will be affected in probably all tumours, at one stage or another, either early or late. So all these rare diseases, I'm talking about rare tumour diseases right now, they were all started, there's 200 families in the world, very few people are affected and everybody said why are you working on this. And now we know that it was the same with a disease called retinoblastoma which is an eye tumour that children get. And it's rare, and people started working on that 25 years ago and now we know that since the pathway is discovered, that this pathway is affected in almost all tumours and now there are drugs made against this pathway. The same is true for the VHL disease and there are at least ten of them. So what is rare at the beginning is not rare at the end. Because a rare disease gives you an entry point into discovering a pathway that is usually very important for a normal cell to become a cancer cell. If you would say, ok, I have somebody that comes up with a prostate cancer; now you find the gene that's responsible for that, that's impossible. There's a hundred thousand genes in there—how do I find the one that caused this? It's impossible to find. But a rare disease means there is one gene that is inherited from your parents and that gene is responsible. And you find that gene and you can understand that gene and you understand the disease and maybe related diseases. So I think in the last 5-10 years a lot of people realised that we don't do anything. Especially philanthropists, nobody will fund us because to the public immediately—initially—it doesn't make any sense to put a lot of money on research for a disease that affects, I don't know, maybe a thousand people in the country.

And what would be helpful for young scientists considering entering this field? What specialties are needed?

For a new person I would suggest you have to work on the protein part of this project. I haven't seen anybody that works, except maybe Ravi Nookala, that works on the biochemical

way: what does this protein do? How does it interact with other proteins? What kind of enzymatic activity does it have? Does it have a function, does it move things or does it...I don't see anybody working on that. So that's—biochemistry of the Folliculin protein—that's kind of a bit underdeveloped.

Where else have you presented your research?

Mostly at these BHD meetings. So every year I go to those meetings. But I think now, with the results we got now, this will probably be presented at many other cancer meetings, metabolism meetings, nutrition meetings, all kinds of things.

And how have you found the Symposium so far?

Very good. Always a very nice symposium. What I like about it is that the people that come here are very open about their research: they present everything they have, they present unpublished data, fresh data. At other meetings you will never see that. People are so competitive. The whole science business, research business, is so incredibly competitive that people would never talk about their research if it's not already published, because they're so scared that somebody else will duplicate it and things like that.

What do you think the BHD research field is going to look like in 5-10 years?

Nowadays research is moving much faster than it used to be. So 5-10 years, I think, first of all the field will grow. It will expand. There will be more and more people. As soon as the pioneer work is done, which is the, you know, long frustrating work that we all we went through, and it is more clear what this gene is doing, other people will join for sure and jump on it. So in 5-10 years, I'm sure these meetings will be two-, three hundred people instead of eighty. Maybe even five hundred people. And there will be so much known about this gene that it will be almost overwhelming. And I'm sure there will be therapeutic approaches that will have been tested in animals, in humans. The advantage of this—the advantage for people you want to treat, people that have this disease, is that for instance the skin lesions are very easy to treat without any fancy clinical trials. Because it's very simple: you just put a cream on, which is much, much easier than giving a pill which would take 10, 20 years of clinical trials and all kinds of difficult long-term things. So I'm pretty sure in 5-10 years you will have

treatments that will be available that potentially could work—maybe not to cure people but to at least make this disease more chronic, more manageable.

So we've been speaking with Dr Arnim Pause. Thank you very much for joining us today.

Thank you.