Interview Transcript – Dr Tim Cash

I'm Jill Woodward, we're at the Third BHD Symposium in Maastricht, and I'm speaking with Dr Tim Cash. Dr Cash, can you tell us about the research that you've presented at the Symposium?

So in my lab we've developed a gene trap mouse model of BHD from which we've derived cell lines to study the cellular functions of BHD *in vitro*, and what we've discovered is basically that BHD or Folliculin plays a role in the TGF-ß signalling pathway to carry out the cell death response.

And why is that important?

This research is very important because currently we don't really know what the cellular or biological role of Folliculin is and that will be important in developing therapeutics in the future for patients.

So can you summarise the results of your research?

So far what we've seen is that when you knock-out Folliculin or BHD in the mouse, the mouse actually ends up dying very early during gestation, which was a bit of a surprise to us, but it indicates that BHD or Folliculin is clearly important in biology and during development.

Also what we learned is that cells that lack Folliculin are actually very resistant to cell death responses, which could have important implications in cancer of course. And we've also learned that those cellular defects in apoptosis or cell death are due to lack of death effectors and defects in the TGF-ß signalling pathway, which is known to be tumour suppressive in many other settings.

Why would cell death be an important thing to focus on?

So when cells are stressed or undergoing damage, it's essential for the organism to eliminate those cells from the body so they don't go on to progress into tumourigenic cells or cancer. So if a cell cannot undergo that process it has a greater potential to form a cancer-forming foci. So in this setting, where we lose BHD, the cell can no longer do it, so

it is important to figure out why the cell is no longer able to do that in the absence of BHD. So in that way we can eliminate those cells that can't undergo the cell death process.

What difficulties or challenges did you experience in working on this project?

Well, certainly Folliculin is a very difficult molecule to work with as it bears homology to no known protein, so I think currently that's the main barrier to studying this protein — is that we have no clues from the primary sequence of the protein itself.

So the model that you are using, are there any advantages or disadvantages?

So, in our lab we developed a gene trap mouse model for studying Folliculin. The disadvantage of this model is that the homozygous mutant animal actually ended up being very early embryonic lethal, which disallowed us from using cell lines derived from that particular animal model.

What diseases or syndromes overlap with BHD, and how would your research contribute to those?

Well certainly BHD has many features that are common to other hamartoma syndromes— that's actually how I first became interested in BHD. I was working in a lab that focussed on Tuberous Sclerosis complex, and one day came across BHD syndrome in the literature, and was struck by the commonalities between Tuberous Sclerosis and BHD, and that both sets of patients get lesions on the face, in the lung, and in the kidney, and that's how this work actually started in my case.

Do you collaborate with researchers in other institutions?

Yes, I have frequent conversations with Arnim Pause in Montreal about what the function of Folliculin might be, and share reagents frequently with many members of the BHD community, including the group at the NCI.

And how's this Symposium been this year?

Well, I find it more and more exciting every year. This year is particularly exciting, seeing the identification of some of the structural elements of the Folliculin protein and its ability to bind GTP – I think that's one of the greatest advances we've made in the last few years in the field. Also the findings in the model organism of the worm, in terms of the metabolic defects, have proven to be really exciting, and will definitely push the field forward.

What advice, if any, would you give researchers considering a move into the BHD research field?

I would say it's a tough field to get into, but all the big questions are still out there, which makes it a very exciting field, and it can be frustrating at times because it's so challenging, but it's a very exciting field because there's a lot of really exciting questions to be asked.

So what's the next step for you and your research?

I'm actually not continuing BHD research, but I may pick it up one day in the future, and if I were to continue in the near future, I would aim at setting up model genetic systems and model organisms in order to do unbiased screens to uncover novel effectors of Folliculin in BHD.

So what will you do instead?

I'm going to be doing a post-doc in Spain actually, focussing on cellular aging and metabolism, which very may well have a role in BHD pathogenesis.

How do you think the BHD field is going to look in the next 5 to 10 years?

Well at the rate it's going, which is pretty fast in the last 3 years, I see us actually coming up with a true function for the Folliculin protein, and inevitably we'll develop novel therapeutics—targeted therapeutics—for the treatment of BHD patients.