<u>Interview Transcript — Dr Doug Medvetz</u>

We're at the Fourth BHD Symposium at the Vontz Center in Cincinnati. My name is Jill Woodward and I'm speaking with Doug Medvetz. Doug, talk about what BHD research projects you're working on at the moment?

What we're really interested in is trying to find new functions of Folliculin, and so we've been interested in finding new interacting partners and so we've actually discovered a new protein called plakophilin 4 or p71 as many people refer to it. It's a fairly uncharacterised protein but what we've found is that these two proteins regulate Rho signalling and also cell-cell adhesion. And so what we've see is when you lose Folliculin or you lose p71 you have an increase in cell-cell adhesion. So in the literature it's known that desmosomes, which control cell-cell adhesion, are important for kidney cancer, so we think we've made a connection between one of the interacting partners and why Folliculin patients might get kidney cancer. But we also think it is important for the lung phenotypes as well, because we feel like since the lung expands and contracts so much that cell-cell adhesion will be really important. And if you have increased cell-cell adhesion, it may be the reason why the lungs form cysts.

And what are the aims of your research?

My biggest aim is to find therapies for patients. Every time I come to these meetings I just get so inspired to—I mean that's really why we do these things, is to find a druggable target for patients, whether it be a drug that can cure the facial tumours, the lung cysts and the kidney tumours. One drug—that would be the overall goal, but I think what's probably going to happen is we're going to find compounds that will be able to treat the kidney tumours or the lungs cysts or a different compound that may treat the skin tumours. So that's sort of what our overall goal is—to find a therapy.

Can you talk about what models you're using and why you chose those particular models?

We've actually developed a new mouse model of BHD, which we haven't actually talked about, but we developed a skin model of BHD. So we did a knockout of Folliculin in the mouse skin. We've found some really interesting phenotypes with the hair and the skin and things

like that. So we use a lot of mouse models, we definitely use a lot of cell models. So the majority of my work is with Folliculin null patient cells; so they're a cell line called UOK257 and they were derived from a BHD patient renal carcinoma. So we've done a lot of our work in those cells. We've also been thinking about using some fish models—so zebrafish models of BHD. The reason for that is they develop a lot faster than mice and so we can learn a lot more in a much shorter period of time.

Are there any models that you think should be developed?

I think there needs to be more mouse models of the disease. There's been a few kidney models in mice and none of them seem to really recapitulate the disease itself. So I think more work needs to be put into mouse models, especially the skin and lung because I mean there's really no models of the lung phenotype or the skin phenotype. And that's one of the reasons why we thought about doing the skin model.

How do you make a mouse model?

The nice thing is for BHD the NCI groups, so Marston Linehan and Laura Schmidt's lab, they've developed what's called a BHD flox/flox animal. And basically what that is, is it allows you to conditionally inactivate *Folliculin*. So basically the whole mouse, every BHD gene in every tissue can be conditionally inactivated. So as a flox animal it's completely normal; so the genes are normal. But if you cross that mouse, if you mate that mouse, the BHD flox mouse, with another mouse which expresses a protein called Cre Recombinase, so the Cre Recombinase will basically go into the gene and cut out the floxed area and then the gene will what's called recombine and so you'll have a non-functional gene. So you have the ability to inactivate *Folliculin* in the kidneys or the lungs or the skin or anywhere for that matter— very similar to a patient right. A patient basically has normal Folliculin in the majority of their body but they lose the protein in the kidney or the lungs due to mutations. So it's basically a way to sort of manipulate mutations in a mouse. It takes a lot of time because you have to mate these animals, and then you have to wait 5, 6 months until they're grown before you start to see anything. But it's—what's nice about generating these mice is a lot of times they do develop the same types of tumours and phenotypes as the human patients do and so then you can treat them with drugs and see what works.

Have you had any difficulties in this project?

Yeah. So, this is actually quite a challenging project to work on. So there is actually another group who found the same interacting protein, plakophilin 4, as we did. So even finding the same interacting protein we are getting different data. So one of the biggest challenges in the field is that this seems to be a pretty complicated pathway that this protein is involved in. And so one day you'll get one result and the next day you'll get a completely opposite result. So it becomes really challenging to know what's real and what's not real. So it's just very—it takes a lot of time and patience. I think that's the biggest challenge to this project, even more so than any other research project. It just seems to be very challenging to get the answers that we really want.

What is a signalling pathway?

So Folliculin is a protein and usually proteins interact with other proteins and then by their interactions with different proteins it causes different functions in the cell. So what many people think in BHD is that it's somehow interacting with multiple proteins and regulating the AMPK pathway which is an energy sensing pathway. So basically the cells in your body can sense when you've eaten or something like that so you have a high energy. So different proteins interact with other proteins when you eat and then they regulate cell growth, cell proliferation and things like that. And then in the opposite case, say you haven't eaten in 5 hours and you're low on nutrients, so certain proteins in your cells can sense that and then they can shut down processes that require energy. And then that way you sort of conserve the energy that you have for the future, things like that. Signalling pathways are really important in cancer because many of them are so hyperactive. So what happens is whether or not your cells have proper energy stores, they just continue to proliferate; so that's the main problem in any type of cancer syndrome like BHD. So you lose Folliculin and there's signalling pathways that are overactive and so the cells just keep proliferating and proliferating. And that's why we look for targets and interactors so that we can find out which pathways are important and then we can shut those pathways down or activate those pathways depending on what's happening and then hopefully slow tumour growth or cure tumours.

Talk about collaborations with other institutions and how this helps your work.

Yeah. So we actually are big on collaboration. So most of our projects we are collaborating with somebody else. There's quite a few BHD groups that are here that we've collaborated with, Vera Krymskaya's group. But we've also developed some collaborations at Brigham and Women's Hospital where we work in Boston with other groups that weren't actually originally interested in BHD. And so we've brought other groups into the field because they have a skill set that we would like to do that we're maybe not experts in. So I feel like the collaborations we are making are actually growing the research community in BHD. I think that's really important. I mean the more people we can get—just anybody we can tell about the disease, I feel like they really get interested because it's so fascinating and such a little amount's known.

So what are your future plans for the project?

I guess the most immediate future plan of this project is actually to get this new discovery published. I mean we'd like people, besides the people in this meeting, we'd like everybody to know about this protein. Because once you start learning about interactors and pathways that Folliculin is involved in, it'll be more and more people interested. So we may find people that are interested in cell-cell adhesion or Rho will become interested in Folliculin as well, as soon as we publish it. So I think that's our most important sort of immediate step. The next step then will be to determine whether or not there's a druggable pathway, so the potential for a therapy in this pathway. And so the Rho pathway is a very drug-targetable pathway, there's actually drugs that either inhibit or activate Rho, so if we can really work out that pathway then we could potentially have a potential therapy for BHD that way. So I think publishing the paper and then moving to potential drug targets is where I would like to see the project go.

And can you talk more about what you were working on before getting into BHD research and how you got into the field?

When I was in my PhD, I studied as a chemist and I was working on developing small molecules for anticancer agents. So that's what got me interested in cancer. And then when I got my PhD and joined Lisa's group I was initially working on tuberous sclerosis complex, which many people have talked about at this meeting. It's very similar to BHD; the patients get very similar phenotypes in the kidney, the lungs and the skin. Lisa had told me about BHD and

nobody was really working on it in the lab, and so I went and I started reading about it and I talked to a few people about it and it just seemed like a great place for me to be. It's a disease where not a whole lot's known, so in terms of my career it's a good place for me—I could make an impact in the disease and I could build a career on it. But I found it fascinating these patients get these really devastating phenotypes and nobody really knows what's going on. So the challenge I think of BHD is what really brought me to it. So it was sort of a stepwise process. Since it is a cancer syndrome and I'm interested in therapies, I thought it would be really interesting to work on.

And do you have any advice that you would give researchers thinking about moving into the BHD field?

I guess the biggest advice I would give them is if you're thinking about coming into BHD, definitely attend one of these Symposia. The main reason I say that is because BHD, it's a challenging field to work in as a researcher, but the patients and the people that are working in the field are so inspiring that you'll get a good appreciation as to why you would want to do this. So I feel like that would be the best way to experience what it's really like. Because it's going to be challenging at times and you're going to get frustrated, but if you meet the patients and you meet the other people who are working hard—everybody is just so personable. I think it's a field that people will want to work in if they get the experience of what everybody is like.

Doug Medvetz, thank you very much for speaking with us today.

Absolutely, my pleasure.