Interview Transcript — Professor Elizabeth Henske

We're on the campus of the University of Cincinnati for the Fourth BHD Symposium. My name is Jill Woodward and I'm here with Dr Elizabeth Henske. Dr Henske, can you tell us about the aim of your research?

One of the aims of our research in Birt-Hogg-Dubé syndrome is to understand the fundamental ways that the BHD protein Folliculin acts in a cell. And to understand the mechanisms through which mutations in the Birt-Hogg-Dubé gene would lead to tumours, kidney cancer in particular, and also we're very interested in why the lung develops cysts and can spontaneously collapse.

You group is well known for major contributions to TSC and LAM, can you talk about how those conditions relate to BHD?

Yes, we're very interested in tuberous sclerosis and LAM, which is also called lymphangioleiomyomatosis, and in fact we originally became interested in Birt-Hogg-Dubé because there seemed to be overlap in the clinical symptoms between TSC and BHD. For example, individuals with both diseases can get benign skin tumours, they can get kidney tumours and they can develop lung cysts and lung collapse. So we thought many years ago that there might be a relationship between how the two proteins, how the proteins that are involved in these diseases function.

How long have you been working on TSC research?

I've actually worked on tuberous sclerosis for my entire career. I became interested in tuberous sclerosis when I was an oncology fellow at the Massachusetts General Hospital and was originally involved in cloning the *tuberous sclerosis 1* gene and I've remained focused on tuberous sclerosis and now also on Birt-Hogg-Dubé syndrome throughout my career.

What BHD projects are you working on at the moment?

Right now we're characterising proteins that the Birt-Hogg-Dubé protein may interact with and trying to understand how that causes the cells that have deficiency in the Birt-Hogg-Dubé

protein to grow abnormally and perhaps to form tumours. And we're also just beginning to look at what happens in the lungs of mice that have mutations in the Birt-Hogg-Dubé gene.

What difficulties have you come across in this research?

Birt-Hogg-Dubé projects have been challenging because the functions of the proteins are not yet completely understood and sometimes in these very early phases of understanding how a disease is caused there are a lot of findings that are hard to understand and hard to explain. And I think the entire field has been experiencing that but at a meeting like this, a lot of different pieces of data can come together and explanations evolve that might explain why one group has one result and another group has another result. So I think, although there have definitely been challenges in the Birt-Hogg-Dubé field, it's moving forward very quickly and I think a lot has been learned even just in the past three or four years.

You led the yeast model for BHD syndrome, how was that helpful for the research?

The yeast model of BHD was very exciting. So that was the first thing that we did when we decided that there might be a link between BHD and TSC. And we already knew that the TSC deficient yeast had a very distinctive phenotype which involves abnormal regulation of amino acid uptake and amino acid levels. And truthfully we expected that the BHD deficient yeast would show the same thing and instead they showed exactly the opposite. It was a big surprise to us and it's something that we are still trying to understand and in particular to understand how that might relate to signalling in the mTOR pathway because the mTOR pathway is very important in tuberous sclerosis and to understand how that might link to Birt-Hogg-Dubé could both tell us about the disease and also help us understand how to treat individuals with BHD.

How often do you see patients in your work?

I'm in an unusual position at the Brigham and Women's Hospital in Harvard Medical School where I see individuals who have cancer, at the Dana Farber Cancer Institute, and then I also see individuals who have LAM and sometimes who have Birt-Hogg-Dubé through the pulmonary division at the Brigham and Women's Hospital. So I have opportunity to see individuals with

kidney cancer and also individuals who have cystic lung disease, and I do that about one-half day per week.

And how does that affect your approach to research?

As an oncologist and someone who's cared passionately about LAM for many years, I think seeing individuals who are struggling with the disease has a—it's hard to put it into words, a very powerful impact on what you do in the laboratory. It's what drives everything that we do: trying to understand these diseases well enough to be participants in figuring out better treatments for the diseases.

When patients present with symptoms of BHD and LAM, do doctors consider that as a diagnosis?

That's a huge problem. I find that even in the Harvard Medical School area, many, many people have not heard of BHD, surprisingly. And I think that increasing visibility of the disease, meetings, having centres of excellence around the world to promote awareness is a very important step and probably there are many many people who have these rare diseases who don't know that they have them. And a lot of that I think has to be driven by patient awareness. Physicians can't possibly keep track of so many different diseases, so I think awareness is a key part of finding out who actually has these diseases and then allowing them to receive the appropriate screening and, particular with BHD, the appropriate screening to prevent kidney cancer or to catch it early.

Do you collaborate with other researchers at other institutions and if so how is that helping your work?

Almost everything we've done in the BHD field has involved collaborations with many other groups. It's a very small field and therefore a very collaborative field and that's been helpful to us in terms of mouse models, antibodies, and just good advice about what steps to take next.

You mentioned you're using a mouse model; why did you choose that model?

Well, the mouse model that we've worked with the most is a model that we think resembles humans who have Birt-Hogg Dubé, where the mice have a mutation in one copy of the Birt-Hogg-Dubé gene. One of the models we'd like to generate would be a model that recapitulates the lung disease in BHD. We don't know very much about why individuals with BHD develop lung collapse and if we could develop such a mouse model it would allow us to figure that out and study it and understand what the underlying mechanisms might be but we haven't yet begun to work on these models.

Talk about the current challenges in the BHD field and how you think things are going to look in 5-10 years?

The current challenges include that we don't have enough tissue from patients to study; that's something that is a challenge in many rare diseases. I think in the next five to ten years though, there will be paradigm shifting discoveries in this field that will position the BHD gene *folliculin* at the centre of pathways that are important in many human diseases but particularly cancer. We saw that same transformation happen with TSC for example. 10 or 15 years ago, many, many people in the cancer field had never heard of TSC. Now virtually everyone has heard of it because those proteins are right at the centre of pathways that are very important in almost every cancer and there's no doubt in my mind that Folliculin, the BHD protein, will have a similar central role in the signalling pathways. And I think we just need a little more data to place it in just the right place and I think that will really change how people think about the BHD protein and also the ways in which different investigators become involved in BHD research.

Talk about the feasibility of developing a drug for BHD and the process of going from bench to bedside?

I think it's very feasible to develop a drug and I think the bench to bedside piece depends a lot on where the drug is in development prior to the recognition that it might be useful in individuals who have BHD. One of the most promising avenues is to take drugs that have already been FDA-approved for another purpose and use them for BHD, repurpose them is the term that's sometimes used for that. I think it's very likely that agents that are already approved for cancer or even for diabetes or other metabolic diseases could end up have efficacy in BHD.

What advice would you give a researcher considering going into the BHD field and particularly are there any specialisations that are needed?

There's a lot to do in BHD. There's so much that we don't know and I think it's an opportunity to learn about a pathway that will become central in understanding cancer and perhaps also in understanding lung disease and particularly cystic lung disease. So I think there's tremendous opportunity, there's a lot to do, it's a really nice community and I would recommend that people consider BHD as they're understanding what pathways will be most exciting to their own research interests.

We've been talking about your group's research; can you talk about the state of rare disease research as a whole?

Rare disease research has come a long way in the past decade or so. I think most physicians recognise that rare diseases are very important and need attention beyond the more common diseases. So I think there's been a lot of progress, a lot more needs to happen for rare diseases and I think that needs to happen at many levels, from the research interest, from clinical trials and the availability of mechanisms to have drugs approved even if there are a relatively few number of individuals who can participate in trials, and then on a whole other level recognising that people need to have heard of these disease in order for them to be correctly diagnosed and that includes the lay public as well as physicians. So I think it's education, research and understanding how do we move drugs forward when we don't have a huge number of individuals to participate in trials.

Dr Elizabeth Henske, thank you very much for talking with us today.

Thank you.