Interview Transcript - Professor Eamonn Maher

Hello, I'm Dr Sharon Ann Holgate and I'm here at the Centre for Rare Diseases and Personalised Medicine at the University of Birmingham today to talk with Professor Eamonn Maher who's doing research on Birt-Hogg-Dubé syndrome, which is being funded by the Myrovlytis Trust.

In the projects that are happening here at the University of Birmingham now, what sort of things are being done, could you give us a summary?

Ok. So really there's three broad themes. One is we're trying to understand more about why tumours are occurring in Birt-Hogg-Dubé syndrome; we're trying to come up with new treatments for Birt-Hogg-Dubé syndrome by looking to see if we can identify drugs that will specifically affect cells in which the folliculin gene is inactivated; and then we also have a clinical arm to the project where we're collecting families with Birt-Hogg-Dubé syndrome and looking through how it's affected them to see if we can understand why there are variations between families and individuals and how Birt-Hogg-Dubé syndrome affects them. And then eventually that will allow us to go on and do clinical trials of new drugs.

Has any of the research you've been doing here actually added to our understanding of the role of folliculin?

So the work we've published so far has suggested that a significant minority of patients who have presented to us with kidney cancer actually have Birt-Hogg-Dubé syndrome as their underlying disorder. So we've now changed our clinical practice so that those patients who present with features of an inherited form of kidney cancer, even though they don't seem to be recognized for having Birt-Hogg-Dubé syndrome, we undertake genetic testing for folliculin mutations on all of that. We've looked into the risk of colon cancer in patients with Birt-Hogg-Dubé syndrome so this is something that's been quite controversial. In our hands we think that there is a risk of colon tumours and therefore we recommend those families where there is a family history of colon tumours with Birt-Hogg-Dubé that they receive screening for that. But there's still a number of unsolved questions there, so we're actually going on to further investigate that. And then in terms of understanding what happens with the disease, we have done—we've some nice data coming through on how mutations in different parts of

the gene can affect the function of the protein, which really seems to suggest that most of the folliculin protein is actually important and there aren't any specific areas that are more important than others. Most of the missense changes that we find probably affect the stability of the protein rather than having a discrete effect on a specific protein function. And then we've identified some interacting proteins that give us new insights into the pathways associated with folliculin, but that work is still ongoing and it's not yet ready to be written on.

So why is the association between colon cancer and BHD considered controversial?

I think it's because there are essentially different studies that haven't given the same answer. So in our European studies we'd find that there is an association, that there is an increased risk of colonic polyps and tumours in patients with Birt-Hogg-Dubé syndrome. But there was a very good study from North America where that wasn't apparent and so this discrepancy might relate to what the particular genetic mutations were in the relevant families that were studied. So it's an area that requires further investigation really just to try and sort out what's going on.

You mentioned some work that you said was getting to the point of starting clinical trials. How far away do you think we are from developing treatments for this?

So, in fact we're collaborating with Maurice van Steensel in Maastricht. And Maurice is starting a clinical trial using rapamycin for the cutaneous lesions of Birt-Hogg-Dubé syndrome and so the plan means extending them and we'll undertake that work in the UK as well. The other work that we've done is to look at cell lines and to try different cancer drugs against them and see if we can find whether there are any cancer drugs that seem to be particularly effective against the cells where the folliculin gene is inactivated but don't seem to have the equivalent effect on the same cells where the folliculin is being expressed. And we've found a cancer drug known as mithramycin appear to be particularly good at killing the cells, the kidney cancer cells where folliculin was missing, so that was interesting.

So how long would you estimate it would take before an effective treatment will perhaps be available to patients generally?

Well, I think there will be treatments available within ten years. The thing that's difficult to answer is whether the treatments that are available, what their side effects will be and whether they will be treatments that you would only use, for example, if you had an advanced problem of Birt-Hogg-Dubé or whether it would be something you would take to prevent the problems. So with the von Hippel-Lindau disease, out of the research that came from that led to the identification of new forms of treatment for kidney cancer. They can also be used for von Hippel-Lindau disease patients. But generally, the conventional forms of treatments, like surgery for kidney tumours, are still the preferred choice because they will actually completely cure it, whereas the medical treatments just control it. So you might imagine something could happen similar with Birt-Hogg-Dubé syndrome that the first treatments may have an effect but perhaps they may not change the management of the condition dramatically. But I'm sure as time goes on and the treatments get refined then we'll move more and more towards medical intervention.

So we've been speaking of the research that you've been doing here in your group, I'd be interested to know what your feeling is on the state of rare disease research as a whole.

I think it's a really interesting time for rare diseases research because most of the rare diseases, about 6000 of them, are inherited. And the advances in genetics have meant that it's becoming easier and easier to actually identify the genes underlying those conditions and so we have identified quite a few genes here for various disorders and we've found that the time taken to identify these genes is less and less, particularly with the advent of second generation sequencing techniques. So what we're thinking longer term now is that in the next few years, most of the genes will probably be identified and really the challenge is going to come up with new forms of treatment for these, and obviously how feasible that will be will vary from disease to disease and what the manifestations are. But that's really why we pulled together this Centre for Rare Diseases and Personalised Medicine because we wanted to put the emphasis on coming up with new therapies, and also to try and pull together the researchers within the university who are working on rare diseases because quite often it's difficult to get funding for rare diseases—it doesn't seem that important because relatively few people [are] apparently affected. But as I mentioned before, it can be that it's very important, you get very important biological insights that are of profound importance. So really, I think it's potentially a very exciting time and of course the main challenge is going to

be to raise the funding that will allow us to proceed as fast as we would like to in unravelling the cause of the disease and then trying to move towards new therapies.

I was quite interested to know, when you're carrying out experimental work, how much are you using classical techniques and how much you're making use of new technologies?

So what the way we've approached it is generally to try and utilise the new technologies as much as possible, but once at the point where they've been established to be better than the current techniques. So we haven't really spent a lot of time in developing new technologies ourselves, but whenever a new technology becomes available that looks to be reliable enough and offers more than the classical techniques, then we've made attempts to go and utilise that. So things like second generation sequencing, we've done a fair bit of whole exome sequencing now. Mainly by collaborating with those groups who've established the technique already. So from our point of view we get the maximum of information in the minimum amount of time and don't waste any of our resources on experiments that shouldn't work or don't work.

So how do you think the BHD research field would look in five to ten years' time?

So I think we're going to know a lot more about what the folliculin gene actually does. And if it's anything like the VHL gene then we'll find that it has lots and lots of different functions. And so I think it's going to be—we'll know more about it, but we'll also realize that the whole story is a lot more complex than perhaps we imagine at the moment. Within ten years I would hope there would be some treatments available that have come directly out of the basic research that's been done in the laboratory. But they won't be, I think, they won't be cures, they'll be treatments that we can use and there will still be some refining to do in terms of developing newer treatments with lesser side effects and that. So really optimistic about the future but wouldn't underestimate the challenges that there are for us to overcome.

Well, thank you very much Eamonn for speaking with me today and best of luck with your research for the future.

Thank you.