Interview Transcript — Dr Frank McCormack

We're at the Fourth BHD Symposium at the campus of the University of Cincinnati. My name is Jill Woodward and I'm speaking with Dr Frank McCormack. Dr McCormack, can you talk about the conditions LAM and TSC and how they relate to BHD?

Tuberous sclerosis is a tumour suppressor syndrome, meaning that it's a condition in which multiple tumours form throughout the body because of the loss of a protein that controls cell growth. When that protein is lost in the heart, heart tumours develop, in the lung, lung tumours develop, in the kidney, kidney tumours develop, and in the skin, skin tumours develop. So it's, like Birt-Hogg-Dubé, it's a genetic condition in which a protein is missing. And it so happens that the protein that's missing in tuberous sclerosis is in the same pathway as the protein that's missing in Birt-Hogg-Dubé. LAM is a condition that often accompanies tuberous sclerosis. It occurs in about 30 or 40% of women who have tuberous sclerosis and in about 10% of men who have tuberous sclerosis. It is basically a metastatic neoplasm, meaning that a tumour forms somewhere, we're not sure where, and seeds the lung with smooth muscle cells that infiltrate and eventually destroy and form cysts throughout the lung tissue. LAM also occurs in a form that is not associated with inherited abnormalities in tuberous sclerosis genes. That's called sporadic LAM; it occurs after embryogenesis, meaning that you don't inherit it from your parents, that the gene defects occur sometime after conception. Sporadic LAM is less common than tuberous sclerosis -associated LAM but we see it more frequently in our clinics, probably because it behaves more aggressively. When you do genetic analysis on peripheral blood in a patient with sporadic LAM, there are no abnormalities in tuberous sclerosis genes. But if you're able to obtain tissue from the actual LAM lesion or the kidney lesions that occur in those patients, they have tuberous sclerosis mutations. So it's a genetic condition but not a transmissible condition. There are no mutations in the germline cells like the egg or the sperm. And the condition cannot be passed on to offspring.

How often do you see patients? And how does that affect your approach to research?

So I see patients every week. Mostly in a half-a-day-a-week clinic. It's a referral clinic for patients with cystic lung disease, so I see many patients with LAM and patients with other forms of cystic lung disease. And that raises a lot of questions for me. Many of the scientific interests I have come from that clinic. I also have a research laboratory that's focused on

pulmonary infections and pulmonary innate immunity. And I hope someday to be doing LAM research in my lab as well. I can't overemphasise or overstate the importance of both doing clinical work and understanding how to make advances in the laboratory. The role of the physician-scientist, I think, is threatened. The funding in the United States at least has taken quite a dip in the last several years. I fear for the fate of physician-scientists and I think they are absolutely essential to making advances in medicine. And especially in rare diseases like Birt-Hogg-Dubé and LAM where pharmaceutical companies are unlikely to become interested in doing trials.

Do you think doctors who see patients with spontaneous pneumothorax consider LAM or BHD as a diagnosis?

I think that's the exception. I think, mostly because of efforts of The LAM Foundation over the last fifteen years, I think most pulmonary doctors have heard of LAM. I don't think most pulmonary doctors have heard of BHD. When we introduce it to fellows, while we train them here, it's apparent they've never heard of it in their residency training. And often when I encounter private practitioners in town, it's not a disease that they're familiar with.

And how feasible is it to develop a drug for BHD?

So the first question for BHD is what the target would be. The most threatening manifestation of BHD is the kidney tumour and I imagine the first trials that will be completed will be targeting that organ. The lung disease natural history is much more variable. Some patients, most patients don't have progressive shortness of breath. Many patients, about a third of patients, will have pneumothorax. But that's a sporadic event. It's not clear that taking a drug on a daily basis to prevent something that could happen sporadically makes a lot of sense. So we'd have to think clearly about what we're trying to accomplish with a pulmonary trial. I think the renal trials and perhaps dermatologic trials will precede pulmonary trials and perhaps we'll learn something from those that will help us in deciding what can be done for the lung.

And can you give us more detail about the sirolimus trial?

That was an investigator-initiated trial, meaning that we started it here at the University of Cincinnati. It was conducted at thirteen sites in three countries. We enrolled 89 patients over a period of two and a half years. The trial took about six years from start to finish. Cost about $8 and a half million dollars. Patients were randomised to receive either sirolimus or a placebo for a year and then to be watched for a year. We followed pulmonary function over the course of that time and also measures of quality of life and pulmonary symptoms and CAT scans of the lung. The most significant finding was that patients who took the placebo lost about 11% of their lung function in the one year on the trial and patients who took the drug had stable lung function with no loss of lung function. The difference was highly significant. When we stopped the drug, both groups declined, so the sirolimus group began to decline again. So it appears that the drug suppresses the destructive process in the lung but doesn't reverse it or put it in remission, just holds it in place. So it raises the question of whether the drug would be needed continuously, whether you'd have to take it for a lifetime basically. And in some ways it makes some sense, because basically LAM and tuberous sclerosis are a deficiency of a protein called tuberin or hamartin. And sirolimus mimics the function of the missing protein. So like insulin for diabetes, you're simply replacing a function that's been lost through a genetic misadventure.

What results have you achieved so far and what do those results mean for the future of LAM research?

As a field, there's has been absolutely phenomenal progress on this pathway—understanding this pathway and identifying targets that are promising for future trials. LAM is one of the most devastating manifestations of tuberous sclerosis, it's one of the most lethal. So it's a prime candidate for future trials but there are also brain tumours and kidney tumours that are targeted in tuberous sclerosis trials. We have a lot of ideas for next drugs and combinations to try. There's several trials that have started up just in the last year around the world. LAM and tuberous sclerosis are an exemplar of what can be accomplished in a laboratory and brought to the bedside for the benefit of patients. I think BHD is going to be the same. It's just as decipherable as LAM and tuberous sclerosis are. We have scientists who know how to dissect the pathway very carefully and find the proteins that can be targeted for therapies. So I think there are going to be great advances in BHD just as there have been in tuberous sclerosis and LAM.

What are the largest research needs in understanding pulmonary symptoms of BHD?

So I think very early, I think patients have to organise in a way that we can ask questions. So for LAM for instance, Sue Byrnes at The LAM Foundation organised basically a 1000 or 1500 patients over the course of the first ten years of the Foundation in a way where we could access their information, know who was available for trials, conduct surveys and questionnaires and learn for instance about pneumothorax. In LAM we did a study and determined that pneumothorax occurs in about 70% of patients with LAM, it recurs in about 70% of patients. Using that information, it's not too difficult to conclude that we ought to fix it the first time pneumothorax happens so that future events are prevented because there's morbidity associated with future events. We also did surveys to determine if air travel was safe. That's been very useful for lifestyle issues for LAM patients. We need to do that in BHD. It's very simple. You need a contact registry through the foundation or some other entity, so that we can design a questionnaire and distribute it and find out how many people have had problems during air travel. That's low hanging fruit and that's perhaps not hard science, that's clinical science, but it's important for patients. And I think that's where we need to start for the lung. And we have to define the natural history of the disease to know what's targetable. We have to know how quickly cysts progress over time, if pulmonary function changes over time. Once we know what those changes are we can determine if we can favourably affect loss of lung function by using various drugs. And it's very possible that many of the same ones that are useful in LAM will be useful in BHD.

You are the Scientific Director of The LAM Foundation. Can you describe the Foundation and what its aims are?

Yeah, so the Foundation was founded by Sue Byrnes and her husband in 1995 here in Cincinnati. I had just met her; I had moved here from Denver. And when I arrived here, there was a letter on my desk, it's actually the office right up there, from her asking if I could do something to help her daughter. And frankly there wasn't a lot I could do—there were no therapies then, we simply mostly observed patients with LAM. But she said instead if you can't help me with her medical issues, can we do something together to start a foundation. So she set about assembling all the patients she could find, and she's been accruing patients at the rate of about a hundred a year for the last fifteen years. And we're up to about 1500 or so total. She also, with help from others on the Board of the Foundation, has developed

effective ways to raise money and so far has raised over $15 million dollars and about $10 million of that has gone into research and I'm proud to say that that research has formed the basis for many of the trials that are underway now.

What do you think the role is for The LAM Foundation? And can you talk about any suggestions you might have for similar rare disease organisations?

We have a big interest in rare disease here in Cincinnati and we're actually in the process of forming a centre for rare lung disease and there's nothing more important than the patient organisation part of this. When things are as rare as LAM and BHD, unless the patients organise themselves it's very difficult for the medical community to do it in a way that can promote trials and get research done. So it's essential that BHD, like LAM, start to organise and to make their patient base available for research and for answering questions.

Dr Frank McCormack, thank you very much for talking with us today.