Interview Transcript — Dr W. Marston Linehan

***I'm Jill Woodward; we're at the NIH in Bethesda, Maryland and I'm here with Dr Marston Linehan. Dr Linehan, tell us what you do and tell us about the Urologic Oncology Branch.***

At the Urologic Oncology Branch, we study both the clinical and laboratory—basic—aspects of Birt-Hogg-Dubé syndrome. We started working on this in the early 90's. We see patients with kidney cancer that runs in families, with hereditary kidney cancers. We have knock-out mice models with a very robust laboratory programme, but our real model is the human model of cancer. And our goal of course is, by studying the BHD pathway both in the laboratory and in our animal models, to develop a therapy for BHD, so that one day we don't have to recommend surgery to these patients. So our clinical approach is to recommend surgery when the largest BHD kidney tumour reaches 3 centimetres, that size. Now, we have not yet had a patient develop metastasis, have the cancer spread, when the patients are managed in that fashion. We've had a number of patients, sadly, who developed metastatic cancer and went on to die, with BHD kidney cancer, sadly. Their cancers either weren't detected and they got very large and they spread or they were very large before we saw them and had already spread. So we're very encouraged about that, we've very encouraged. Now these patients—we switched now to managing many of these patients—instead of doing an open operation, doing them with a robot, doing robotic surgery. We've always felt that if we could do these surgeries minimally invasively, in other words with less incisions, that would be a benefit to these patients. So in many cases we're able to do that.

***Dr Linehan, talk about the process of getting a drug from the lab to the bedside. How feasible is that?***

I think getting from the gene to a drug is very feasible. Although I'm humbled by the complexity of that journey. Every cancer gene is different and every cancer gene we're going to have to fight one at a time, including *Folliculin*, the BHD gene. We—and I say we meaning the field—know a lot and are learning a lot about this gene and this pathway. We already have some very clear directions on potential therapeutic approaches. The way you identify drugs is by looking at these pathways and predicting what might affect them. We test these. And we made a kidney cancer cell line from one of our patients with BHD so we can grow that kidney cancer in experimental animals and see how drugs work there. We can look at these drugs in

the laboratory. We can also look at our transgenic models to see how this class of drugs or this drug will work. I have held off so far on doing a clinical trial, because it's just judgment. Because I want to go with the best possible drug. I don't want to delay the work by doing a drug that's only part way. So it's just a judgment call. We're getting close to the point of starting trials. I would be surprised if we did not initiate a trial of systemic therapy of patients with BHD kidney cancer either later this year or early next year—spring of 2012. We will see. We're looking at a number of candidates right now, we are very encouraged about it, but it's going to be a long process.

***Can you talk about the other forms of hereditary kidney cancer and how that affects our understanding of BHD and vice versa?***

We study seven differing types of kidney cancer, of hereditary kidney cancer. We study von Hippel-Lindau, VHL, a hereditary type of clear cell kidney cancer. We study hereditary papillary renal carcinoma, which is a very rare type of Type 1 papillary kidney cancer. Birt-Hogg-Dubé of course. We study another less rare type of inherited kidney cancer called hereditary leiomyomatosis renal cancer or HLRCC. And we study families—recently we have expanded our study of families with something called succinate dehydrogenase kidney cancer. Each of the genes and the pathways of those genes that cause these different types of inherited kidney cancer are different from each other. However, we have found that they all have in common that each one of these pathways is fundamentally a metabolic pathway. So we have learned a lot about BHD, the *Folliculin* gene pathway, from studying these other pathways. And we've learned a lot about them by studying BHD. It was BHD that originally got us in to understanding that kidney cancer is fundamentally a metabolic disease. Now when you think about it, targeting a metabolic disease is very, very different than the traditional way we think about treating cancer. So I'm very hopeful that understanding this fundamental process is going to give us approaches to therapy that we never would have dreamed of.

***Doctors who treat BHD seem to agree that apart from avoiding smoking there aren't very many lifestyle factors that a BHD patient can do themselves to avoid getting cancer. However, I recently read a book by T. Colin Campbell called <u>The China Study</u> in which he suggested diet may play a role in tumour growth. What is your opinion on that?***

I'm not aware of that study exactly that you're referring to. But the more I study these cancer genes, the more I study these cancers and these pathways, I think diet and exercise are incredibly important. I think that in some ways, exercise may be the best drug for cancer ever developed. The more we study what that does, how energy consumption affects these cancer pathways. I wouldn't be surprised at all if diet didn't play a huge factor in many cancers and also kidney cancer. If you look at all the cancers in the body and you look at a relationship between body mass index, how heavy people are, and their incidence of cancer, kidney cancer is among the highest. There's a very clear correlation between body mass index, overweight, and incidence of kidney cancer. So it wouldn't surprise me at all if that wouldn't be seen also in the families. We have not studied that specifically although it's just a matter of getting people to do it, I mean getting enough people to do it. We have the data for that, we're hoping to look at that this year. But I think that's incredibly important. I wouldn't say under-appreciated, because a lot of scientists know this is important. But the more we study it in all of our kidney cancer genes, it just looks like one of the most central part of this cancer pathway: energy consumption.

***How will new technology affect kidney cancer research?***

It took us nearly seven years to find the BHD gene. We did it, you might say now, the old fashioned way. We got all these families, take their blood, extracted their DNA, ran genetic linkage analysis to trace the gene in the families. Today you can do that work with whole genome sequencing, sequencing all the genes in the body, and I'm sure do that much more quickly. Well, it's the same thing with understanding the fundamental aspects of these cancers. In other words, we're using all sorts of new technologies, mass spectroscopy, liquid chromatography, in some cases whole genome sequencing, in some cases whole genome array studies, whole genome array studies of microRNAs, all sorts of new technologies. And those things, those types of techniques, can just make them go quicker, give new insights you wouldn't have known before. Whereas in the old days, this wasn't that many years ago, we used to look at expression of one gene at a time to see if a certain gene was turned on or maybe one protein at a time. Now we can look at 37 thousand genes at a time so we can look at whole clusters of genes. Many times the problem you get into is you get so much information sometimes, it's a challenge to interpret it all. But that can help enormously.

***Based on your experience in learning how to do research, what advice would you give an early stage researcher?***

I think that for young person coming into the field, I can't think of a more exciting thing to do. This is a very big question, cancer, and we have a long way to go, but we know a lot and there are a lot of tools to use to study. I had this meeting with one of the leaders of NIH and we were just talking about things and he said to me: Marston, you have been doing translational research 25 years before the term was even invented. By that he meant—translational research means doing things that relate to patients, using patients as a model and going to the laboratory. I said to him that's the only model I know, that's the only model I have ever done is studying the human model of cancer. So, I would say for a young investigator coming into the field, for him or her, if they can, get into an environment where what they are studying is very translational to the human model, to humans with the cancer. It not only makes it more exciting, but it's not just that; you learn an enormous amount from patients. If you're working in this area, just try and do the best science you can and try and relate it as much as you can to the patients with the cancer. Because otherwise, if you're not careful, you can spend your entire life studying something that doesn't—might be an important thing—but it doesn't relate to human cancer and we need those people. We need them, working on helping these patients.

***Dr Linehan, thank you very much for your time today.***

Thank you, I enjoyed it.