Interview Transcript - Dr Masaya Baba

I'm Jill Woodward, I'm at the NIH in Bethesda, Maryland and I'm speaking with Masaya Baba who's a staff scientist at the National Cancer Institute. Masaya, what BHD project are you working on currently?

I have been working on Folliculin protein function to find the binding protein and post-translational modification, and also I made BHD knockout mouse model and FNIP1 knockout mouse model. And currently I'm focussing on analysis of FNIP1 knockout mouse model.

And you led the development of the mouse model for BHD syndrome. How has this been helpful in BHD research?

So far we have reported two mouse model. One is kidney-specific conditional BHD mouse model, and the other is heterozygous knockout mouse model. And kidney-specific knockout showed very dramatic phenotype in a very short time. So they developed huge kidney, more than 10 times heavier and then died of renal failing up to three weeks of age. So because of dramatic phenotype and short life span, I think that model is useful for drug screening. And for heterozygous mouse model, that model mimics human BHD syndrome, which produces totally same kidney tumour to human. So we think that model is also useful for drug screening.

What have been some of the difficulties or challenges that you faced in working on this research?

So when I started BHD research in March 2003, because BHD protein Folliculin is a totally new protein, so almost nothing is known about that protein. Folliculin doesn't have any known functional domain or any homology to known protein. I had to do everything which I could do, so like: starting identification of endogenous protein, or subcellular localisation, or post-translational modification. I tried everything which I could do: tried to get the binding protein or making knockout mouse model. Finally I got binding protein which is FNIP1 which is also totally new protein and didn't give us any clue to understand that function. So working on totally new protein is hard and challenging, but I also enjoy it, it's fun and I think rewarding. So difficulty is working with Folliculin.

And can you tell us what the next steps are for this project?

So, next steps: we are getting several clues from our mouse model. Based on that, we want to clarify the actual molecular mechanisms how BHD work as a tumour suppressor or how those phenotype is caused in mice. And then I think that will help us to understand the mechanism of BHD syndrome. And then our ultimate goal is: based on those understanding, finding new effective therapy for the kidney cancer.

Talk about other diseases or syndromes that might overlap with BHD and how your research might play a role in understanding these syndromes.

Yes, I think there should be some overlap in terms of function and also BHD syndrome is classified as a hamartoma syndrome, which include Tuberous Sclerosis Complex or Peutz-Jeghers syndrome or Cowden disease. So interestingly, all of them are involved in mTOR pathway; also in energy sensing and metabolism. So I think there should be some overlap. Also, I think Folliculin should have more important proteins than we expected. So analysis of Folliculin may contribute to further understanding of kidney cancer, maybe as a type of cancer.

What advice would you give an early stage researcher, what's been the most important thing you've learned about the research process?

Although it might be just my research style, but I think one of the most important things is working with your own hand. Of course you need a strategy and a plan based on your working hypothesis, but you will not know the outcome until you test for yourself. So to me that's one of the most important things in research.

How does mutation of FLCN lead to BHD syndrome?

Most of the mutations found in BHD patient predict loss of function of BHD protein Folliculin. In kidney tumour we see the second-hit mutation or LOH [Loss of Heterozygosity] in the other allele, so I think loss of function of Folliculin protein, complete loss of function of Folliculin

causes BHD kidney tumour in BHD patient. I don't have enough evidence about the lung cysts or fibrofolliculoma if they really caused by complete loss of function or not.

Can you talk about what you were working on before you got into BHD research?

I got training as an urologist in Japan. I have seen many patients with kidney cancer or some other urologic cancer. So that motivated me to do research and I got a PhD course. And then first I started my research in Von Hippel-Lindau protein analysis, which is a tumour suppressor gene and the loss of that causes kidney cancer also. And then after I got PhD, actually I attended a VHL meeting and met researcher from NCI and then heard that they are almost cloning the new tumour suppressor gene from BHD syndrome patient. So I was very excited about that, so I applied as a post doc in NCI.

Where do you see the BHD field in 5-10 years?

So I think BHD research is developing very fast these days, so I think we will figure out the molecular function of BHD protein and FNIP1 and FNIP2. And then maybe in ten years we will figure out how BHD syndrome — the molecular mechanism of BHD syndrome—and then I hope we will find out effective therapy for BHD syndrome.

Masaya Baba, thank you very much for joining us today.

Thank you very much.