Interview Transcript — Dr Vera Krymskaya

We're here at the Fourth BHD Symposium. My name is Jill Woodward and I'm speaking with Dr Vera Krymskaya. Can you tell us the aim of your research?

I'm a basic scientist. So my interest is science and advancing science, to start with—that's if you ask my basic interest. I did my PhD in Institute of Biophysics in Academy of Sciences in former Soviet Union then. But my interest is actually how to translate the basic science which is often looked as, you know: it's basic science, it's too far from life. But I think I'm really excited in the work that I do, that I could bridge basic science to the diseases and people and maybe eventually, well, at least help to prevent disease development or stop [it]. Or actually, ultimately all of us working on it: can we find a cure? That's the ultimate goal.

Your group has made important contributions to the understanding of TSC and LAM. How do TSC and LAM relate to BHD?

Well, I happen to work in pulmonary diseases at the University of Pennsylvania School of Medicine and we apply our knowledge in basic signal transduction mechanisms which regulates cell proliferation, growth. And then actually, I was focusing my studies on asthma where we have airway remodelling, smooth muscle remodelling, and studying vascular diseases also where [there is] vascular remodelling. And it's very unusual process where smooth muscle all of a sudden starts to grow. So pulmonary lymphangioleiomyomatosis, it's a rare lung disease which characterised by abnormal growth of smooth muscle-like cells in the lungs, and growth of those cells cause lung cysts. And Birt-Hogg-Dubé syndrome also cause lung cysts—I mean there is, one of the pulmonary manifestations include lung cysts. So that's the long way how I came to BHD: because my interest in lung diseases and also the mechanism, basic mechanism which makes destruction of lungs and how we could prevent that.

You're a member of the LAM clinic in Philadelphia. Can you describe the clinic and talk about whether there would be a potential to have something similar for BHD?

Yes, I'm very glad that we have LAM clinic. And actually I wanted to say little—a few words about LAM and then this disease. Because I think this is great and an example of how only in

ten years—the gene function was discovered ten years ago—I mean the gene was linked to LAM, it was 2000, then in 2002 gene was discovered. And just how important [it is] to find the function of the gene, because once you find the function of the gene then you could look for the drug. And then what our contribution to the field was that we were able to dissect—first time and still only in the world group which successfully dissected primary LAM cells from human lungs. And then we were able to identify mutations of *TSC2* in those cells and then show that if we take a drug which is already approved by FDA, rapamycin, and we used that drug on human LAM cells at physiologically relevant doses and we showed that we could just knock off the growth of those cells. So that was our contribution. Other people using different models showed that we could also use rapamycin and then prevent growth. And that led in the year 2003 already to start first clinical trials. And so it is very good example why it's so important to find the function of the gene. So in BHD, well, that's what we want to do. And LAM clinic, going back to your question. Well, that progress that we made ten years ago brings awareness of LAM and then of course, at Penn, patients come to see our pulmonary division physicians and pulmonologists. And then we have around 40 patients with pulmonary LAM which see at Penn pulmonologists. So it is very important, why?—because LAM clinic, it's not only pulmonologists because also, LAM, it's also kidney manifestations potentially or other [symptoms] linked to Tuberous Sclerosis, so it's also involving gynaecologists, pulmonologists, also experts in renal manifestations—so this is what clinic means. And then can something like that—could be with BHD? Yes it is. We have experts in genetics and people who study Birt-Hogg-Dubé here, I mean at Penn. And I know them and we talk about this—that we eventually we may have a BHD clinic at Penn.

The University of Pennsylvania is setting up a Center for Orphan Disease Research and Therapy. How do you think the centre will affect rare disease research?

We are very fortunate that gifts were made to University of Pennsylvania last year in summer which enable us to found the centre. It is hard task but centre has opportunity to advance orphan and rare diseases research and therapy and clinical trials and so that's what my hope is. And we are from pulmonary diseases at Penn, [we] are natural part of that, and I have been involved in first steps in that centre and hope we can make some impact. That's our goal, that's our ultimate goal: to help people and find new treatments.

So what were you working on before you got into TSC research?

Well I was—actually I was postdoc in pulmonary studying signal transduction mechanisms which regulate vascular and airway remodelling. And that's where studying smooth muscle remodelling led me to LAM, where it is very unusual manifestation of disease—it's just smooth muscle growth tumours in the lungs. So that kind of led me there. But my major passion is signal transduction: so what makes cell which is normal, abnormal.

And what BHD projects are you working on at the moment?

Few years ago we—I heard about this disease and you know it was like 'hmm that's very exciting' and it's very puzzling because it has lung cysts. And also some evidence showing that it may—signalling-wise it's in the same pathway potentially where is *TSC2* which is cause of LAM, mutation of *TSC2* is cause of LAM. So that became exciting and interesting. Well, we did some pilot study, which was funded by Myrovlytis Trust, which is interesting on cell base which allows us to make first steps and figure out what works and where we could go in that field. Also we have now other grant by Myrovlytis Trust on BHD research, so we are searching. We are searching function of BHD because that's the major goal.

And what difficulties have you faced in this project?

Well, BHD doesn't have, you know, in the sequence it doesn't have any function. So how do you find function of protein which doesn't have function? Well at least it binds FNIP—now it was great that result was found. So it has FNIP binding protein, FNIP1 and 2, which binds, and then binds AMP kinase, so it show us where direction goes. But still, given what is published, it's very hard to find function because it depends on cell type, it depends on conditions. And so it is really, really hard. Like we were—with LAM I learned about function of TSC2 in 2000, year 2000—I didn't know anything about TSC2, but then in 2002 we already published paper—we found the function. Only two years. Well I don't know—we were lucky. But with FLCN, well I know about FLCN for five years and we can't find any function. So that's frustrating.

Can you talk about any models that you might be using in your research? And what models you'd like to see developed?

Well, it was very generous from Laura Schmidt and Marston Linehan to share with us their cells, unique cells which they dissected from BHD patient's kidney which naturally do not have FLCN. That's a great help, that's very important to have them, it's very fortunate. So we work with that—it's very good. So we use that. And of course it would be wonderful, wonderful—well, it would be great to have knockout of FLCN in lungs and see whether we could recapitulate that. But, you know, I am sure other people than us are working on that, but we still don't have that.

Do you collaborate with other BHD researchers at other institutions, and if so, how does this help?

So of course Laura and Marston they are very helpful and they have expertise. Because they discovered the gene. They are a major experience source and, as you could see at the meeting [Fourth BHD Symposium], their knowledge is vast. Also with Lisa Henske, with Andrew Tee. These meetings are very, very nice, because you have opportunity to talk and to see, and that's in itself collaboration and networking. That's how we got reagents and knowledge and besides knowledge, but also we share what we have.

How do you think the BHD field might look in five to ten years and how might that compare with LAM?

Well, you can't compare to another disease, it's so unique. You know, each disease is. And I said LAM it was lucky. Lucky in a good way because there's hard effort—[efforts] were spent by patients and scientists and we all just got lucky. BHD in five years? Well, I do hope that we will have real breakthrough. We should have breakthrough in finding the function.

We've been talking about the research that your group is working on. Can you talk to the state of rare disease research as a whole?

Actually I am hopeful. Even in the last years, few years, in the last maybe three, four years, awareness about rare diseases has really, really increased markedly. And you know there is always—there is now we have Rare Disease Day, global Rare Disease Day, which is on last day of February each year. So I think I am very hopeful. There is evidence. Twelve years ago, I didn't know about TSC, I didn't know about LAM. Twelve years ago. And many people didn't.

And how many people now know about this disease. And awareness now raised markedly. So I think that will help. And also at the NIH we have also big attention, at least in this National Heart, Lung, and Blood [Institute], NHLBI, and there's Office of Rare Diseases and there's big attention to that, that we have to pay. So I'm hopeful, as I said. I think it will get better.

We've been speaking with Dr Vera Krymskaya of University of Pennsylvania. Thank you very much for spending some time with us today.

That was my pleasure; thank you for inviting me.