Transcript

Mona- Welcome to the Inside WIMM podcast; the people behind the science at the MRC Weatherall Institute of Molecular Medicine at the University of Oxford an institute we affectionately know as the WIMM.

Catherine- I'm Catherine Seed, the WIMM's Public Engagement and Communications Officer.

Mona- And I am Mona Bassuni, a post-doctoral researcher in the Ovarian cancer group, led by Professor Ahmed at the WIMM.

Catherine- This podcast features our interview with Dr Kathryn Robson. Kathryn just retired in December 2022 after spending 40 years working at Oxford. It was so wonderful to sit down with her and learn about her research journey, the beginnings of the Institute, and her plans for retirement.

Mona- Kathryn has had such a broad ranging career with research spanning malaria, hemochromatosis, and population genetics. First, we talked about her path into science after completing a degree in biochemistry at University College London.

Kathryn-I completed my undergraduate honours degree in Biochemistry in 1976. And then was fortunate enough to be awarded a scholarship from the Burroughs Welcome Foundation to do a PhD on Foot and Mouth Disease virus at the Animal Virus Research Institute at Pirbright.

Catherine- Could you paint a picture of what it was like in the foot and mouth lab?

Kathryn- Very bizarre is the way I would describe it. You ended up being a terribly clean student. The whole of the foot and mouth laboratory was a containment Level 3 facility. So basically, you went into work in your home clothes. You stripped down, walked through a dry shower barrier, put on clothes that they provided you with, and then you got dressed and you went into work. And when you left work you showered, and you washed your hair. And then you put your own clothes on, dried your hair and went home. It did mean that you didn't actually need to take a shower or a bath at home and a lot of your laundry therefore was done for you. It was a bonus that you wouldn't necessarily understand when you were given the post.

Mona- What were your next steps after your doctorate?

Kathryn- I went to a conference at the end of my second year and was fortunate enough to meet someone who gave me some, again very wise advice. And that was to apply for a postdoc then, rather than wait till I finished my PhD, so I wrote five letters to the labs I thought I wanted to go and do a postdoc in, and I received four offers and the lab at the top of my list was Berto Malley's Department of Cell Biology at Baylor College of Medicine in Houston. So that's where I ended up for three and a half years. And I learnt how to clone and sequence genes and the project I had was to clone and sequence the gene for the enzyme phenylalanine hydroxylase, which is what is mutated in the inherited disorder phenylketonuria (PKU) . It was at time believed PKU was believed to be a disease of Northern Western Europeans. It was not thought to be elsewhere and because my boss was Chinese, he had Chinese contacts and it turned out that 10% of adults in Chinese mental institutions were there because they had undiagnosed PKU. It's now diagnosed because they know to look for it.

I started applying for jobs back in the UK and there was a job advertised in Oxford led by David Weatherall and it was to clone and sequence globin genes. So, I thought I can clone and sequence any gene because that's what I've been doing in Houston. So I applied and got a very lovely letter back, saying terribly sorry, the post has been filled. PS Would you like to work on cloning and sequencing malaria genes? So I wrote back immediately and said yes please, because it linked my interest in infectious disease with the experience I'd got in working in cloning and sequencing genes. So I arrived in Oxford in April 1983. We ended up making expression libraries and someone from my Pirbright days was generous enough to make me two very, very long oligonucleotides at no expense and we use them to screen the library. And we found the gene that we intended to find, and we found a gene we weren't intending to find, and the gene we weren't intending to find turned out not to be known about at the time, but it shared with the circumsporosoite protein the same motif EWSPCSVTCG. And that's very unusual motif. It's found in a number of other proteins such as thrombospondin and properdin. And it turns out that both Trap (Thrombospondin-related anonymous protein) we now call it adhesive protein, and circumsporosoite protein are on the surface of the sporozoite and the sporozoite is the form of the parasite that the female mosquito injects when she has a blood meal and it has to find its way to her to a hepatocyte, which it in facts and it then takes seven days to go through the life cycle to release merozoites and the merozoites then have to find a red cell, infect a red cell and then you have a 48 hour cycle where new merozoites are released from an infected red cell and what we didn't know at the time was that TRAP is a key protein in how the sporozoite moves. So, think of snail and slug trails that you see. That's exactly what happens with both circumsporozoite protein and TRAP. So it is key in how the. Sporozoite moves and finds and recognises the hepatocyte. And it's now ended up being in vaccine trials.

Mona- So as a researcher, can you tell us about David Weatherall as a scientist and a person?

Kathryn- David was the loveliest person you could ever wish to meet. He was generous with his time and generous with his science, and he was very, very insightful. And this was the advantage he had as a clinician, because he understood the disease. And he also understood that if you were good doing good science, you needed to be allowed to do good science because that way there would be discoveries made and during the time that we were on level 7 in the JR, when we were in the Nuffield Department of Medicine, there were a huge number of breakthroughs made and that was basically because he left people to get on and do interesting science.

Mona- And you arrived before the institute took shape?

Kathryn- When I arrived in Oxford the concept of the Institute of Molecular Medicine was being hatched. And where the Institute now is, was a white building called the Nuffield Institute for Medical Research, and that forms the two floors of the white building of the current Institute. The rest was a car park and some pine trees. So, the Nuffield Institute for Medical Research was used by a number of researchers. The only one who stayed on was someone called Colin Jones, everybody else was rehomed. And the building was stripped internally back to the bare brick and totally refurbished. And the first people to move in were the Neurosciences group who came up from London. There was a group led by Andrew McMichael who were coming from surgery who were immunologists, and you had the malaria group who worked on Level 7 who moved in. I had different space on level 7, so I didn't actually move with the malaria group. I moved in April 1989, when the brown building was completed. What was special was everybody was using the same sort of techniques, and so some were using it to study immunological processes, others haematological and others infectious diseases and others genetics. And you have to realise the time between 1986 and 1989 was when PCR came of age. It had just been discovered. So rather than having to do a whole

lot of basic cloning, M13 as a vector sequencing system had come really very much online, so sequencing was much more efficient than when we were doing Max and Gilbert sequencing. PCR meant that once you got some sequence, you could use PCR as a process to choose where you wanted to sequence. You didn't have to play the fragment game or the cloning game, you could actually just move your primers along, so you know there was a period in time where I was sequencing the TRAP gene in different malaria isolates, and I did 60 KB's worth of sequencing in probably 3 months, which would previously have been absolutely unheard of, but it was because technology had moved on.

Catherine- And but I assume that's a lot easier when you're surrounded by people using (the same techniques)...

Kathryn- It's a lot easier when you've got people around who may have the kit you might need to borrow because there weren't that many PCR machines around.

Catherine- So how do you then move from malaria to hemochromatosis?

Kathryn- That is an interesting story. At the time we had a quinquennial MHU (Molecular Haematology Unit) review and we thought malaria, the malaria gene TRAP was exciting. But we couldn't convince the MRC that it had anywhere to go. We didn't know what it did, and it wasn't until we could actually play transgenics that we knew what it was, so it was felt that I was a bit of an outlier in the Molecular Haematology Unit and therefore I needed to do something that was more related. One of the issues with thalassemia patients is they have secondary iron overload due to the high turnover of red cells and problems with erythropoiesis. Hemochromatosis is a disease of primary iron overload, where there is the inability to sense iron levels correctly, and so you take up too much iron from your diet. You don't have a way of secreting iron other than by blood loss. So, if in the case of thalassemia, you're having to give people blood transfusions you're giving them the extra iron in the form of the blood transfusion. They've got no way to get rid of the excess. OK, so the hemochromatosis gene was not known at the time. It was known genetically that it was on chromosome 6 because there was very close linkage to the MHC Class 1 gene HLA-A. And if you talked to people at the time they went, oh it's going to be within 50 KB because it's so tightly linked. We did a very key experiment, but at the time we weren't fully aware of how key it was. It turned out that when the gene was cloned it was actually five megabases away from HLA. Not 50 kilobases. So basically we were looking in an unmapped part of chromosome 6 and nobody was looking in the right place, so we pointed X marks the spot you're on the wrong island. A big pharmaceutical company cloned it, they really threw everything at it and it turns out that it is primarily a disease of northern Europeans, 80% of people who develop the disease have a homozygous for the same mutation. It's known colloquially as the C282Y mutation. The protein is nothing like anybody expected, it looks like an MHC Class 1 gene. It doesn't have a groove for peptide and the mutation actually results in the failure of the 3rd loop to actually form a disulfide bond and it has a role in regulating, transferrin and transferrin receptor, and that's how it works. But basically, in looking at hemochromatosis we have uncovered and we is not just me, it's a group who had interest in hemochromatosis. We have uncovered a pathway of handling iron, discovering things like a little peptide hormone hepcidin, which is for iron what insulin is for glucose and it's the hepcidin that is made by hepatocytes that controls how much iron is taken up from the gut. And failure to make hepcidin results in a very severe form of juvenile hemochromatosis and there are other genes that we've identified that are fully penetrant. Some are autosomal dominant and affect iron uptake from the gut and others give you juvenile hemochromatosis, so we've uncovered a pathway, and that's been very exciting and it's consenting patients that have allowed us to do this.

Catherine- How on Earth does that then move to looking at human migration.

Kathryn- As the human tissue designated individual, I ended up taking custody of David Weatherall's DNA freezer of the South Pacific. And there were people who wanted to throw it out and I had to fight long and hard for it not to be thrown out and David wanted it kept. And David was happy for me to manage it. And at the same time we had three different requests, one via Doug, one via someone who'd worked with John Clegg, who'd worked very closely with David and had been involved in working with some of the samples previously. And one with David Weatherall, and everybody wanted to use the same technique, but they wanted to use the same technique but to get a different result. I know that sounds a bit bizarre. We had population linguistic people who wanted to look at DNA patterns using single nucleotide polymorphisms to look at whether there were polymorphisms linked to linguistic patterns. We had other people wanting to look at population migration and archaeology in the South Pacific. And other groups who were studying infectious disease in the Pacific populations and they needed to know whether in fact, genetically the population they were studying was more genetically at risk than the surrounding islands. But the technique everybody needed to use was single nucleotide polymorphisms. So I said, hey folks, we're only going to thaw this DNA once. It's very, very precious. We don't know whether the SNP analysis will work, but in fact we were fortunate because the DNA had been collected in the 1980s and was very concentrated, it was perfectly fine. It had been stored at minus 20 and it probably had undergone a couple of freeze thaws, so the DNA went off and because the three groups were made to collaborate instead of doing a low level SNP analysis, we did a much deeper SNP analysis and we all collaborated. And that has led to a number of publications over the last few years in journals such as Science and Nature. So, I may have been the safety officer, but I was doing some science in the background. And it's now going off for sequencing so it's going off the whole genome sequencing and the point you need to understand is that we had the ethics that the samples being collected under in the 1980s was for thalassemia studies so we couldn't reconsent because the samples had been totally anonymised. We went to the university committee OxTREC to say, 'what should we do?' and they said it's actually unethical not to reuse the samples because this population has been underrepresented in all the global genetic studies and there is a lot for them to benefit. So, we looked at the consent that John Clegg had got in his filing cabinet. And there were letters from Ministers of health for this island and that island and that government. So, we contacted the embassies, and they said please feel free to reuse the samples, we've got too much to gain. By saying no.

Catherine- How did you move to the health and safety role?

Kathryn- How I got into health and safety was the university insists that each department and each building has a health and safety committee, and Andrew McMichael was the Director of the Institute from 2000 when David Weatherall retired until 2012, when Doug Higgs took over. He asked me to be the Institute safety officer. And at that time, it was basically chairing three committee meetings a year and not much else. Things have moved on on the safety front and it became much, much, much more of a hands-on job. And we had a QR in 2000 and ? - it was the first QQR Doug had. And the MRC needed to cut budgets and the budget they cut was mine. So, my science, my hemochromatosis went. By then we were handing over the hemochromatosis diagnostic service that we'd built up to the NHS, and that has expanded such that they now do parallel sequencing of six genes that could be mutated at once so. We've seen what was lab(work,) being translated into diagnostics, so that's revolutionised that. So in a way, it wasn't a bad time, but I'd also started because Doug had asked me to start doing studies as the gene is expressed in red cells, so we were doing some transcriptome work, but it wasn't far enough progress, so I ended up the group closed,

and I ended up doing health and safety and at the same time Human Tissue Authority legislation came about.

Catherine- How did things shift as of March 2020 and what work was going on behind the scenes?

Kathryn- We had to get risk assessments in place for working with COVID. Nobody in this building had any experience with COVID. Now it was another thing that I had to be able to bring to the table is I breed pedigree cats as a hobby. And there is a infectious condition in cats called feline infectious peritonitis and that is due to a coronavirus. So, I was more aware of what coronaviruses can do and how coronaviruses can mutate than probably anybody else in the building. So, I brought that so we were working 24/7 to get risk assessments in place, get people trained up and put controls in place that meant people could come into the building safely. It meant sticking up signs everywhere, keeping everybody two metres apart. Putting in electronic controls for booking space, which meant that people could emotionally feel safe when they were working because they were going to be under stress to get through the experiments and get the data that was required.

Mona- And you and you probably have quite a good overview. What are some of the highlights that just stand out from your mind in terms of the type of COVID research that went on?

Kathryn- The number of publications and the huge collaborations that went right the way across Oxford. I mean, science is competitive, but you have to realise everybody in Oxford worked together and that was really quite amazing. You had some people who were B cell experts who were doing the B cell work. The T cell expertise was in the Institute, so all the T cell stuff was done and that was a major strength of what Oxford was able to offer.

Mona- So of all these roles and research experiences, which one is your favourite?

Kathryn- I would say probably TRAP. Once we realised how important it was, and we'd always believed because the central portion was so heavily conserved and a lot of malaria genes are very, very sequence variant, and it had this unusual sequence because you don't shove tryptophan into a protein just for the sake of it. It's a very expensive amino acid and it's got a very bizarre shape so it's there for a reason and by doing some sequence alignments I realised that we had a magnesium binding site. And it was a protein made-up of various domains and therefore it had a function. What we didn't know until too late for me was what that function was.

Catherine- Which was?

Kathryn- Basically, parasite, sporozoite migration.

Catherine- And I know you've been a significant voice in driving forward public engagement throughout the WIMM. How did you come to public engagement? And how has that shifted?

Kathryn- That came about because of the work on hemochromatosis in that the country has a very proactive, hemochromatosis society, and those researching on hemochromatosis were always invited to address the society at their AGM when it was held in London. So, every June I would go down to the hemochromatosis society, talk to patients, get to meet patients, give them advice, explain what research was being done, how the diagnostic service was being improved. And we had two lots of funding from the European Commission. The second lot of funding was the funding that I managed, and it was a team of 11 investigators across Europe. And that was to increase the awareness of the disease, because treatment's dead easy, you take the excess iron off in blood and the blood service can use the blood if you haven't got any other complications, so it's a win win situation. But presentation is very vague. It's I feel a bit unwell. I feel a bit tired. And you had to

move it up the GP sort of well, you're 40, cut down the alcohol bit more exercise, eat a better diet and so we were offering free diagnostic service and that sort of brought to life what was going on. And because of that and then actually only doing health and safety for a day and a half a week, with the HTA I had time on my hands when I wasn't doing health and safety and we had at the time a computer, a member of staff on the IT team who was on the PTA of his local primary school in Abingdon. And that school had on a Friday afternoon s programme which was to bring in outsiders and I had to prepare five 1 hour slots. So, one of the slots was on genetics and because of the cats I used the cats and I used Lego because that was what they had in school as genes and we made chromosomes from building Lego together and the different colours were different genes.

Catherine- When you say cats, did you actually take cats in?

Kathryn- Yes, I did take cats in. I had at the time a cream point, Aurora, who'd been mated to a seal point and cream point females can only produce if they're mated to a cat that's not ginger, can only produce tortoiseshell females, and there were three tortoiseshell females in the litter. And needless to say, one of the children went. Please miss, why don't they look like Mummy or Daddy? Because I'd bought photographs in and I then had to explain the process of X inactivation to. 9, 10 and 11 year olds. Well, on a tortoiseshell, the X inactivation is random, and you see it as ginger and colour in different spaces. So I was able to explain very easily to them and they all got the concept of X inactivation and I had to explain to them that X inactivation had first been described by Mary Lyon at Harwell and that school in Abingdon had parents working at Harwell.

Catherine- And what do you think the value of public engagement is?

Kathryn- I think it improves people's science. Another course I did with the MRC was basically if you're designing studies, if you talked to the patients, there may be something that actually costs you nothing to put into a study, but is actually going to strengthen the science of the work that you're doing and its application to helping treating patients. It can be just putting an extra question into a consent form or an extra question into a circular information, sort of, you know, "we would like to hear from you if you've got bony ankles", because it turns out that in hemochromatosis most patients who develop the disease end up with a particular bony bit to their ankle, and it's unique to them. So what wasn't known until somebody asked was that actually it's almost diagnostic of the disease, so if it's somebody who turns up in a rheumatology type clinic, if they feel it or they need an ankle replacing or whatever, you can say actually, you've got hemochromatosis that's not being recognised, but it's actually joining up those dots and in many cases you need the patient. It's a two way. It's not doctor patient, it's patient- doctor and patient-researcher as well.

Mona- Where are you at and what are you looking forward to do?

Kathryn- I'm retiring in 10 days time.

Mona- OK, so what's next?

Kathryn- What's next is, I'm a mad keen gardener, so I've got stuff to do in the garden. I have finally bred the elusive lilac tortie tabby point birman (cat). Who I took to a show 2 weeks ago and I will be showing her next year when she's an adult. I so I've got the cats. I've got the garden and I will do some museums, galleries and gardens.

Mona- This has been Inside WIMM. If you like the podcast please subscribe, like or review.