Disease Models & Mechanisms 6, 6-8 (2013) doi:10.1242/dmm.011429

Driving change in tuberculosis research: an interview with Anne O'Garra

Anne O'Garra is Head of the Division of Immunoregulation at the MRC National Institute for Medical Research (NIMR) in Mill Hill, London. In this interview, she recounts the excitement of her early career discoveries on cytokines and T-cell differentiation, and discusses progress on tuberculosis research by her group and multiple collaborators.

Anne O'Garra was born in Gibraltar in 1954. After completing her scientific training in the UK, she went to the DNAX Research Institute in California in 1987, where she spent 15 years working on fundamental principles of T-helper (Th) cell differentiation, cytokines and immunoregulation. In 2001, she returned to the UK to initiate the Division of Immunoregulation at the MRC National Institute for Health Research (NIMR), where she continued working on cytokines and cellular differentiation, as well as expanding to investigate the immune response to tuberculosis (TB). She divides her time between London and Paris, where her husband, Paulo Vieira, is a researcher at the Pasteur Institute.

What made you decide to pursue a career in research?

For one reason or another I became interested in science as a child. I went to a girls' school run by nuns, but at 16 I had to go to a boys' school to take the science classes that would allow me to prepare for my A-level exams. At age 18, my family encouraged me to go to a further education college in the UK so that I could finish my A-level exams in an appropriate setting. However, I then discovered that I couldn't get a grant to go to university in the UK, having only lived there for a short time. So, I worked as a research assistant for 3 years, during which I became interested in microbes. I then did a BSc in microbiology and biochemistry at the University of London, followed by a PhD at the NIMR with Barry Ward, focussed on bacterial adhesion. Unfortunately, Barry left after 10 months, but by this time I had linked up with another generous investigator, Michael Parkhouse, who became my mentor. He was working with monoclonal antibodies, which I needed for my project.

Working with Michael Parkhouse was my first real exposure to immunology, having had only a short course on the subject at university, and I kept on thinking about it. The institute was (and is) very multidisciplinary, and there was lots of opportunity for interaction in the famous NIMR bar. Through these interactions I became very interested in cellular differentiation, and I quickly learned that the haematopoietic and immune systems were ideal for studying this. I was then lucky to get a postdoctoral fellowship at the NIMR with Gerry Klaus to study cytokines and B cells. The main finding during my postdoc was the discovery of interleukin-5 (IL-5), a factor that acted on both B cells and eosinophils (O'Garra et al., 1986; Sanderson et al., 1986) (note that IL-5 was initially referred to as IL-4). This was very exciting, as it was the earliest evidence that cytokines were pleiotropic (that is, that a single cytokine could induce effects in different cell types) – IL-5 worked on B cells and eosinophils!

After that, I decided I needed to do another postdoc before I could run a group in immunology research, as both PhD and postdoctoral fellowships were each limited to 3 years in those days. I'd only spent 3 years

working on immunology – I definitely needed more training and experience before starting my own group, and I wanted to continue working on cytokines. I went all over the United States looking for the right position, and I ended up deciding to go to DNAX (now part of Merck, but at that time part of Schering-Plough Research Institute). The reason I chose DNAX is because it was a small basic research institute where they had joined cell and molecular biology to study cytokines – and they were doing very exciting work. For example, the year before I joined, Tim Mosmann and Robert (Bob) Coffman had published the first paper on the identification of Th1 and Th2 cell subsets, which was a very fundamental finding in immunology (Mosmann et al., 1986). In addition, Kenichi Arai was Head of Molecular Biology, and he and others had already cloned several cytokines. Others at DNAX, namely John Abrams and his group, were making vast numbers of antibodies against cytokines. I started as a postdoc at DNAX in 1987, and was lucky to be at the right place at the right time to obtain an independent position as a senior scientist.

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When I arrived at DNAX, I started by making antibodies to IL-5. As I gained more independence, I began working on antigen-presenting cells and wished to determine whether, when they were appropriately stimulated, they could drive either Th1 or Th2 differentiation. Before long, things just started exploding. We discovered that B cells made IL-10, and that IL-10 suppressed T-cell differentiation indirectly via effects on macrophages and dendritic cells (another early example of pleiotropy!) (Fiorentino et al., 1991). IL-10 had just been cloned at DNAX by Paulo Vieira, who was at that time a postdoc with Kevin Moore, and is now my partner of 22 years! Around this time we also started a long-term collaboration with Ken Murphy (at Washington University, St Louis), who had a T-cell-receptor transgenic mouse that we needed for our experiments. Our studies led to the identification of IL-12 as a cytokine produced by macrophages and dendritic cells that drove Th1 cell differentiation.

When did you begin working on pathogens?

At DNAX, we were using in vitro systems that allowed us to work out fundamental differentiation pathways and signalling networks, and to identify the important transcription factors. But, by the mid 1990s, I had started to work on pathogens such as *Listeria*, *Legionella* and others – basically, we used any pathogen that told us something about the cytokines we were studying. These pathogens mainly helped us look at the role of IL-12 and, later, IL-18 in the Th1 response and in protection against pathogens.

What has been the most exciting discovery of your career?

There are certain discoveries in each phase of my career that stand out. During my PhD, getting an assay to work whereby bacteria stuck to buccal epithelial cells was very exciting. It was visually rewarding: you could see the bacteria adhering to the cells, and this could be blocked with antibodies that I had produced against the bacteria. During my postdoc at the NIMR, the most exciting finding was that the cytokine we were studying (IL-5) activated both B cells and eosinophils. In those days, you cut pieces out of a gel, immersed them in medium, and then tested the supernatant for activity. I still remember the day when David Warren and I had our hand-drawn plots showing that the same factor (purified by our biochemist collaborator Tony Magee) activated B cells and eosinophils. It took a while to convince the field that a cytokine could be pleiotropic: back then, it was thought that B-cell factors acted on B cells, and so on. Now we know that it's far more complex than that.

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What made you decide to return to the NIMR?

At that time, Paulo was working in Lisbon, Portugal (his home country) after returning from DNAX, and later moved to the Pasteur Institute in Paris – but the UK attracted me back. So, I looked at various positions in the UK, and I chose the NIMR mainly because of its multidisciplinary environment, and the opportunity for interaction between different divisions. Also, I knew from my past experience here that, as well as being highly competitive at an international level, the NIMR was (and still is) a very friendly place – very people-focussed – which was important to me. I was asked to initiate a new Division of Immunoregulation, which was meant to interface between the Divisions of Immunology and Infection; there was a lot happening in both of those divisions, but there was not enough interaction between them. I returned to the NIMR in October 2001 and set up this new division.

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What encouraged you to begin working on TB?

At that time, the Director of the NIMR was John Skehel, and he said to me, "O'Garra, now that you're going to start this division, don't you think it's time you worked on something that actually kills people?". That made sense to me, so I considered the killer pathogens: I could work on HIV, but my experience with mouse models would be wasted; there was malaria, but Jean Langhorne was already working on the immune response to malaria at the NIMR; and there was influenza, but I was daunted by the importance of the type I interferons (these are very complex – we now know of 20 that bind to just one receptor). Of course, this is ironic, as we've recently discovered that type I interferons are important in the immune response that contributes to the pathogenesis of TB! Anyway, in the end, I chose to work on TB. This is an important disease caused by infection with a deadly pathogen, and it fitted well with my background. The NIMR also has a strong history in this area: in particular, Philip D'Arcy Hart made some very important discoveries in TB research, including pioneering TB treatment and the discovery that *Mycobacterium tuberculosis* resides in the phagosome.

We began by setting up aerosol mouse models of TB, which hadn't yet been established at the NIMR. We worked on mice for a few years but, to make progress, we really needed to work on humans. This first began through a link with Onn Min Kon, who heads up the chest clinic at St Mary's Hospital, Imperial College, in London. He sent a registrar named Matthew Berry to work with me for 3 years, and Matthew really helped to initiate the study. Douglas Young, who had recently become Head of the Division of Mycobacterial Research at the NIMR, also had a real vision for directing TB research. This vision led him to recruit Rob Wilkinson to his Division – with Rob and his team being based in Cape Town.

At this stage, we didn't have any money for TB research. I wrote grants for the project, but no-one was interested in funding a mouse immunologist to do human studies. That didn't daunt us, though, and we kept going. I was able to shift some of my core NIMR funding awarded for cytokine work to support some of these studies – without that flexibility, the project would have been a disaster! Eventually, we got some funding from the Dana Foundation (www.dana.org/) – this is a small foundation that funds basic researchers to begin working on human disease. Ralph Steinman, who was a dear friend and a very caring mentor, told me about the foundation, and was very excited about my launching into research on human disease.

It wasn't until 2004, during a visit to Jacques Banchereau's institute (the Baylor Institute for Immunology Research; BIIR) in Dallas, that I realised how we were going to do this project. During my visit, I met Virginia Pascual, a paediatric rheumatologist and immunology researcher who had identified distinct blood

transcriptome signatures for several inflammatory and autoimmune syndromes. Although TB was different, in that it was a lung infection, I thought this approach might work – that maybe we could identify a blood signature that could differentiate latent from active TB. So, we collaborated with Jacques' group and with Damien Chaussabel, a young investigator recruited by Jacques to the BIIR in Dallas who had developed an excellent approach for simplifying complex datasets into something meaningful. We initially looked at transcriptomes from a small cohort of patients in London, and then expanded the study to larger cohorts in the UK and in South Africa. In parallel, we worked out the immunology in my lab at the NIMR. We reported on this study in 2010 (Berry et al., 2010), and then published a follow-up paper in which we showed changes in the blood signature in response to drug treatment; these changes are evident as early as 2 weeks post initiation of treatment, which is exciting from the point of enhancing the clinical management of TB (Bloom et al., 2012).

What would you say are the three most urgent challenges in the TB field?

I believe they are to improve diagnosis, drug monitoring and prognosis (i.e. to predict which individuals with latent TB will go on to get active TB). This is why we chose to look at latent versus active TB in our studies. 1.4-million people die each year from TB and there are more than 9-million people infected. It's estimated that one third of the world's population is infected or has been exposed to the infecting pathogen, *M. tuberculosis*, but only 10-20% go on to get active disease. However, there is currently no way to predict who will progress – there are no biomarkers. We don't even have a reliable way of telling who has active disease and who has latent disease, unless the individual is sick. If we could determine who had active disease, who had latent disease and then, in turn, who would progress from latent to active disease, we could treat TB much more effectively. Even then, existing treatment is arduous and toxic, and multi-drug-resistant strains are a problem. Also, the only vaccine we have against adult pulmonary TB has very variable efficacy – from 0-80%. There are so many challenges.

What is the outlook for your work on TB?

First, we're using what we've learned from the human blood signature to improve our mouse models. Most mouse models are produced on a C57BL/6 background (or sometimes 129) because that's what knockouts are made of. However, C57BL/6 mice are relatively resistant to *M. tuberculosis* infection. So, we're now infecting more susceptible mouse strains to see if we can find blood signatures and pathology in mice that resemble the human situation more closely. We're now also infecting mice with clinical isolates of *M. tuberculosis*, some of which induce more type I interferon than the regular lab strain.

Together with Damien Chaussabel, we're also setting up a modular analysis for inflammatory, autoimmune and infectious diseases to look for disease-specific blood signatures in mice. These signatures can be obtained from about 200 µl of mouse blood (i.e. you can keep the mouse alive), and be used to monitor the immune response through infection, chronic disease, vaccination and other manipulations. Findings in mice can then guide more targeted studies in humans.

We're also carrying out a longitudinal study with collaborators in Leicester, UK (Pranab Haldar and Gerrit Woltmann) to determine whether our blood signature can predict which patients with latent TB will go on to develop active TB. In addition, we will collaborate with Rob Wilkinson, Clif Barry and eventually Carl Nathan to monitor responses in patients receiving new TB drugs. We also have links with the Institute Merieux (www.institut-merieux.com/uk/), who has funded our next programme, which aims to develop our blood signature as a diagnostic tool and to measure responses to drug treatment.

Do you have any advice for young scientists?

For students: follow your passion! Do science because you have a burning desire to discover things – because you're excited about your data and have a thirst for new knowledge. Discuss your data, don't be afraid to question it, and get input from others. Present it at conferences whenever possible and eventually in papers, because that's how we move science forward – by communicating it. Also, make sure to interact with your mentor and collaborators with energy and fervour. For young group leaders: remember that you can't do it all on your own – take the time to find excellent mentors. And always keep the big picture in mind: relate what you're doing in experimental models to the human disease.

As well as doing research, you are on many committees and boards, and dedicate time to being an editor. How do you juggle everything?

I'm organised, I compartmentalise different tasks and I work hard, sometimes until very late. But I always take time for people – I don't like to rush that. And all of these other activities I'm part of, they all teach me something – they enrich my life and my work. Learning is such a great luxury and privilege.

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If not science, what career would you have pursued?

Probably music – I played the piano and sang, although not well enough to make a career out of it. In science, I think I might have been interested in oceanography if not immunology. I heard a seminar on oceanography at the Royal Society recently and it was fascinating!

DMM greatly appreciates Anne O'Garra's willingness to share her unique thoughts and experiences. She was interviewed by Sarah Allan, Scientific Editor for DMM. This piece has been edited and condensed with approval from the interviewee.

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