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Working together toward vaccines and biomarkers in the real world

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It started at school. I went to a girl's school, Alexandra School and College in Dublin, where both our physics teacher and our chemistry teacher had PhDs and were excellent and inspirational teachers. And in a very early science exam I got 99/100. Somehow from then on it seemed clear to everyone (but also to me) that I would be a scientist. The high mark was of course a woeful way of measuring the skills I would later need, as at that stage a good memory would suffice. Those who know me well will share my exasperation that I obviously wasted some useful brain cells in those early years as my ability to remember facts is now rather embarrassing, and to remember faces or names even more so.

There was never a question of whether or not I would go to University, just what subject I would study. My father had qualified in medicine and dentistry, but I never fancied medicine; I was not at all sure I could either cause pain (in retrospect an odd way of viewing a healing profession) or cope with people vomiting. I was right about this latter concern, as I later found out when taken on tours of TB wards with my stomach heaving as people generated and spat out sputum. Anyway, there seemed to be general agreement that Natural Sciences in Trinity College Dublin was where I was heading and as is usually the case, I had a marvelous time at university.

Natural Sciences in Trinity was a 4 y honors course, where you started out with physics, chemistry and biology and gradually reduced subjects to end up with one subject in your final year. Initially I was certain I wanted to be a chemist. But by the second year I had moved to Chemistry, Biochemistry and Microbiology, by year 3 it was Biochemistry and Microbiology and in the end I got a degree in Microbiology. Some part of this was that I was not happy with equations or too much maths, and less so with the Krebs cycle or too many pathways. But much more than this was the fact that I could see the bacteria. Somehow this made them real in a way molecules could never be. We also had some outstanding microbiology lecturers, who were young, and passionate about their subjects, including the recently appointed Tim Foster, and Mary McLoughlin who taught us immunology. For my Finals, I tried to do a project on bacterial chemotaxis which completely failed to work, and then unexpectedly (as I was considered to be a safe Upper Second class degree) narrowly got a First. I am grateful that they explained this so narrow margin so clearly to me, to prevent me having any delusions for the future.

Just as whether to go to university was never the question, just what to study, there was no question of whether I would do a

PhD, just in what and where. I could have decided to research antibiotic resistance and bacterial plasmids, and have wondered since how my life would have gone if I had, as this was the early days of bacterial genetics – but I applied for a dullish microbiology job in Kent. And as I had another application pending with someone in London, and as Finals loomed and my options for trips to the UK would be limited I rang John Greenspan who was advertising the London-based job. The result was an informal interview and a paid research assistant post allowing me to do a PhD working on autoimmunity, on Sjogren's syndrome in man and its NZB/NZW model. The post was in a Pathology Department in the Royal Dental Hospital of London.

I loved London. I felt I had finally got to where things happened, and with new found friends and Stephen who became my life partner enjoyed art, music, theater, Indian food and more. The science was stimulating too. This was the dark ages for human T cells. Martin Raff had made one anti-monkey thymus antibody that seemed to react with human T cells, but while staining macrophages for lysosomal enzymes I noticed that many of the T cells had dot-like staining too.¹ Those T cells had lysosomes, something that as we all moved into multiparameter flow analysis had been forgotten- but they must be still there. John Greenspan gave me supervision and freedom, until he left for San Francisco half way through my PhD, thus giving me unlimited freedom – but leaving me with the promise of advice from John Playfair at the Middlesex Hospital Medical School.

That led to a postdoctoral position with John Playfair working on vaccines for malaria, my first introduction to vaccines. Those were great years. Ivan Roitt's Immunology Department at the Middlesex was large, energetic, and stimulating. I traveled to international immunology meetings, although never to anywhere where there was malaria. It was an absorbing and fascinating time, although in retrospect we were more interested in how immunity to malaria worked than in trying to design a vaccine. I had my name on my one and only Nature paper, I found that malaria parasites were killed by hydrogen peroxide,² and my work began to be noticed. However, by then I was in my early thirties and just as for those at the same stage now, the future looked insecure.

So when someone said that Keith McAdam was returning from Boston to set up a new Department of Clinical Tropical Medicine at the London School of Hygiene & Tropical Medicine, where I had already had some enjoyable collaborations,



About Hazel M. Dockrell.

Dr. Dockrell received her PhD from University of London (1978) and after a brief interlude as a Research Associate at Middlesex Hospital Medical School (1978–85), she joined London School of Hygiene & Tropical Medicine, where she is Professor of Immunology and Special Advisor on Overseas Programmes in Africa. She has contributed to the understanding of the immune responses to tuberculosis and the BCG vaccine, and to the development of TB biomarkers. She has played a major role in the establishment of international collaborative efforts to develop TB vaccines and to identify correlates of protection for TB. Dr. Dockrell is a member of the British Society of Immunology, Royal Society of Tropical Medicine & Hygiene and American Society for Microbiology.

I went to see him. And just as for John Greenspan, he had a job to offer me, although he wanted someone to work on human T cells in leprosy. This was a great period and good fun too, with Keith's charisma and the optimism of a new and truly multi-disciplinary department. I lost a lot of ground, years probably, as I knew painfully little about T cells (other than that they had a few lysosomes) and nothing about leprosy. But within the year, I had been allocated a Pakistani clinician PhD student, Rumina Hasan, and went to visit her at the Aga Khan University (AKU) in Karachi, Pakistan.

That first visit to Pakistan was a real turning point. I saw the human disease, leprosy. It was hard to study as *Mycobacterium leprae* would not grow and the patients were reluctant to donate blood no matter how few teaspoons you said the large syringe held. But just as for those bacteria I had seen down the microscope, leprosy was real. When I returned, my father, a wise man, commented that I would have been changed by this experience. I was, having been taken out of my cosy environment to the reality of life in low and middle income countries. We analyzed T cell responses to newly produced recombinant leprosy antigens, and cloned T cells. We demonstrated what seemed to be leprosy transmission in an old folks' home in the UK.³ I discovered what it meant to really collaborate with someone, working more closely with Rabia Hussain at AKU than with anyone else before or since.

Over the subsequent years I was seduced from leprosy into tuberculosis, which led to studies in Portugal and The Gambia - including the role of mycobacteria-specific CD8 T cells⁴ - and was then challenged by Paul Fine to explain why BCG gave variable protection. Working with Paul and the Karonga Prevention Study (KPS), also changed me. Epidemiologists are different

from laboratory immunologists in many ways, but doing immunology in 500 or more BCG vaccinated individuals allows you to see differences far more clearly than when you do small-scale immunology on groups of 10–15 donors. We exploited a diluted whole blood assay developed by Rosemary Weir for her PhD project on leprosy in Nepal⁵ and compared how BCG induced immunity in Malawi compared with the UK.^{6,7} This marked my move into human vaccines. Despite the big push to develop new TB vaccines, we had never properly understood why BCG gave variable protection, and still don't. To directly compare BCG-induced protective efficacy in the UK and Malawi would have required studies much larger than ours, but we did show that the same vaccine, given initially to adolescents and young adults, and then to infants, induces different immune signatures in Africa and the UK.^{6,7} We have continued to explore how environment impacts immunity in Uganda with Alison Elliott's group, and in the UK, now led by Steven Smith in my group,⁸ and how co-infections with helminths and co-morbidities like diabetes impact on immune signatures. This all matters as many of the new TB vaccines would be given after a priming vaccination with BCG - and any factors affecting how BCG works might also affect other live mycobacterial vaccines, or the boosting seen post-BCG with antigens delivered by vaccines or with adjuvant.

The move into vaccine biomarkers also connected us to a European community working on TB vaccines. We have been partners in European consortia including TBVAC, NEW-TBVAC and TBVAC2020, managed by the TuBerculosis Vaccine initiative, TBVI (www.tbvi.eu), which has brought links to scientists including Helen McShane in Oxford and Tom Ottenhoff in Leiden and in consortia that aimed to support cross-disease vaccine development such as TRANSVAC and EURIPRED. We were partners in a Bill and Melinda Gates -funded Grand Challenges 6–74 project led by Stefan Kaufmann in Berlin, that helped identify a gene expression profile that predicts those who are silently progressing to TB disease,⁹ and studies led by Gerhard Walzl at Stellenbosch University and Jackie Cliff at LSHTM have demonstrated gene expression changes in TB, including during TB treatment.¹⁰ This connectivity has been another game-changer. My research family became worldwide, and all the better for this, although the TB Centre (<http://tb.lshtm.ac.uk/>) and the Vaccine Centre (<http://vaccines.lshtm.ac.uk/>) are now bringing stronger cross-faculty links at LSHTM. Biomarkers remain our key interest as having a protective biosignature to measure would really facilitate the development of new TB vaccines.

People have often asked why I have remained at LSHTM. Because it became my life and perhaps too much so. Because it never made me feel unequal as a woman scientist, or that not being clinically qualified was an issue. For other reasons too, including a wealth of opportunities to collaborate internationally. Over time, as well as Pakistan and Malawi I have had the Nepal years, the Gambia years, the Portugal years, the Mexico years - and these days my main links are with Entebbe, Cape Town, and Seoul. Apparently as a child, when I asked could we go somewhere different the day after visiting one of the best beaches south of Dublin, my father said "if I was taken to Paradise one day, I would want to go somewhere else the next day." LSHTM has certainly given me plenty of opportunities to travel. To work with people based in a country also enables you

to see that country in a very special way. To work in a field that never, never stops changing means you never get bored. I am lucky that through all this I have had an incredibly supportive partner who never tells me not to go or not to work, but skilfully books the odd tickets for the theater and meanwhile does all the shopping and cooking.

I also stay because LSHTM has given me, someone always looking for the next change, a wealth of different roles in a one-world environment. I have been in charge of the research degree program, an MSc course, a department and a faculty, and performed other roles (currently as Special Advisor on Overseas Programmes in Africa) as well as carrying out research. But it is more than that. The LSHTM has a mission, to “improve health worldwide.” Despite the RAEs, the REFs, the QAAs, Brexit and more, we have a collective core motivation. Partly because there is still so much disease. But also because a succession of special students keep coming. They come from affluent Europe, the UK or the US, but also from Asia, Africa and South America. They have often given up much to get to us, and more while they stay with us. We boast that education changes lives, but our students often miss long periods with their children, and pay large sums to come to London. So of course we want to help them achieve their potential. Especially when so often they are what re-energises and motivates us, and they then bring us further connections and opportunities.

What strikes me most as I write this is that it is, and was always, the people that matter most. Vaccine research is not performed by individuals working in isolation - we need teams and consortia to design, test and improve vaccines. We also need teams to identify correlates of protection for TB vaccines, which will work in the messy real world where we highly variable humans have co-infections and co-morbidities. Working together is productive and rewarding. We do not yet have a new TB vaccine, nor biomarkers of protection, but collectively, we are making progress.

Some special people brought me into science, gave me opportunities at key points throughout my career and continue to help me enormously - I thank all those named and not named.

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