Immunology across two islands: understanding the research landscape of Aotearoa

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Abstract

In the unique landscape of immunology research in New Zealand, this article explores the collaborative networks spanning the two main islands, through a conversation with Associate Professor Joanna Kirman and Dr. Robert Weinkove. The discussions delve into their dynamic collaborations with countries like Asia, Australia, and the United States from their labs at the University of Otago and the Malaghan Institute respectively, provides insight into the translational research landscape of New Zealand, and the integration of Māori culture into all aspects of scientific research and clinical practise. Kirman's work in understanding immunological memory in tuberculosis and Weinkove's research in cancer immunotherapies, particularly CAR-T cells, are highlighted. The natural beauty and accessibility of New Zealand supports it's research diversity.

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Title: Immunology across two islands: understanding the research landscape of Aotearoa

Running title: Immunology in New Zealand

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Graphical Abstract

New Zealand's unique landscape in immunology research, spanning its two main islands, is characterized by vibrant collaboration between institutions such as the University of Otago and the Malaghan Institute of

Medical Research. This article features discussions with Associate Professor Joanna Kirman and Dr Robert Weinkove about their international collaborations, New Zealand's emphasis on translational research, and the incorporation of Māori culture into all aspects of scientific research and clinical practise.

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`image1.emf` available at https://authorea.com/users/666133/articles/667123-immunology-across-two-islands-understanding-the-research-landscape-of-aotearoa

Graphical abstract image. The beauty that is New Zealand (L to R clockwise from top: Riverton Southland, Raglan Beach, Doubtful Sound, Aurora (not the cytek version) from Ōtepoti/ Dunedin and sunset at Raglan Beach.

Abstract

In the unique landscape of immunology research in New Zealand, this article explores the collaborative networks spanning the two main islands, through a conversation with Associate Professor Joanna Kirman and Dr Robert Weinkove. The discussions delve into their dynamic collaborations with countries such as Asia, Australia, and the United States, from their labs at the University of Otago and the Malaghan Institute respectively, provides insight into the translational research landscape of New Zealand, and the integration of Māori culture into all aspects of scientific research and clinical practise. Kirman's work in understanding immunological memory in tuberculosis and Weinkove's research in cancer immunotherapies, particularly CAR-T cells, are highlighted. The natural beauty and accessibility of New Zealand supports its research diversity.

Article

Spanning two main islands, New Zealand is a unique country in the landscape of immunology research. The country's vibrant research ecosystem fosters collaborative networks that extend from national medical research institutes, including the Malaghan Institute of Medical Research in Te Ika-a-Māui / North Island to world-renowned universities such as University of Otago in Te Waipounamu / South island. In this article we engage in conversation with Associate Professor Joanna Kirman and Dr Rob Weinkove, about their dynamic collaborations with diverse countries including Asia, Australia and the west-coast of America, discuss New Zealand's strong focus on translational research and discovery, and consider the inclusion of Māori culture and perspectives, into the experimental design, application and health outcomes of scientific research in Aotearoa11[Aotearoa loosely translates from Māori as the "land of the long white cloud." It has been used by Māori to refer to the country for decades, i

Associate Professor Joanna Kirman (Figure 1) is a distinguished immunologist and Associate Professor at the University of Otago, whose work has made fundamental discoveries in understanding the generation and maintenance of immunological memory in tuberculosis in order to improve global vaccination strategies. Joining Kirman in our conversation is Dr Robert Weinkove (Figure 2), an esteemed clinical haematologist and Clinical Director at the Malaghan Institute of Medical Research, investigating novel cancer immunotherapies with a focus on the potential of CAR-T cells in blood cancers.

JB: I'm excited to have both of you speak about Immunology in New Zealand, drawing on your diverse backgrounds and your geographical divide. To start, I'd be very interested to know what got each of you excited about immunology. What led you to where you are now?

RW: I'm a clinician by training, having trained in haematology in the UK and Germany. In haematology, we spend much of our time treating immune system cancers, in fact, we mainly treat cancers of antigen presenting cells (cancers of B cells and myeloid cells). We often treat with various forms of immunotherapy, including allogeneic bone marrow transplantation, which itself can be regarded as an immune system transplant. We do it all by recipe, essentially, empirically following specific protocols - giving a bit more cyclosporin or steroids if patients get graft-versus-host disease and giving a less if they don't. In London, I would see patients for whom these transplants would go very well, and others for whom they would go very badly. And while the chances of success are often weighted one way or another, it feels a bit like a roll of the dice each time I refer someone for an allogeneic bone marrow transplant. What became fascinating for me, was

the chance to use much more targeted immunotherapies, with more defined risks and benefits. The field of human cancer immunotherapy has taken off, particularly during the last five years with the uptake of CAR-T cell therapies and bispecific T cells, so for me it's an exciting time to work at the interface of immunology and haematology.

JK: My excitement about immunology started while I was doing undergraduate biochemistry and I took an immunology paper in my last year. I just loved it. I went on to do a summer project, where I then proceeded to switch departments and undertook an honours project in Immunology. I thought, "this is what I want to do" and I've stayed in immunology ever since. I can't put my finger on what it was about immunology that captured me, perhaps the complexity of the network and how it all fits together. Its intriguing how it all kind of makes sense and then it sort of doesn't. It really got my imagination going and has ever since.

JB: Throughout your immunology journey, what do you think has been your most significant discovery or contribution to immunology? It doesn't have to be Nobel prize winning, it can be tiny, but what do you look back on and think of how proud or excited you are about that part of your immunology research to date.

JK: For me it has been recognising very early on that TH1 T cells were not the Holy Grail that people had thought they were in terms of vaccines for tuberculosis (TB). Coming to that realisation and very early on when most people were still chasing after T cells is one really significant part of my research. We published a commentary review early on summarising some of the perspectives on DNA vaccines and the role of protective memory T cells, and after I recently presented a careers talk for the New Zealand branch of the ASI, I realised even in my PhD I was writing about these perspectives. It's just taken a very long time for some of the TB community to think outside of the conventional box in terms of looking beyond adaptive immunological memory and considering that there are other cells that are doing things that are pretty important with regard to immunological memory.

RW: For me, the first immunology work that I did was my PhD with Professor Franca Ronchese and Professor Ian Hermans at the Malaghan Institute. I'd generated the topic myself based on what my supervisors were doing and my interests in haematology. I was interested in the immune system dysfunction that you see in patients with blood cancers, including chronic lymphocytic leukaemia (CLL), and studied natural killer T (NKT) cells in this condition. I have to say, the experimental work was horrible! Human NKT cells are rare at the best of times, and when you've got a patient for whom 99% of the circulating cells are leukemic cells that you have to deplete before you can do anything else, it's really hard to do functional assays. I've remained interested in this field, because what's happening with blood cancers is that we're getting better and better at treatment, and at keeping more patients alive for much longer, but infection is a growing risk. In fact, it's getting to the point with CLL and some other blood disorders that we will soon see more people dying of infection than of the malignancy itself. It's been great to have been able to take part in design of a new international platform trial examining antibiotic prophylaxis and immunoglobulin replacement in patients with CLL and related conditions through the Australasian Leukaemia Lymphoma Group and with Monash University. We've described the immune dysfunction, and can now contribute to overcoming it through to what hopefully will be a practice-defining study. What's most exciting to me at the moment in my own lab is our work on an unusual CAR-T cell construct, which uses part of Toll-like receptor 2 as a costimulatory domain – we have completed a dose escalation phase 1 clinical trial with this new CAR T-cell construct, and are now in dose expansion (clinicaltrials.gov NCT04049513).

JB: You've both made some landmark discoveries, but in such different fields. I would now like to talk about something you just touched upon Rob, in regard to your collaborations with Canada and also Monash University in Australia. As you both do very different types of research, how do you each find the research landscape of where you are situated in respect to collaborations in your institutes/Universities, across New Zealand and internationally?

RW: I'd say New Zealand's a bit like Australia in that the journeys between major cities are quite long by road, so we tend to fly between cities. I don't feel any more distant from Dunedin or Christchurch than I do from Auckland, even though Auckland is on the same island as Wellington, so I wouldn't say the Cook Strait

itself is a big barrier. There is always a degree of siloing within and between institutions purely because you are most familiar with the people work with every day. One comment I'd like to make is that I always thought I would retain strong European collaborations having worked in the UK and Germany, but time zones make a real difference. Recently, we've had more productive collaborations with Australia, China and the West Coast of the US, I'm thinking in part because the time differences are friendlier.

JK: I completely agree. My main collaborators are based in the US, one of my postdocs from my lab just spent 6 months working with a group over there, but the collaborators do tend to be more on the West Coast. The time difference is hard when you're trying to have meetings and maintain collaborations. As Rob said, particularly in Dunedin in the South Island, we have fewer flights coming in and out than in Wellington or in Auckland which are both in the North Island, so it is actually quite a mission to get to another city. Our ability to travel was also stunted over the past couple of years due to the pandemic.

JB: Rob you are in a medical research institute and Jo you are at a University, both in very different geographical locations. What are the research focuses like where you are? Is there quite unique research or technologies where you are?

JK: It's not too different in terms of the research coverage. In both places there are cancer researchers and infectious diseases researchers. We probably don't have anyone, and I don't know whether the Malaghan has anyone who's just doing pure immunology without an applied nature to it.

RW: The Malaghan Institute is quite focussed on translational immunology – in recent years we have run clinical trials of dendritic cell vaccines, CAR T-cells, experimental hookworm infection, and observational vaccine studies. We do have some pure immunology too; for example, Professor Franca Ronchese has a programme investigating dendritic cell (DC) biology.

JB: Would you say that most immunologists in New Zealand are doing quite translation focused research? Does this mean most researchers have good clinical or hospital connections?

RW: Our main granting bodies see a pathway to translation as a required or very important feature of funded research. That does influence what people do. One important point to make its that the health system here is stretched, as it is around much of the world at present. So, while there's often a desire from scientists to collaborate with hospitals, the capacity of the hospitals to assist needs to be considered. Navigating that interaction is much of my day-to-day life – it's interesting to come up with creative solutions for getting translational work done. We're fortunate to have a Good Manufacturing Practices (GMP) facility with a licence for manufacturing lentiviral vectors and CAR-T cells, which means we can run early phase CAR-T cell in-house. This emerged as a result earlier dendritic vaccine trials, first started by Dave Ritchie, now in Melbourne, with Ian Hermans. We're seeing more and more applications of Immunology: new immunotherapies for cancers and non-malignant disorders, monoclonal antibodies for everything, and RNA vaccines. It's hard to find much immunology that hasn't got some potential link into the clinic.

JB: Just highlighting your comment about the GMP facility. Is that also for commercial purposes? Do you see much commercial translation going on in New Zealand?

RW : Our funders are keen that we seek commercialization opportunities. For our own CAR-T cell programme, we've set up a couple of start-up companies as a way to bring in commercial funds. We don't have a Medical Research Futures Fund (MRFF) or equivalent here in New Zealand, so it is important to identify other sources of funding.

JK: I suppose we have different strengths and linkages. For example, my lab (Figure 3) is looking at a disease, TB, that's not particularly common in the South Island. We do have the Centre for International Health at the University of Otago, down in Dunedin and they have clinical collaborations in locations where TB is endemic. For example, one of my collaborators has linkages to Indonesia, where they have established clinical studies looking at Bacille Calmette-Guérin (BCG) vaccination and transmission in highly exposed individuals, which is something that we just can't do in New Zealand so there is a potential then to set up more trials. In Dunedin, we've got a very high incidence of colorectal cancer, probably higher than anywhere

else in New Zealand, so there's a quite a few groups looking at colorectal cancer and the immunology behind it. There are also other labs developing linkages with the Pacific, to research the diseases that are affecting people in Pacific nations in order to find ways of supporting them, so we do go beyond our little city.

JB: You've both touched upon different forms of funding, so I'm interested to understand what the funding landscape is like in New Zealand?

JK: It is tight, which is something I don't think anyone would disagree with. We've got our staple grants including Health Research Council (HRC) and Marsden, and also have some larger of pots of money that are very focused. These strategic funding opportunities include the RNA Development Platform and Te Niwha, the Infectious Disease Research Platform.

RW: There are Ministry of Business Innovation and Employment (MBIE) funding streams, which we've made use of, that have strong commercialization angle. I'm not sure that any of the funding opportunities in NZ are all that different to anywhere else. One thing to note is that the size of most HRC grants hasn't gone up for many years, which makes it hard to cover salaries.

JB: Along the lines of funding and research opportunities in New Zealand, what are the opportunities for PhD students and early career researchers (ECRs) coming to New Zealand? Are there competitive fellowships or other financial supports they can apply for?

JK: International students are eligible for university PhD scholarships. They generally have to be very high achieving students to be successful. All of our grants, for example, can have a PhD student written into them and it would fund any PhD student who applies. There are also some of the centres of research excellence which offer opportunities for potential students to apply for funding.

RW: It's not infrequent that we recruit postdocs from overseas, usually as a later stage ECR, as we are looking for people with unique skill sets to add to our research expertise and grow our lab. We also encourage people who've done a PhD with us to go and gain experience at overseas labs and grow the group's international reputation. We also hope to get those people back to NZ later on, to run our labs in the future.

JB: What has impressed me over the years, especially with the more kiwi's22Kiwi is a slang term for a person from New Zealand. I've met regardless of their profession, is their understanding, inclusivity and genuine connection to Maori culture. How do you incorporate indigenous culture considerations into your research and in the medical research landscape in Aotearoa?

JK: I think that all laboratories in New Zealand try to uphold tikanga Māori / Māori customs and ideals. For example, in terms of not storing certain things together that shouldn't be together, researchers would not store animal cells and human cells next to each other. There are certain types of practises that we try to make sure we adhere to and many of them are really interesting. For example, our PC-2 practises align really beautifully with a lot of tikanga Māori. There's an idea of tapu and noa33Tapu is te reo Māori for sacred or restricted; noa is te reo Māori for common or ordinary., such as it's offensive to sit on a table as the table is tapu whereas our bottoms are noa. Equally so, in a PC-2 lab you would never sit on a lab bench. These practices align quite beautifully with each other. Implementing tikanga Māori in the laboratory is something that probably most laboratories would do now, but we're still on a learning curve as well. We might be a bit further ahead than in Australia, but we're still learning. One of the big things that we're really trying to do is build capacity within the Māori and Pacific population so that we have research leaders who identify as Māori or Pasifika as currently there are very few. We are also working to make our labs a welcoming place for our Māori and Pasifika students. This is the reason I am learning te reo Māori.

RW: The impact and the consideration of Māori health in the NZ health sector is something that can't be overstated. The Treaty of Waitangi is regarded as the founding document of New Zealand, and has been interpreted as requiring equity of health *outcomes* for Māori, not just equality of healthcare access. There's a clear and immediate imperative to try and achieve that, which is a really big task, because there are social and economic inequities as well. Equity of health outcomes for Māori is a huge focus in the health service and in the way the government is investing into health research. For example, for our CAR-T cell trial, I have

a monthly meeting with a Māori haematologist and equity specialist. We look at enrolment rates, and we have changed elements of our patient information sheets and our inclusion criteria. As a result, we are seeing good representation of Māori among CAR T-cell trial participants. Then there is the element of tikanga, or cultural protocols, relating to cells and genetic code, as Jo has said. When I first came to New Zealand in 2008, I perceived a reluctance to conduct genetic research involving Māori. I think that this view has changed, because it's clear that to gain benefits of health research, Māori participation is key. Importantly, this research has to be conducted with Māori researchers helping to determine the research questions, and as part of the research team. At the Malaghan Institute, a Māori steering group, Te Urungi Māori, helps guide us. My lab co-supervises a Māori PhD scholar undertaking a mixed-methods PhD, part of which involves looking at tikanga relating to CAR-T cell therapies. It will take time before we have a truly representative senior research workforce, but I'd say these efforts are clearly underway.

JB: The research landscape definitely sounds unique in New Zealand, and I am sure enticing for many. I have great memories of New Zealand, and I would like to hear, apart from the research, why should people consider coming to New Zealand to work?

RW: The outdoors! New Zealand a fascinating country, and is simply beautiful. You can drive from one side of an island to the other in a day and see mountains or volcanoes, and two different coasts. You can walk in the bush, go skiing or mountain biking, or go surfing. Nature offers amazing activities for your downtime.

JK: I live in a much smaller city than Rob and, at the end of the day, you can go and do some really cool things. Everything is just a short drive away, even in Wellington. In Dunedin everything is 10 minutes away and in Wellington it's probably 20. Everything is very accessible.

JB: Thank you to both of you for providing so much insight into the accessibility and inclusivity of New Zealand research and healthcare outcomes.

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Figure captions

Figure 1. Associate Professor Joanna Kirman, University of Otago.

Figure 2. Dr Rob Weinkove, The Malaghan Institute.

Figure 3: Students from Associate Professor Joanna Kirman's lab and Professor Roslyn Kemp's lab at University of Otago holding unicorns after a Cytek flow cytometry course (L to R: Brad, Meg, Shima, Doug, Rory and Riya).