Interview with an Immunologist: Dr. Tania Watts

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Dr. Tania Watts

Dr. Tania Watts received her Ph.D. in Biochemistry from the University of Alberta. She then went on to do a post-doctoral fellowship at Stanford University studying T lymphocyte activation, which is where she first began to develop her passion for immunology. During her post-doctoral work, Dr. Watts helped to provide the first evidence for the existence of a ternary complex existing between MHC II, peptide antigen, and the T cell receptor. In 1986, Dr. Watts took up a faculty position at the University of Toronto Department of Immunology, where her research has been focused on T cell and viral immunity. Her work has focused on the immune responses to viruses such as influenza, HIV, and most recently, SARS-CoV-2. Her team has helped to uncover a novel inducible T cell co-stimulation pathway that contributes to T cell activation. Dr. Watts' group has also been interested in studying viral immunity in humans. During the 2009 H1N1 influenza pandemic, Dr. Watts collaborated with Public Health Ontario to study H1H1 immunity in Toronto. Recently, Dr. Watts' has also published a study focused on comparing the immune response to influenza and SARS-CoV-2 in immune cells isolated from COVID-19-recovered patients. One of her more recent leadership roles has been serving as a member of the COVID-19 advisory group for Ontario, where she has helped to educate and inform the public on scientific advances regarding SARS-CoV-2 vaccines and immunity.

DF/LD: Dr. Watts, the past few months have been quite eventful in the world of SARS-CoV-2 and COVID-19 immunological research, including your own work on the SARS-CoV-2 immune response – could you begin by describing what impact the COVID-19 pandemic has had on your research program as well as introduce your recent foray into SARS-CoV-2 research?

TW: Well, it came as a bit of a shock to all of us in the third week of March when we were given just a few days to shut down our research labs for everything but critical research. My research program was about 80% mouse research and 20% human research at the time, so we were in a bit of a scramble trying to figure out what to do. My initial reaction was to tell all of the members of my lab who had to take public transit to stay home and work virtually. I placed people within walking distance of the lab on the critical list so that they could come in and continue to look after the mice. We really weren't sure what was going to happen or what the best way to proceed was.

After the initial shock dissipated, I started to think "*Well, we're experts in viral immunology, we should do something*" - fortunately, I have colleagues in Dr. Mario Ostrowski and Dr. Allison McGeer, both infectious diseases clinician scientists, so I reached out to them about the possibility of setting up a project focused on studying human T cell responses to SARS-CoV-2. Once we finalized our idea for the project, there was a bit of a scramble to get all of the necessary biosafety approval, but we began our work on SARS-CoV-2 immunity. I am very fortunate to have an extremely smart and hardworking PhD student in Jaclyn Law, who in the past few months has had to completely pivot her PhD thesis work towards focusing on SARS-CoV-2 immunity. It was also a very active collaboration with members of Mario Ostrowski's team contributing their assays and expertise as well. We've published our first paper on this topic this past November in the Journal of Immunology and have a number of follow-up projects ongoing. One upcoming project that I'm very excited about is a collaboration with some of my clinician colleagues that will focus on capturing individuals coming for vaccination who are on immunomodulatory medications. These patients aren't included in clinical trials for vaccines, so we're really interested in characterizing the immune response that these patients develop. Do they still generate a strong response after one or two doses of the vaccine? Or will they require additional doses to reach the same level of immune response in the general population? I think that this project is a great opportunity to apply basic immunological principles to real world patient scenarios, and really highlights how much focus has been placed on the realm of immunological research amidst the COVID-19 pandemic.

Overall, the pandemic has definitely had an impact on my research program, and while we've been able to get the lab going again at 50% capacity, many projects are still on hold. Of course, compared to those who have lost loved ones, lost their jobs, or have been isolated from their families - the research problems pale in comparison. My group has been very fortunate that all of our family members are safe, and that the University has allowed us to continue to pay our trainees while they work from home.

DF/LD: Can you briefly expand on your research into SARS-CoV-2 immunity and highlight, from an immunity standpoint, what makes SARS-CoV-2 differ from influenza?

TW: Sure, so one of the main experiments that we carried out in our recent paper was to isolate immune cells from patients who had recovered from SARS-CoV-2 and stimulate them with components of SARS-CoV-2 or influenza, a virus

that most individuals already have some pre-established immunity to. In doing so, we hoped to better understand what kind of specific immune response that SARS-CoV-2 induces, and potentially gain insight as to why some patients develop more severe COVID-19 outcomes than others.

We found that all of the patients selected for this study generated memory responses to both influenza virus and SARS-CoV-2; however, there were significant differences in the nature of the immune responses to each of these viruses. While the influenza-specific memory response was dominated by CD8+ T cells, the canonical killer T cells classically responsible for cellular/viral immunity, the SARS-CoV-2 T cell response was dominated by CD4+ T cells and was associated with a more inflammatory cytokine profile. Our findings suggest that the immune response to SARS-CoV-2 is much more inflammatory than that of influenza and may be less efficient at eliminating virally-infected immune cells, which may indicate why COVID-19 causes more severe outcomes than influenza.

DF/LD: As a quick follow-up question, the COVID-19-convalescent patients recruited to your study had recovered from the virus within the last 4-12 weeks: Do you think that the differences in immune response to SARS-CoV-2 versus influenza may begin to normalize over time, or do you think that the CD4+ skewing and the increase in inflammatory mediators may be unique to the SARS-CoV-2 immune response?

TW: Right, so I think that once you generate a memory response, the response shouldn't be overly inflammatory, so this is a good question and was also a focus of one of the reviews of our paper. However, the inflammatory environment that is present upon T cell activation tends to result in epigenetic changes that persist in the T cells, which results in long-term changes. This is something that we are starting to look at in a longitudinal study where we are taking samples from the same people for whom we had a sample at 4-6 weeks after COVID-19 symptom onset and are looking again at 8-10 months. So great question, we hope to have an answer to this in the coming weeks.

As an aside, we are also interested to see how immunological memory will compare between naturally acquired COVID-19 and vaccine-mediated responses. The virus has a lot of immune evasion mechanisms, and it has been published that it downregulates the MHC Class I molecule, which might explain the poor CD8+ response, and that it interferes with the type 1 interferon response, which may also change the whole profile of what cytokines you get first. Conversely, with the vaccine, you present an ideal set of circumstances and hope to get a more classical immune response - with early data showing good antibody, as well as CD4+ and CD8+ T cell responses. It will be interesting to see how those responses persist in real world samples, and in those on or with immunosuppression.

DF/LD: Your work on SARS-CoV-2 immunity involved the use of immune cells from COVID-19-convalescent donors as well as the use of synthetic components of the SARS-CoV-2 virus – did you face any challenges or barriers in accessing this patient population and/or the viral components in such a short timeframe, and still in the midst of an ongoing pandemic?

TW: I am very fortunate to have a strong network of collaborators that were instrumental in allowing us to very quickly begin working in the field of SARS-CoV-2 immunity. Dr. James Rini, already an expert on coronaviruses prior to the pandemic, was able to provide us very early on with some purified SARS-CoV-2 S protein that we were able to use in our study. Dr. Ostrowski and Dr. McGeer, both clinicians, were crucial in recruiting patients to be a part of this study. Dr. McGeer, through a network of her colleagues, was able to refer patients to us. Dr. Ostrowski directly met with the patients and was able to recruit 13 of them who agreed to leukapheresis, which was great because it gave us a very big sample of their white blood cells so that we could not only carry out our early experiments, but also optimize and standardize our assays so that going forward we would just need a small blood sample from volunteers to track immunity. This experience really highlights the utility of collaboration and the importance of PhD scientists, such as myself, having a strong network of clinical collaborators who actually see and interact with patients, which is a crucial component of study recruitment.

DF/LD: In addition to your own research program, we have seen a significant amount of SARS-CoV-2 and COVID-19-focused immunological research and collaboration coming out of Canada from both a local (University of Toronto) and national level – can you comment on the rapid mobilization of Canadian immunological research expertise and resources in focusing on COVID-19?

TW: It has been a terrible pandemic and it has flipped the world, but if there is a silver lining, it's been the collaboration. The community is being kept very busy with this, with everyone writing and also reviewing more grants than ever, and it has been great to see the hard work that so many people have stepped up to do - particularly the hard work of the trainees, who are going into the lab and taking the subway, while I am running everything from home on Zoom. The collaboration in Canada has been really amazing. For example, in addition to the collaborations we have already discussed, I've also been able to collaborate with Dr. Jennifer Gommerman, a member of the immunology department here at the University of Toronto, who has been studying the role of mucosal IgA in SARS-CoV-2 infection, as well as Dr. Anne-Claude Gingras, a proteomics expert who is a national leader in the development of high-throughput serological assays. They were a part of a team for a successful SARS-CoV-2 CIHR application that I had led back in the spring.

Access to funding and donations from research foundations have been crucial in enabling this kind of research productivity and collaboration in Canada. Specifically, donations and funding from the Mount

Sinai Foundation and Government of Ontario have been instrumental in helping drive the research of some of my collaborators here in Toronto, and I was fortunate early on to get a "FAST grant" from the Thistledown Foundation. These early sources of funding were very important and actually allowed researchers to get going, because the normal peer review process of grant funding can take some time. Some of us just started doing the research with the hope that we would get funding. I was also fortunate because I had a Foundation Grant from CIHR - which is an ideal grant to let you pivot and say 'hey, let's look into this', if important questions come up. More recently, my colleague Dr. Mark Silverberg and I were fortunate to receive a generous donation from Juan and Stefania Speck to fund the observational study on the effect of immunomodulatory drugs on the SARS-CoV-2 vaccine described above, which will be carried out with our colleagues Dr. Robert Inman, Dr. Vinod Chandran, Dr. Vincent Piguet, and Dr. Anne-Claude Gingras. Donations such have this have been crucial in helping to upstart Canadian research. So overall, both flexibility in funding and private donations were important to our personal response, and these all helped supplement the federal dollars that had also been rapidly mobilized.

DF/LD: Less than 1 year into the COVID-19 pandemic and we already have many front-line healthcare workers and essential workers vaccinated or in the process of being vaccinated – given the immense international focus on SARS-CoV-2 research, were you surprised at all by the rapid development and deployment of vaccines for this virus?

TW: Looking back on the year, it's been incredibly fast. Would I have predicted it? I don't know. mRNA vaccines had been under development for many years, mostly with a focus on cancer vaccines. The idea was that you could take a small tumour-associated antigen and give it to cancer patients in the form of an mRNA vaccine so that they develop an immune response towards the tumour. However, none of these vaccines managed to progress beyond Phase I/II trials. So, we definitely had the technology ready, but it was still quite impressive and heroic at how quickly it was translated and mobilized. It's very important to educate and remind the public that we haven't skipped any safety steps in the development and clinical trials of these vaccines. They've gone through the same rigorous evaluation process as other vaccines and medications - we've just been able to fast-track a lot of the administrative and financial assessment steps due to heavy financial investment. So overall I think it's been really impressive, and it really makes me feel proud to be a scientist when you see how your community can rise to the occasion.

DF/LD: The COVID-19 pandemic has really highlighted the important marriage between basic science and translational research, as basic scientific discoveries surrounding SARS-CoV-2 immunity and virology are being rapidly incorporated into medical research and informing public health policies – how intertwined do you feel the world of basic immunological research is with the world of translational medicine, and do you believe the COVID-19 pandemic may have any impact on this relationship going forward?

TW: Yes, I think that clinician scientists, focused primarily on translational medicine, fill an important niche in the landscape of immunological research. You can have clinical researchers solely in the clinic, you can have individuals such as Dr. Mario Ostrowski with an active lab doing bench science and clinical research, and you can have pure, bench science PhD researchers like myself. We really need that continuum, because, as you could imagine, it may be very challenging for infectious disease doctors on the frontlines to also maintain a research lab. So, going forward, we need to make sure we protect the time of and invest in these scientists, and that will facilitate valuable bench-bedside and bedside-bench research.

DF/LD: One of your newer leadership roles has been serving as one of the members of the COVID-19 advisory group for Ontario – how has your experience been as member of this panel, and how important is it for academic experts such as yourself to be involved with the communication of scientific evidence to the general public?

TW: Right, so I was familiar with Dr. Adalsteinn Brown, whom I know through my involvement with the Centre for Vaccine Preventable Diseases hosted by the Dalla Lana School of Public Health. When Dr. Brown was involved in forming the COVID-19 advisory group, a table that includes virologists, infectious disease doctors, epidemiologists, modelers, and public health leads from Ontario and the University of Toronto, they also wanted the perspective of an immunologist.

My role is primarily limited to immunology, for example, when something about the vaccines, or how they work, or how the immune response works, comes up. I do not have the expertise to judge some of the other aspects, but it has been really interesting to listen in on the discussions of my expert colleagues and gain a new appreciation for research across disciplines. Often, we are very siloed, and so I am mainly speaking with bench scientists in immunology, but the individuals from, for example, public health are doing something very different, and so when we all get together in these kinds of groups, you can really start to appreciate what the other groups' expertise contributes.

As an immunologist and someone who is knowledgeable about viruses and immunity, I feel it is my duty to be available to answer questions and help communicate with the public, especially as the vaccine has come on board.

DF/LD: Aside from your research, what has been your personal experience with the COVID-19 pandemic, and is there anything you are excited to get back to once we have achieved good vaccination rates and herd immunity?

TW: Well, I don't think I have stayed in Toronto this many

months in a row for decades - I'm used to travel and meetings, and so being in my house, other than for a walk around the neighborhood every day, is confining. But I think I'm lucky that I'm busy with the research because it keeps me engaged, and I am sure we are all looking forward to socializing and exploring the world again.

DF/LD: As a quick follow up question, where would you want to travel?

TW: I was really lucky because I had just been to South America in February, before the shutdown, and was hiking in Patagonia and in the Atacama Desert. It was really great, and I got one of my dream trips in before the pandemic - so I am not trying to think too far ahead, but I will wait for the pandemic to be over and then I will figure out what I want to do next.

DF/LD: Thank you so much, Dr. Watts.