

Interview with Dr. Jen Gommerman

UTMJ Interview Team (Kathleen O'Brien and Alexandra Florescu)



Dr. Jen Gommerman

Dr. Jen Gommerman received her Ph.D. (Immunology) at the University of Toronto in 1998. She went on to do a post-doctoral fellowship at Harvard Medical School studying the complement pathway and then joined Biogen Inc. as a Staff Scientist in 2000. During her tenure at Biogen, she became interested in B cells, multiple sclerosis, and the TNF superfamily of molecules. After 3 years in Industry, she returned to Academia as an Assistant Professor (Immunology)

at the University of Toronto in 2003, and in 2015 was promoted to full Professor. Dr. Gommerman's basic research continues to focus on how members of the TNF superfamily of molecules regulate immunity and autoimmunity. Her team has uncovered a novel gut-brain axis that regulates neuroinflammation. With respect to translational work, Dr. Gommerman has been examining the role of B lymphocytes in multiple sclerosis patients, and she is the lead investigator on a study examining the effect of global migration on susceptibility to autoimmune disease.

UTMJ: To start off, could you tell us a bit about your career trajectory and how you got to where you are now?

JG: Okay, so I'm kind of home-grown because I did both my BSc and PhD here in immunology. I had studied signal transduction in mast cells doing my PhD but I wanted to move into a lab where I could really try to understand immunological questions in the intact animal. And so, I went to Harvard and worked with a guy named Michael Carroll on the complement pathway. He had just made complement knockout mice and was discovering that complement proteins are not just important in acute inflammation but also play more subtle roles in the adaptive immune response. So I worked with him for a couple of years and collaborated at the same time with some folks in industry at Biogen, a major company in Cambridge, Massachusetts. Then the opportunity came up for me to cross the river and go work there and it was a good time to do that so that's what I did, and I was a scientist in Biogen for three and a half years. And then a posting came up for an assistant professorship here and I applied, came and interviewed here the day before SARS broke in Toronto...and then had to wait quite a while for an answer because everyone was quarantined. Anyways, it all worked out and I started my lab here in September 2003 and have been promoted up to professor now and in the last eight

years have also taken on a major administrative role as the graduate coordinator.

At first my lab was dedicated to further understanding some of the things I've worked on in industry around this pathway called the lymphotoxin pathway, and I ended up going more and more into gut immunology because we know that this pathway is quite important in gut inflammation and more specifically in generating immunoglobulin A responses which is the humoral immune response of the gut. And so that brought me into the trajectory of gut immunology, at the same time we'd been looking at this pathway in an animal model of multiple sclerosis (MS) called 'Experimental Autoimmune Encephalomyelitis' or 'EAE', and somehow these two fields ended up sort of converging in my lab – now we are very interested in the gut-brain axis and how this can affect diseases such as MS but also other broader ranging health issues.

UTMJ: You have a lot of exciting research going on and we are wondering if you can expand on your findings related to the microbiome.

JG: So I want to qualify I'm not a 'microbiome researcher' (although I'm not sure what that means), but what we don't do is we don't go in and look at microbial communities and attempt to understand how those communities are formed, how they're maintained, the metabolites they produce and so on. We get help to do that because that is not our core expertise. However, we have the ability to change microbiomes in our mouse models, or even introduce microbiomes from human subjects into our mouse models and then ask how that impacts the immune system. Probably our best paper on looking at that was our recent publication looking at these mucosal B cells – these are called plasma cells, they're B cells that make lots of antibodies and they can live for a very, very long time, up to decades in humans. What we found was that unexpectedly these cells that like to live in the gut and make IgA can get recruited to extraintestinal tissues. In particular we looked at the brain during EAE (the multiple sclerosis model) and sure enough they can be recruited to the brain where they actually dampen inflammation. In the context of the microbiome we did an experiment where we altered the microbiome by introducing a single microbe (a protist) into a pre-existing microbiome and that did reduce the disease that we were looking at! We postulated, although we didn't prove it directly, that this could be because of even more migration of these intestinal plasma cells to the Central Nervous System (CNS) and they might have more potent anti-inflammatory activity. Because the gut microbiome

can promote different types of immune responses, it can be a bad guy or it can be your friend in terms of tuning less inflammatory-type immune responses, or, and there's not many examples of this, but there are some that show that there can be outgrowth of microbes that either favour a more inflammatory immune response or fail to develop these anti-inflammatory feedback mechanisms.

UTMJ: Just following up on that, you have a lot of findings about IgA plasma cells that can prevent against the development of multiple sclerosis or help to dampen the disease, and that these cells come from the gut and then go to the brain. What's the future directions of the research that you're doing as it pertains to how the microbiome impacts the immune system?

JG: I mean we're not at a stage in microbiome research I think where we can say 'take this microbe and you are going to feel better'. I think what we do need to understand is whether some microbial communities will promote wellness maybe in the context of some of the already established therapies. For example, in MS, one of our best therapeutic tools is Rituximab, or Ocrelizumab, which is anti-CD20. This is an agent that gets rid of B cells but it spares plasma cells, and one thing we're interested in looking at is whether the mechanism we described in the paper you're talking about, whether it is operational in the context of Rituximab treatment. Rituximab treatment, for example, doesn't work very well in the progressive form of MS, so maybe one thing we can do is augment its efficacy by promoting an anti-inflammatory microbiome at the same time. In the future, I think we'll hopefully be looking at therapies that involve replacing microbiomes with healthy microbiomes, for example, what we already do in the case of *C. difficile* infection. Or maybe even more practical is to look at the metabolites that come from those microbial communities and using those as treatments in disease because it can be hard to change an established microbiome.

UTMJ: And specifically, for the lab that you're running, do you see a future for incorporating further microbiome research?

JG: For sure, so thanks to Dr. Dana Philpott we have a germ-free vivarium at the University of Toronto. So what that means is you can house mice in this facility that lack a microbiome, and when you do that it provides a blank slate for introducing new microbial communities. One thing we're really interested in doing is looking at patient microbiota in these mice and starting to ask: what are the aspects of patient or healthy microbiota from healthy controls? Something I am really interested in is how microbiota change with age, or if you're chronologically aged, how you can somehow make lifestyle choices that keep your microbiota healthier. I think those are big questions and the best way to answer those questions are in these germ-free mice. Now it's not a perfect system, and in fact a paper just came out in *Cell*, a commentary, that was

sort of a little more negative about this approach. However, it still remains our best tool for looking at causality in changes in microbial communities, and in particular clinical phenotype. That's research that is going on at UofT and that is definitely where my lab's going.

UTMJ: Can I just ask a more technical question...In terms of getting mice that don't have a microbiota, how do you ensure that? How do you actually go about doing that?

JG: So you have to do a sterile C-section. And then to propagate strains you would implant an early stage embryo into a germ-free foster mother, because you inherit the microbiome of the vaginal canal as you're born. It's later replaced with more complex microbiota, but if the mom is germ-free and in a germ-free environment then the offspring will be germ-free as well. But it requires a lot of rigour to maintain a germ-free facility. The facility is a vacuum but all it takes is a few little bugs and now you are not germ free anymore – you have a flourishing community.

UTMJ: You have spoken a lot about animal research, but your lab has also seen findings in humans. What are these?

JG: In our paper, we collaborated with a group at UCSF and they were able to show that in MS patients, there was a change in the level of IgA in the gut during an MS flare or relapse. Although we didn't have direct evidence for this, we wondered if it was similar to what we were seeing in the mice – that the IgA producing cells were leaving the gut in order to put out a fire somewhere else, in this case in the brain. I know that this UCSF group has followed up on that and they will have some work forthcoming in not too long.

UTMJ: The microbiome has been getting a lot of 'hype' recently... What do you think about all of this hype and about the future of the microbiome research in general?

JG: Every field struggles with this – every time there's new excitement around a scientific advance you start thinking 'silver bullet', that this is going to be it, this is going to solve all of our problems. When you think about it, one of the best therapies we have for a lot of different chronic diseases is good diet and exercise. In fact, let's use that as an example: good diet and exercise. Okay, that makes your disease better. But what's the molecular mechanism for why that works, because for example not all MS patients are able to exercise or having a good diet can be expensive or out of reach if you live in a food desert. So, we really need to understand what those molecular mechanisms are so that we can hone in on what exactly is beneficial about those approaches. The microbiome is the same way, so right now we're just grappling with the fact that the microbiome is so complex that of course there is going to be a lot of discoveries in the field that we'll have to think about and ruminate on before we can really put them into

practice. I think that while us scientists are usually very careful about communicating these things to the public, the media is not so good at conveying what we get excited about. We have a long way to go. Because people don't want to hear that, they want to know that they've got their silver bullet and they have it right now. But it's going to take time to really understand the molecular mechanisms behind why microbiome A is disease prone and microbiome B is disease resistant. But that's essential if you're going to make movements forward.

UTMJ: A lot of people talk about the gut microbiome, but there are microbiomes on the skin, etc. Do you think that a lot of the focus has been on the gut or do you see movement looking at flora elsewhere?

JG: Well, both. We've been rightly focused on the intestinal microbiome because it is the richest source. It's an incredibly diverse ecological community. I think for sure, there is more and more research on different microbiomes – here at U of T, I know that Rupert Kaul has been looking a lot at the microbiome of the reproductive tract. Skin microbiome is clearly very important in diseases like psoriasis and acne, for example. All of these things are super important. It is just that the gut has the richest source of microbes, so that has been a major source of study. And, I think intuitively and as clinicians, you have probably heard this a lot too, if your gut is not well your body is not well – and there has to be some reason for that. Anatomically, I think there are some interesting connections between the gut and the brain that we are curious about.

UTMJ: Our journal is often read by people involved in clinical work – how well melded do you find basic science to be with translation into clinical practice?

JG: Well, it is way better than it used to be. I would say I have just as many clinical colleagues as I have basic research colleagues, and I think we do a pretty good job at working together. But this has taken time. There used to be a time even as little as ten years ago, where the basic scientist was supposed to really focus on animal models and in-vitro models and not go beyond. We were somehow almost discouraged from doing translational work. It is totally different now. To get funded, you don't have to show that your work has translational evidence, because there is an important place for purely discovery research, but a lot of people do. For me, it has always been a part of my approach, perhaps because I worked for a drug company and I saw all stages of clinical development from earliest bench research all the way to the design of drug trials and seeing the results of trials come in—that is a super exciting arc that I really like. Overall, I think it has gotten a lot better, but it takes a team. The old model of 'one researcher, one grant and one lab' still happens and it can be effective but there is a lot more team research now.

UTMJ: What can people do to build on that and further the number of basic discoveries that make it into the clinic?

JG: [Laughs.] We can be less busy. Honestly, I think the will is there, it is just finding the time to work together, to do meaningful science together. The will is there. And I know for clinician-scientists, protected time is really important. I can't comment on that because I am not in that world, but that would make sense to me. You just need the time and the bandwidth to be able to meet and work together. And the funds. [Laughs]

UTMJ: What have been some top moments that have made you go "wow, I am really happy to have the job I do"?

JG: There is my research job and there is my administrative job. I have had moments in both, so I can give you an example of each.

We did some work back in 2011 where we had this Lupus animal. But we were already thinking in terms of the gut. When we looked in the kidneys of these mice, which were nephritic, we noticed that the classical antibody deposition you would normally see in a nephritic kidney which are IgG complexes, weren't IgG, they were IgA. We took this beginning observation and we worked it all the way to the end. It turned out that these mice which overexpressed this cytokine called BAFF developed a disease that is very similar to IgA nephropathy, a disease that is actually the most common form of glomerulonephritis and has no treatment. So that was cool, and the other thing we noticed in these mice is that if you took these mice and made them germ free, so got rid of their microbiota, their kidney disease went away. The overexpression of the BAFF cytokine was not sufficient to drive the kidney disease, the microbiome was an important cofactor. The third big thing in this paper, is we thought, if BAFF drives this disease in mice, then maybe there is a similar pathway going on in humans. We found two cohorts of IgA nephropathy patients and we measured in the serum of these patients the level of BAFF and the level of the related cytokine APRIL, which shares the same receptors as BAFF. BAFF levels weren't elevated in the patients, but APRIL levels were. So we published both the mouse and human data in this JACI paper. And the paper got completely ignored. We were very happy with the paper and it was actually a collaboration between myself and Biogen, so it was nice to continue to work with Biogen on that, but it pretty much got ignored by the IgA nephropathy community at least – actually pretty much by everyone. [Laughs]

A couple of years later, fast forward one or two years, two big Genome Wide Association Studies (GWAS) papers came out (where you look at all the genetics of a patient group compared to controls). In the IgA nephropathy group, one of the top hits was APRIL. Still our paper was ignored, in fact I don't think our paper was even cited by either of those studies. Fast forward a few more years, and someone had the bright idea of testing the drug Budesonide in IgA nephropathy patients – maybe they

read our paper, I don't know, but basically the concept is that Budesonide is a steroid that you take orally and it is non-absorbable. So, it inhibits the immune system all the way along the intestinal tract. This has been the only drug that has worked in Phase II IgA nephropathy patients – I think a Phase III trial is underway. But it worked! It didn't cure them, but it had an effect. This is a disease that had previously just been treated with global steroids. So now we have two pieces of information – APRIL is elevated in some patients and these patients appear to respond to immunosuppression in the gastrointestinal tract. I thought our paper would never be cited, but then out of the blue, I got an invitation to keynote the IgA Nephropathy Society meeting in France. All of a sudden, people were reading this paper, and it wasn't being ignored any more. And it was the literature that did that – it wasn't that I was going around on a soapbox saying “hey, listen to our paper, read our paper!” [Laughs] It was that the field took care of it, and there were of course other papers coming out too that were hinting that this disease may have a link to the microbiome, to mucosal immunity and certainly has a link to these cytokines. I think it has actually informed clinical trials – I know an anti-APRIL antibody is being considered for IgA nephropathy and there are these Budesonide trials, and people are actually starting to look at the microbiome of these patients. I think scientifically that was a really big win because it taught me that sometimes your

work will get ignored, for sure, but if it really has a clinical impact, hopefully it will emerge in time. To see that it is part of that clinical picture is really rewarding. I don't want to imply that our paper was the only paper that has directed the field like this, but it's a piece and that feels good.

Is that a good story? [Laughs and smiles.]

Just from being a graduate coordinator, watching people graduate – going to their thesis presentation and seeing where they go afterwards. I have this nice picture that I tweeted in the fall when I was giving a talk at Harvard, and there were seven or eight U of T students that were all at different stages of their careers in Boston and they had come to see my talk. I knew them as students so that was a really big moment.

UTMJ: Those were all our questions, unless there was something else you wanted to share with our readers.

JG: Just to underscore that I am not a microbiome researcher. I am an immunologist that has recognized the microbiome is a major influence on the immune system, and that is my perspective. So, I wouldn't describe myself as an expert microbiologist, because I think all immunologists have to understand the microbiome. That should be your top statement. [Laughs]