Lyle McKinnon Interview

Our January-February Immunologist of the month is from the University of Manitoba. Lyle did his PhD at the University of Manitoba focused on understanding HIV-specific cytotoxic T lymphocyte (CTL) responses and HIV diversity under the supervision of Frank Plummer. His postdoctoral work was carried out at the University of Toronto on defining mucosal HIV target cells in the female genital tract, with Rupert Kaul. During his training he spent ~10 years in Nairobi, Kenya carrying out field research including epidemiological and immunological studies of high risk men and women. He then spent >3 years at CAPRISA in Durban, South Africa continuing his work in mucosal immunology in the context of HIV prevention trials in women.

Since 2015 he has been an Assistant Professor in the Department of Medical Microbiology and Infectious Diseases and Community Health Sciences at the University of Manitoba, with cross appointments at CAPRISA and the University of Nairobi. His research interests include understanding the causes and consequences of inflammation in the female genital tract, HIV target cells including those that home to the gut, and HIV transmission in men having sex with men in Kenya.

Name: Lyle McKinnon

Current position: Assistant Professor, Medical Microbiology and Infectious Diseases, University of Manitoba. Cross-appointed at CAPRISA (Honorary Senior Scientist), University of Nairobi and the JC Wilt Infectious Diseases Research Centre

What you research focus is: My lab focuses on mucosal immune aspects of HIV transmission and pathogenesis. This includes analysis of specimens collected from the gastrointestinal and female genital tracts of men who have sex with men, female sex workers, and young women from Kenya, South Africa, Canada, and Thailand. A central focus of this work is on understanding inflammation and HIV target cells at sites of exposure, replication, and where latent reservoirs are maintained. We are interested in defining causes of inflammation and mechanisms by which it might enhance HIV entry and persistence. Many of these studies include prospective designs and characterization of immune responses ex vivo, correlating them to clinical outcomes.

What interesting discoveries has your research group made? How has it impacted the field of Immunology ? We recently showed in collaboration with CAPRISA, the US Military HIV Research Program in Bangkok and others that the gut-homing integrin a4b7 was a predictor of HIV acquisition and disease progression in women, supporting a role for this population as an important early HIV target cell that may contribute toward gut damage (Sivro et al Science Translational Medicine 2018). At CAPRISA we've shown that genital inflammation, defined by the number of elevated cytokines in cervicovaginal secretions, was a strong effect modifier that negated the protective effects of topical tenofovir in preventing HIV (McKinnon et al Nature Medicine 2018). These findings echo our parallel collaborative work showing that a diverse vaginal microbiome, which is associated with vaginal inflammation, also reduced tenofovir efficacy (Klatt et al Science 2017). Several follow up studies are focusing on dissecting inflammation more carefully to determine mechanism, as well as exploring causes

of inflammation including host genetic predictors. This is of great interest, as it may inform HIV prevention. One important study in this regard is the Transitions study of young women from Mombasa, Kenya, where we have demonstrated that sex and sex work may have an important role in inducing dysbiosis and inflammation.

We showed that elevated mucosal cytokines are associated with an increase in HIV target cells and decrease in mucosal barrier function (Arnold et al Mucosal Immunology 2016). A similar phenotype was observed for vaginal dysbiosis (Zevin et al PLoS Pathogens 2016). These studies suggest that the inflamed, microbial diverse environment of the female genital tract might increase the likelihood that HIV can penetrate the initial barrier and gain access to a sub-mucosa that contains more concentrated and available HIV target cells. We are now applying these findings to rectal immunology, where less has been demonstrated regarding HIV acquisition in humans. We are working on a series of studies in men who have sex with men (MSM) in Nairobi, who are at very high risk of HIV acquisition. We have shown important rectal microbiome differences between MSM and heterosexual Kenyan men, and characterized the mucosal and systemic immune impact with respect to potential HIV risk factors. We are now looking to extend these studies in a prospective fashion. Finally, in addition to mucosal immunology research, we are interested in better understanding the evolving epidemiology in key populations in Kenya (Cremin et al Lancet HIV 2017), South Africa, and elsewhere, in order to best incorporate this important aspect of HIV research into our immunological approaches..

What’s the role of integrins in T cell homing ? T cell homing is controlled by expression of homing receptors expressed on the cell surface, and expression of their receptors on the high endothelial venules in tissues. One of the important homing molecules for gut immunity is alpha-4 beta-7, which

binds to MAdCAM-1. Since a4b7 is induced on T cells that become activated in the gut, this provides a feedback loop by which gut-relevant T cells are likely to return to a tissue where they are functionally useful. Other integrins that are related to a4b7, due to sharing of one receptor pair, include a4b1 and aEb7, which are involved in inflammation (particularly in the central nervous system) and tissue retention, respectively.

How does cell homing affect HIV infection? The concentration and/or phenotype of CD4+ T cells that home to mucosal surfaces influences the likelihood that HIV infection will become established. Additional cells then home to these surfaces during acute infection. Homing of HIV-infected cells to distal lymphoid and mucosal tissues is important for dissemination of the HIV reservoir, an initial insult that sets the stage for the remainder of HIV pathogenesis. One particular subset called central memory CD4+ T cells preferentially home to secondary lymphoid organs, and likely comprise an important reservoir due to their quiescence and longevity. Depletion of central memory cells may also contribute to pathogenesis. Another important reservoir site is within the germinal centers of lymph nodes; one contributing factor for this is thought to be poor access of CD8+ T cells and NK cells that do not express CXCR5, a homing receptor required for germinal centre access.

Finally, for HIV vaccines, homing of ideal effector and memory cells, some of which may home and become tissue resident, may be critical for achieving protection. These are only a few examples of how immune cell homing is a key factor in HIV transmission and pathogenesis.

Why did you become an immunologist? I was drawn to the topic as an undergraduate. The combination of relatively simple concepts on the one hand (host versus pathogen, avoiding the dangers of immunopathology) and the complex solutions to these concepts that have evolved over time were fascinating. How can

a very small inoculum of pathogen lead to effective immunity in an environment where millions of other similar-looking microbes must be ignored for the successful maintenance of homeostasis? The evolution of B and T cell receptors, the MHC/HLA system, and generation of antibody responses were similarly fascinating. The second important factor was the gap in terms of understanding immunology in humans, which for HIV meant understanding both epidemiology and international health. Since then, there have been an amazing number of translational discoveries in human immunology, especially in autoimmunity and cancer. Despite its complexity, the sheer speed and scale of the advances of the past 2-3 decades make this one of the most interesting areas of medicine at the moment. Also, I was bad at math, currently trying to get better!

Advice for grad students and early career scientists ? Study math? I would say it’s important to try to have a list of options open as to what you’d like to do after, whether it is a PhD or an MSc. First all, is a PhD required for what you want to do? If it is a PhD and a postdoc is next, the postdoc is really critical for angling toward a career goal. The time goes fast and it’s important to build a network that provides the next job often years in advance of it actually materializing. Even if that network is really a collection of potential job options. A key aspect of networking is not to always be after something. Be interested in what interesting people do, and try to keep things focused on the research as much as possible. It is highly advantageous to get an early paper, whether that means writing up a method or a preliminary result or helping with someone else’s paper. Papers are critically important, and at an early career stage even one good one can help to differentiate you from others. It is very worthwhile to be helpful, to be a positive influence in another person’s project even if it isn’t clear how it will benefit you. Science is collaborative, and what you can give to someone is likely to come back in many returns. For your

own work, you need to know more about what specifically you're doing than anyone, it is important to become an expert in the details, as this is what makes science work/not work. You need to read extensively. It can also be useful to acquire a broader knowledge, as this will certainly come in handy later on, but it can't be at the expense of not getting the fundamentals done. Experience in helping with peer review and/or grant writing can be invaluable if it's available to you. Lastly, for publications you need to be persistent. Something that takes many years is not too late if you can still wrap it up. It is easiest to start projects, but very difficult to finish. As an early career investigator, I've taken the position of saying yes to "everything" (not predatory journals or conferences, but everything that is "reasonable"). The idea being that I don't know if and when I'll ever be asked again. This is of course within reason of what I think I can deliver on, but the point is that maybe a diversified portfolio is a good idea.

Interview by Kenneth Omollo