

Michael Betts



Professor Michael Betts earned his PhD in 1998 from the University of North Carolina in Dr Jeffrey Frelinger's lab working on human T cell responses to HIV. He continued this work during his postdoctoral fellowship with Dr Rick Koup at the University of Texas Southwestern Medical Center and then at the NIH Vaccine Research Center. In 2005 he started his lab at the University of Pennsylvania, where he continues to research the immune response to HIV and other viral infections in humans, most recently working on COVID-19. He maintains active collaborations in Latin America, Europe, and Africa, where he is involved in both immunology research studies and training of new investigators.



His continued contribution to the world of immunology includes contributing significantly to Immunopaedia course material. We are proud to have Professor Betts as our immunologist of the month for July 2022. See below his interview with Immunopaedia's Stefan Botha.

What is your educational background? What have you studied and why did you decide to pursue immunology as your research interest, with a specific focus on human T lymphocyte function during infection?

My first exposure to immunology occurred during my undergraduate studies at the University of Maryland in College Park. We were fortunate to be located near the National Institutes of Health, and every other year an Immunologist from NIH (Dr Michael Potter) would come to the University to teach a graduate level Immunology course. As a senior I took that course simply out of curiosity; I had little exposure to Immunology prior to that. It ended up being the defining course for my entire undergraduate education and prompted me to pursue a career in Immunology. I initially started as a technician in a vaccine lab at the US Food and Drug Administration studying antibody responses in mice, then moved onto studying human T cell immunology during my graduate work at the University of North Carolina in the lab of Dr Jeffrey Frelinger. I haven't varied far from that direction since that time, continuing work on human T cell immunology during my postdoctoral fellowship with Dr Richard Koup at the National Institutes of Health and then subsequently forming my own lab at the University of Pennsylvania in 2005.

I have always found T cells to be fascinating in their functional properties and capabilities. They are crucial to our survival, and even specific functions that they mediate can be critical to effective pathogen control. I like to think about them as nearly autonomous cells living within us, without boundaries or organ restriction. They can go nearly anywhere in your body to do their job, and then function within those different environments in specific ways to mediate protection.

What was it like to work in immunology when you started out your academic journey?

I look back at what I learned as a lab technician fondly. This was in 1990, when flow cytometry was just becoming mainstream, ELISpot assays had just been invented (with no pre-coated plates), and we would isolate human T cells using sheep red blood cell rosetting or glass wool purification

(things that Miltenyi fortunately replaced!). I ended up being the flow expert in my lab- the master of a FACScan, the first mass production Becton Dickinson 3 colour flow cytometer. It seemed so powerful at the time!

How has your research contributed to a better understanding your research area?

If there is one resounding theme in human T cell immunology, it is that we never really understand exactly what and how T cells are mediating their functions. I have always been highly sceptical of dogmas in the T cell field, especially when it comes to translating concepts/models/themes from mouse models into humans. I feel that my research has contributed to T cell research in several ways. Over the years I continually found myself in situations where assays did not yet exist to answer the questions that we had to understand human T cell responses. This resulted in invention and adaptation of multiple different T cell assays over the years, many of which are standards now in the field. From years past these include peptide arrays for mapping T cell epitopes, T cell polyfunctionality, and CD107a degranulation assays. More recently these include strategies to assess CD8+ T cell perforin mediated killing responses and CD8+ T cell transcriptional regulation. I also feel that our work has redefined concepts about protective T cell immune functions in the context of viral infections including HIV, and more basic themes of T cell trafficking in humans. Most recently we have begun efforts to understand T cell reservoirs in HIV infection using single cell analysis- now being able to resolve the epigenetic and cell surface characteristics of single infected cells directly from the blood of people living with HIV.

You seem to have such a great lab dynamic and group, just from a quick review of your lovely website (<https://www.bettslab.org/>), how important are healthy relationships and collaboration in academia?

I view my lab group as an extension of my family in many ways. It is critically important that everyone gets along and appreciates each other and their respective expertise. A happy lab gets more work done! Over the years, my lab has had its ups and downs with lab members, but overall, the experience has been wonderful.

The reality of science in the 2000's is that no one person can possibly be the expert in everything. Realizing this as a scientist, and admitting when you need help, is critical towards success. I often tell my lab members never to burn bridges with anyone. Remember, nearly anyone that you meet in science is not far removed from someone that you know or knows you. Your reputation therefore proceeds you, and reputation is everything as far as collaborations go. I have had great collaborations over the years, some of which I have maintained since I was a graduate student. Some of these collaborators have gone on to be close friends, and even in one case, godfather to my youngest daughter. Others have fallen by the wayside as interests evolve and the need for scientific interaction waned.

You have travelled a lot during your career. Do you have some preferred places or stories that you want to share?

The two places where I have travelled most often are South Africa and Mexico. Each location has specific wonderful memories of friends and the work done, trips which continue even now. For some reason, either on purpose or by accident, my trips to South Africa have often occurred over my birthday, including my 40th. I still maintain that because I wasn't home for that, I technically never turned 40 (my family disagrees). This, of course, omits the fact that my birthday was celebrated with friends during my trip in Johannesburg that year at a fantastically inappropriately decorated Thai/Vietnamese restaurant that has since closed.

Can you give some advice to early-stage immunologists and

clinician-scientists?

Always maintain an open mind about immunology- there will be an exception to every rule, and your hypotheses will be wrong 50% of the time (or more). Embrace those times when your hypotheses were incorrect- that is when you learn the most, and when you stand the chance to redefine models or discover new directions to research. The key thing here is to follow your data – immunology will lead you into unpredictable directions and trying to stay locked into your original hypotheses with fancy gymnastics will only make things worse.

What do you hope to achieve once you decide to hang up the lab coat?

Well, the answer to this will evolve over time as I get closer to that fateful day. Currently, I would hope that our work understanding HIV reservoirs will result in the discovery of novel strategies to directly target the HIV reservoir through immunologic (hopefully cytotoxic CD8+ T cells!) strategies. Perhaps more importantly I hope that I have been able to train and support the next generation of human T cell immunologists to look first and ask questions afterwards.

Other than that, I hope to achieve a really great vegetable garden.

Interview by Stefan Botha