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PEOPLE & IDEAS

# Cindy Ma: Science is often not black and white, and the answer usually lies in the grey

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**Professor Cindy Ma heads the Human Immune Disorders Laboratory at the Garvan Institute of Medical Research. She is a member of the Garvan Faculty, holds a conjoint appointment with UNSW Sydney (School of Clinical Medicine, Faculty of Medicine and Health), and is an NHMRC of Australia Investigator Grant Fellow (L1). Her research interests lie in the study of human diseases of the immune system such as primary immunodeficiencies due to inborn errors of immunity (IEI), resulting from disease-causing monogenic germline variants. Another area of research her laboratory is perusing is the pathways that cause severe allergies and atopic diseases such as atopic dermatitis and food anaphylaxis.**

**Please tell us a little about yourself and how you first became interested in science.**

I grew up in Canberra, which is the capital of Australia. No one in my family had a background in science, but I was always very academically driven, wanting to either do law or medicine. In my final year of high school, I decided to pursue medicine and moved to Sydney. In those days, there was no medical school in Canberra, so I enrolled in a Bachelor of Medical Science at the University of Sydney, hoping to then get into postgraduate medicine at the University of Sydney. In my final year, I majored in immunology and cell pathology, and this was where I was first exposed to science—the cell pathology course only took six students and we did a rotation in four different laboratories and had to write up a research report after each rotation; it definitely got me interested in science. The immunology course only took 25 students and was run by Helen Briscoe, and she is the reason I fell in love with immunology. All our lectures were held at the Centenary Institute of Cancer Medicine and Cell Biology, whose executive director at the time was Prof. Tony Basten. I didn't know it at the time, but I was being taught immunology by some of the greatest minds in Australian immunology and clinical immunology, including Tony Basten, Barbara Fazekas, Phil Hodgkin, Rob Brink, Nick King, Gary Halliday, Warwick Britton, Stephen Adelstein, and Rob Loblay. They are the reason I decided to do an undergraduate research year and then a PhD in immunology.

**Tell us about your career trajectory and what led you to becoming a group leader.**

I definitely did not start out wanting to be a lab head and running my own group. It was very serendipitous when I finished my PhD; I visited several labs in Europe and the USA for postdoctoral positions, but back home Charles Mackay and Fabienne Mackay had started growing the immunology research programs at the Garvan Institute and it felt like a good place to do a first postdoc with so many immunologists under the one roof. I was fortunate enough to get a fellowship to support my salary and the momentum just continued whereby there were always new and interesting projects to work on. This enabled me to get funding and promotions internally.

**How did you first become interested in working on human primary immunodeficiencies?**

I first became interested in working on human primary immunodeficiencies during my PhD from Stu Tangye—he had just come back from his postdoc in the USA and was starting his own lab. When I was looking for PhD projects, he spoke to me about this rare primary immunodeficiency X-linked lymphoproliferative disease (XLP) due to loss-of-function variants in *SH2D1A*, which encodes signaling lymphocytic activation molecule–associated protein (SAP). As SAP was a small adaptor molecule expressed in multiple cell lineages, it was not obvious how the absence of this protein resulted in the clinical phenotype of XLP patients—susceptibility to EBV infection, fulminant

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infectious mononucleosis, hypogammaglobulinemia, and lymphoma. And so, we started setting up robust in vitro assays capable of interrogating human lymphocyte, mainly B and T cell, functions. One of the major findings from my PhD revealed that B cell development and function in XLP patients were entirely intact, and B cells from XLP patients were capable of proliferating and undergoing immunoglobulin isotype switching to the same degree as B cells from healthy donors if given the correct stimuli (Ma et al., 2005). It was exciting at the time as this was when the role of T follicular helper (Tfh) cells was coming to light. I also realized that the same scenario applied to a lot of human primary immunodeficiencies and inborn errors of immunity (IEI) that even after the gene defect is elucidated, it's often not entirely clear how this results in the clinical manifestations displayed by affected individuals. Part of the challenge in the field of IEI is determining these mechanisms. And that's where basic, clinical, and translational immunology really come together.

**What are you currently working on, and what projects are you most excited about?**

It's still a very exciting time in the IEI space as we are still discovering novel genes that result in IEIs—the last International union of immunological societies (IUIS) update was reported in 485 IEIs (Tangye et al., 2022) and the next update will include over 550. We are lucky enough to still be working at the forefront of this on monogenic causes that are yet to be reported, with strong collaborations with other leaders in the field. As more and more genes are discovered we start to piece together the pathways that maintain protective immunity. However, a relatively new direction of the lab has been on atopic diseases. Over the years, I have worked on IEIs that have atopic disease as a clinical manifestation such as loss-of-function variants in *STAT3*, *DOCK8*, *STK4*, *ZNF341*, *IL6ST*, and gain-of-function variants in *STAT6*. We are hoping to leverage mechanistic insights from our work with these known IEIs that present with atopic diseases to provide insights into allergies in the general population. I'm surprised how much we still don't know about allergy and IgE!

**Please tell us about some work in your field that you are currently interested in. (For example this could be a lab, an early career researcher, or perhaps a future direction you think the field is going in.)**

I'm very interested in the recently coined group of "primary atopic disorders." Gain-of-function variants in *STAT6* were reported for the first time in 2023 (Sharma et al., 2023; Suratannon et al., 2023; Takeuchi et al., 2023), and I think this is just the beginning of what will be a long list of genes implicated in IEIs that primarily present with early onset severe atopic disease. I'm interested in what we can learn from these IEIs when it comes to allergies in the general population. I also find the work on human organoids is really interesting and can be a way forward in regard to modeling human systems in vitro.

**When you first became a group leader, how did you gain confidence in your new role, and was the transition to independence easy to achieve?**

I think because the transition to my current position has been gradual over many years, I've picked up things along the way and the confidence comes from experience. For instance, I didn't go from $n = 1$ person in the lab to the size it is today; it has been gradual, and with each step, you learn how to adapt to different styles and determine what works and does not work.

**What are some of the qualities that you learned during your graduate studies or postdoc that you maintain and foster in your own lab?**

I learnt very early on in my scientific career that "science is often not black and white, and the answer usually lies in the grey." There are exceptions—for example, when we were working on why patients with hyper IgE syndrome due to loss-of-function variants in *STAT3* are susceptible to recurrent candida and staph infections, and revealed that in the absence of intact STAT3 signaling, you do not generate Th17 cells as the cytokines required for their generation—IL-6, IL-23, IL-21—are STAT3-dependent (Ma et al., 2008). This was very black and white. However, when we were trying to decipher the humoral defects displayed by these patients, we found this was multifactorial and not due to one mechanism—there is a B cell–intrinsic component (Avery et al., 2010) and a B cell–extrinsic component due to defects in B cell help from $CD4^+$ Tfh cells (Ma et al. 2012, 2016)—and I consider this the grey as there is not one answer. I also learned that "the data doesn't lie," but it's how we interpret the data that results in different opinions and results.

**Mentorship in science is extremely important. What are some qualities that students and postdocs should look out for in potential mentors?**

Mentorship in science is extremely important, and it's good to see that most scientific institutes/organizations now have formal mentoring programs. From my experience, mentors come in many different forms and I seek advice from different people depending on the situation. We all come from different backgrounds, and there isn't one person that has had the same life experiences as me. My advice would be to surround yourself with a diverse group of people, each with traits you aspire to. Especially in today's times where everyone is so time-poor, time is everything, so my advice would be to pick a lab or supervisor that has the time to invest in your training and mentoring.

**Where do you find inspiration for your work, and what motivates you as a group leader?**

I love the field I work in; I love trying to piece it all together and the satisfaction that comes with working it all out. It sounds very cliché, but ultimately making a difference in the lives of the individuals and families affected by the disorders we work on. I'm very lucky to be working with a great team of extremely bright people, many of who I consider friends outside of work.

**While not in the lab, how do you like to spend your time, or alternatively, how would you *like* to spend your time?**

How do I like to spend my time outside of work? I was recently asked this same question, and I didn't think the person knew how to respond to my answer! I was at a function, and as we were sipping champagne and watching the sunset over Sydney Harbour, one of the hosts asked what we liked to do outside of science, and while others commented on music, art, and gardening, appreciating the immaculate garden we were surrounded by, all I could say was I have three young children whose numerous extracurricular activities take up all my

time outside of work! I do come from a relatively large family, so there is always some sort of gathering or celebration. I love catching up with family and friends over a nice meal and a glass of red wine. However, definitely outside of the lab, but not strictly outside of work, one of the perks of science is the many conferences we attend, and the interesting places we get to go. Having been in the field for some time, some of my closest friends are scientists that I get to travel with. Recently, I spent a couple of days exploring Paris with three such friends—even my life is no longer black and white, split between work and non-work, with a definite space for grey.

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