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PEOPLE & IDEAS

Vijay Rathinam: Cherishing the small victories

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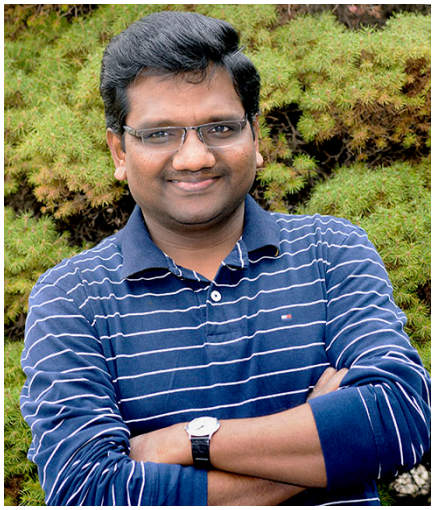
Vijay Rathinam is an Assistant Professor of Immunology and the Director of the Graduate Program in Immunology at UConn Health. His work is focused on understanding pathogen recognition by the innate immune system, specifically how the inflammasome is activated by Gram-negative bacteria. I caught up with Vijay to find out more about his journey in science.

Where did you grow up?
I grew up in Namagiripettai, a small town in Tamil Nadu, a southern state in India.

When did your interest in science begin? What was your first experience of science?
I was a first-generation college student, and I did not grow up thinking about science. Until the globalization of the Indian economy diversified job opportunities in India, the school education in India was formulaic and pretty much geared toward making doctors (medical, veterinary, and dental, arguably in that order) and engineers. Following the modus operandi of doing well both in high school (academically) and on a standardized test for admission to professional schools, I joined the Madras Veterinary College to become a veterinarian. During my first couple of years in veterinary school, I learned a lot about basic sciences such as physiology, biochemistry, and microbiology. After transitioning to the clinical segment of my veterinary medical education, it did not take much for me to realize that clinical practice was not my cup of tea! I was much more curious about fundamental biological principles and pathophysiological processes. So I decided to go to graduate school in the US.

That meant taking another standardized test, the GRE, which was unsettling for two reasons: the verbal component of GRE requiring English language proficiency and the cost. Complaining about "what doing well on the GRE has to do with one's success in graduate school"' was a regular topic of conversation among many of us who wanted to do a PhD in the US at that time. Almost two decades later, it is good to see a serious debate on the reliability of the GRE as a predictor of graduate school success and many graduate programs reconsidering GRE as a requirement. In any case, I did not do well on the GRE (in the verbal part, of course). I failed to secure admission to a PhD program, perhaps due to my low GRE score and a lack of any serious research experience. This was a stressful time, as I had to make up my mind about what I wanted to do. With my parents' backing, I decided to do a master's program in India to gain more research experience and prepare more for the GRE. After the master's program, with a much improved GRE score on the retake, my second attempt at gaining admission to a PhD program in the US was successful.

Where and with whom have you studied (undergraduate, graduate, postdoc)?
I joined an interdisciplinary graduate program, Comparative Medicine and Integrative Biology, at Michigan State University, and I did my PhD research in the laboratory of Dr. Linda Mansfield. The Mansfield laboratory was working on an enteric bacterium, *Campylobacter jejuni*. Much of the work in the laboratory focused on developing mouse models for *C. jejuni* infection and understanding bacterial virulence mechanisms. Linda was brave enough to ask me to come up with a research project on my own. It took me a while to figure out a research topic that was interesting to me, and eventually I decided to study the host–pathogen interaction during *C. jejuni* infection in the context of dendritic cells. Since this project was entirely different from anything going on in the laboratory, everything had to be set up from scratch, involving a lot of troubleshooting, and I just loved it. My dissertation work demonstrated *C. jejuni*–induced activation of dendritic cells, the mechanisms involved, and its impact on T cell activation.



Vijay Rathinam

As I wanted to delve deeper into the molecular basis of innate immune recognition of microbes, I joined Dr. Kate Fitzgerald's laboratory at the University of Massachusetts Medical School—a place to be for innate immunity research—for my postdoctoral training. I consider this a turning point in my career. If there is a checklist of qualities of an ideal postdoc mentor, Kate

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Vijay Rathinam and his wife and colleague, Sivapriya Kailasan Vanaja, and their boss, Nilaa Rathinam, a first grader!

would tick all the boxes. Kate is an amazing scientist with an infectious enthusiasm for research, and the well-rounded training that I received during this period was key to my growth as an independent scientist. My postdoctoral work demonstrated the role of AIM2 (Absent in melanoma), an innate immune receptor for cytosolic DNA, in host defense (Rathinam et al., 2010). My subsequent work identified type I interferons as a key licensing signal required for the cytosolic LPS sensing pathway to become active during bacterial infections (Rathinam et al., 2012). Subsequently, I started my laboratory at the UConn Health School of Medicine in 2014.

What interested you about your current area of study?

Innate immune sensing is central to the activation of the host immune response. A diverse set of germline-encoded receptors surveys nearly all cellular compartments for the presence of pathogens and their products. Such compartmentalized surveillance of microbial products has emerged as a key strategy by which the innate immune system gauges the severity of a microbial threat and mounts commensurate defense responses. I am fascinated by an emerging array of pattern recognition receptors in the cytosol and how they sense intracellular invasion of pathogens. I find the host's differential reactions to intracellular vs. extracellular sensing of pathogens intriguing. Particularly, inflammasome-mediated sensing of pathogens and the ensuing inflammatory cell death response are exciting to me.

What are you currently working on? What is up next for you?

I have a long-standing interest in understanding the innate immune basis of infectious and inflammatory diseases. Our work aims at decoding fundamental mechanisms in intracellular innate immune recognition and signaling during bacterial and viral infections. My laboratory currently works on cytosolic sensing of bacterial LPS. It has been known for a long time that TLR4 is the innate immune receptor for LPS. Surprisingly, we learned in the past few years about the existence of a TLR4-independent sensing of LPS that gains access to the cytosol by a family of inflammatory caspases such as caspase-11 in rodents and caspase-4 and caspase-5 in humans. Remarkably, the host response to LPS in the cytosol is characterized by an inflammatory and lytic form of cell death and IL-1 activation (Rathinam et al., 2019).

As the subcellular site of LPS sensing dictates how the host responds, we became interested in understanding how LPS attains access to the cytosol. My laboratory recently discovered that outer membrane vesicles (OMVs), bona fide secretory vesicles released by Gram-negative bacteria, act as the vehicle that mediates the cytosolic localization of LPS. OMVs activate the cytosolic LPS sensing pathway, leading to pyroptosis and caspase-1 activation (Vanaja et al., 2016). Demonstrating a necessary role for OMVs for intracellular LPS release during bacterial infections, genetic attenuation of bacterial OMV production diminishes their ability to activate caspase-11–dependent cell death and IL-1 responses. This work provided key mechanistic insights into a previously unknown yet critical upstream event in the cytosolic LPS sensing pathway. Currently, our group is working on various molecular and cellular aspects of cytosolic LPS sensing and its implications for host defense and inflammation. The expanding number of immune surveillance pathways in the cytosol does not operate in a vacuum, and in fact, more than one pathway is simultaneously engaged during infection with live pathogens. In this context, an additional focus of my laboratory is on the cross-talk among these different surveillance mechanisms in the cytosol and what that means for host defense at the whole organism level (Banerjee et al., 2018; Rathinam et al., 2010). Inflammasome-based host responses have been implicated in a variety of human diseases including but not limited to sepsis, atherosclerosis, and neurodegenerative disorders. Therefore, expanding our understanding of inflammasome signaling events at the molecular level could potentially reveal new targets for the therapeutic management of the above described diseases.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader? What were you unprepared for?

I was fortunate to have supportive PhD and postdoc mentors who had faith in my research potential and provided me the freedom to explore my research ideas. What I learned during my postdoc years, scientifically and otherwise, laid the foundation for me to be an independent investigator. Additionally, the whole biological system perspective that I gained from my veterinary medical training provided me with unique insights into intriguing biological problems. Together, these training components made me better prepared scientifically to lead a research group. However, there are a lot of skills that you learn as you go; among which, I would point out a few: developing research ideas for grants and grant writing, prioritizing research projects of interest on the basis of scientific and practical reasons, as well as recruiting talented individuals to the laboratory and mentoring them.

What has been the biggest challenge in your career so far?

I would say every step of my career was a challenge in its own way. Having said that, I regard something related as a main challenge: my better half, Sivapriya Kailasan Vanaja, whom I met during my master's in India, is also a scientist and has her own laboratory at the UConn Health School of Medicine. Finding two PhD, postdoctoral, and finally tenure-track faculty positions at the same institutions—without compromising each other's scientific interests and ambitions—was our biggest challenge so far.

What hobbies do you have?

I love photography. Though the time available for this has dried up lately, I make an effort to do some photography on vacations and during my travels for scientific meetings (one more perk for going to meetings in great places). Currently, I am building up my portfolio to do a photography exhibit someday. I am also an audio

enthusiast and avid cricket fan—no surprise there for the latter, for someone who grew up in India.

Any tips for a successful research career?

Research is a challenging but rewarding career. With the caveat of "easier said than done," I would say some of the qualities that enhance the odds of being successful in research are passion, perseverance, resilience, and the courage to go beyond one's comfort zone. Research is teamwork, and developing that skill right from the beginning can only help. Also, I would emphasis for prospective doctoral and postdoctoral trainees that it is important to find the right laboratory and mentor that would be compatible and suitable for their professional interests, short- and long-term. Finally, to borrow from the inspiring writing of Dr. Ron Vale (Vale, 2019), enjoy the basic discovery and cherish small victories!

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