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PEOPLE & IDEAS

Nan Yan: Innate immune signaling goes beyond viral

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Nan Yan studies the physiological function of innate immune signaling in the absence of pathogen infection.

Born and raised in the Henan province in central China, recognized as the origin of the Chinese civilization and home to the famous Shaolin Kung Fu, Nan Yan loves science as much as photography. His pictures reflect the breadth of life—from unusual angle shots of everyday objects to landscapes of national parks—and can be a mirror of the scope of his research. Throughout his academic career, Nan has turned his hand to almost anything: He has cloned new human genes, found regulators of germ cell development in flies, and uncovered new molecular ins and outs of the innate immune system.

Nan majored in biological sciences at Fudan University in Shanghai, China, but then moved to the U.S. in 2000 to pursue his PhD in the laboratory of Dr. Paul Macdonald at the University of Texas (UT) at Austin. His thesis focused on the translational regulation of mRNAs during *Drosophila* embryo development. He swapped flies for mammals as well as the topic for his postdoc and joined Dr. Judy Lieberman's laboratory at Harvard Medical School in 2006, where he investigated HIV-1 host–pathogen interactions. Nan set up his laboratory in 2011 at UT Southwestern Medical Center and continued in the immunology field but tilted his research toward the function of the innate immune system in monogenic rare diseases.

We spent some time with Nan to learn a bit more about his current work (and also had the privilege of seeing some cool pictures he took with his Fujifilm X-H1 camera!).

What was your first experience of science?

During my senior year of college, working in a human genetics laboratory that contributed to the Human Genome Project. At that time (late 1990s), the efforts of the laboratory I joined were directed toward cloning and sequencing new human genes; I helped with running PCRs, Northern blots, sequencing gels, reading A,C,G,T bands out of radiographical films, and reporting the coding sequence of new genes to the NCBI database. Most of the genes we identified did not have any known function or existing literature. For an undergraduate like myself, it was quite exciting to appreciate that there is so much that we don't know about biology and gene function.

You started in genetics but ended up working in immunology; could you tell us about your scientific journey?

I've switched gears a couple of times throughout my academic career. During my graduate thesis in the laboratory of Dr. Paul Macdonald, I studied how the RNA-binding protein Bruno binds to the 3′UTR of the oskar mRNA and regulates protein translation and development of *Drosophila* body pattern (1). It was fascinating to me that a tiny change in the nucleic acid sequence of an mRNA can drastically disrupt the head-to-tail development body pattern of a living organism!

After graduate school, I wanted to move from *Drosophila* to the mammalian system for my postdoc studies. I had a general interest in viruses and immunity. I reached out to several laboratories and eventually joined Dr. Judy Lieberman's laboratory. In Judy's laboratory, I focused on HIV-1 host–pathogen interactions. At that time, very few host factors were known for HIV-1, and the RNAi technology was just becoming available. I contributed to the first genome-wide siRNA screen for host factors required for HIV-1 replication in a human cell. We uncovered hundreds of host factors that are essential for nearly every step of the HIV-1 life cycle (2). It was astonishing how little we knew about the underlying mechanisms for most of these viral–host interactions. I eventually settled on studying one of the host cytoplasmic DNases called TREX1. I found that HIV-1 exploits TREX1 DNase activity to hide its viral DNA from innate immune DNA sensors (3). Thus, TREX1-proficient cells are blind to HIV-1 infection and support full viral replication, whereas cells lacking TREX1 can detect HIV-1 DNA and trigger a potent antiviral response. This study also launched my independent career; I started my laboratory in 2011 centered on the innate immune response to HIV-1 infection.

Nan Yan. Photo courtesy of UT Southwestern Medical Center.

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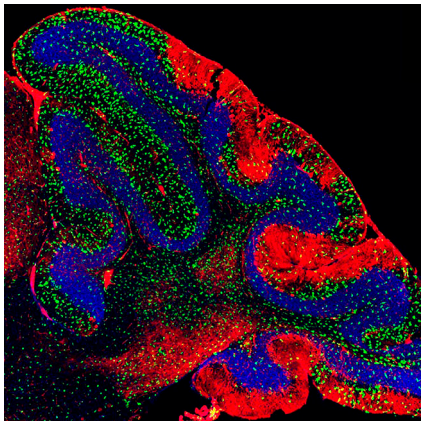


Immunofluorescent staining of *Npc1*-deficient mouse cerebellum, with Purkinje neurons in red, activated microglia in green, and nucleus in blue. Massive microglia infiltration and loss of Purkinje neurons cause severe neurological disease in NPC. Image courtesy of Ting-Ting Chu, Yan laboratory.

What interested you about innate immune signaling?

Innate immune signaling pathways are fascinating because they are precise, robust, and highly effective. They are widely expressed in many cell types in the body but remain "quiescent" when the organism is healthy, so we only get to see them in action when they detect a microbial infection. Although some microbes may trigger multiple innate immune signaling cascades, each pathway recognizes a unique component of the pathogen, so compared with other biological systems where redundancies and crosstalks are commonly seen, innate immune signaling pathways always are simple and clear cut, at least at the molecular level, and yet important for host defense and tissue physiology. It's surprising how much of the inner workings of innate immunity we have learned through the lens of pathogens!

What are you currently working on, and what is up next for you?

Inborn errors in innate immune genes are associated with many autoimmune and autoinflammatory diseases in humans. How a single gene mutation triggers a precise innate immune signaling pathway whose activation results in a systemic multi-organ autoinflammatory disease is puzzling, so I recently became very intrigued about several rare diseases of this kind, collectively known as type I interferonopathy. When a virus elicits the innate immune signaling, regardless of the pathway, the type I IFN response is usually set in motion. However, when the same innate immune pathway is chronically activated in an autoimmune or autoinflammatory disease, we see different types of clinical presentations. In many cases, the disease mechanism goes beyond just "too much interferon," and, in some cases, interferon or immune response are not even the root cause of disease. Taking our favorite stimulator of interferon genes (STING) pathway as an example; it causes systemic multi-organ disease in Aicardi-Goutières syndrome, which is classically known for this innate immune pathway. STING activation also causes inflammatory lung disease in STING-associated vasculopathy with onset in infancy that are independent of IFN (at least in mice). We and others have recently showed that STING also drives neurodegenerative diseases such as Parkinson's disease (4), amyotrophic lateral sclerosis (5), and Niemann-Pick disease type C (NPC; 6).

A major goal of my laboratory is to understand the physiological function of innate immune signaling in noninfectious settings; in addition to its well-recognized role in host defense, innate immunity could also have a broader role as the guardian of tissue development and homeostasis. Just like how viruses helped us to identify components of innate immunity, I believe inborn errors diseases of innate immunity will help us understand physiological functions of innate immune signaling; they usually have fewer overlapping signaling pathways being turned on, so they are ideal for mechanistic studies as a reductionist approach. For each research project, we try to cover a broad spectrum, from molecular mechanism to cellular function to tissue pathology and animal behavior to therapy. Often, it takes several years and multiple papers to fill all the gaps, but we try our best. Rare diseases are not receiving nearly enough research attention compared with common illnesses, although many textbook discoveries are made from studying them!

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

I learned that a group leader should lead by example; your presence on the bench, your joy about doing science, your excitement when seeing a positive result or read an exciting paper, your logic on how to make the best out of a failed experiment, etc., are all invaluable micro-learning lessons for people around you. What I become today was in large part from watching my PhD and postdoc mentors, who were key influences early in my career, and how they operate in and outside of the laboratory.

My PhD mentor Dr. Paul Macdonald taught me the importance of the scientific discipline. I remember in the early years of graduate school, Paul frequently corrected me on how to state a conclusion more precisely without overinterpreting or being vague, and how to design a better experiment with meaningful controls. I still remember with pride the day in which I showed Paul a fly genetics experimental design to address multiple layers of regulatory mechanisms on a single mRNA. Paul said to me: "Nan, you are now ready to do science!"

From my postdoc mentor Dr. Judy Lieberman, I learned to consider the physiological relevance of the scientific findings and how to put a spotlight on the science in writing. Judy's grants are always a joy to read, incredibly accessible to scientists from different backgrounds, and have a clear focus as well as the mechanistic depth to address a key biological question. The manuscripts and grants we edited together were the best academic writing classes I could ever have. I also learned how to manage a research project, from setting a vision to procuring research materials, collaborators with specific expertise, and how to deal with setbacks while moving the project forward.

I was not prepared for the financial side of operating a laboratory. Everyone understands that you need grants to keep a laboratory running, but how you maintain productivity despite inevitable ups and downs in funding is something you must learn on the job.

What is the best advice you have been given that you share with your mentees?

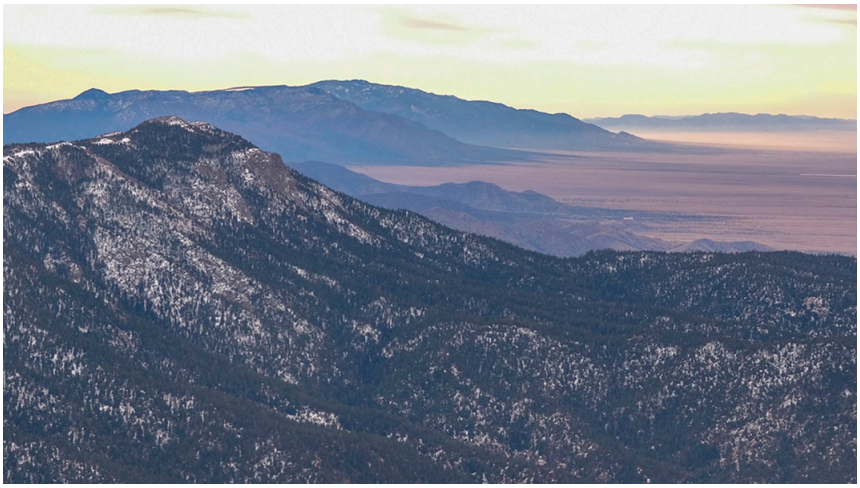
Be passionate about science, but don't be too emotionally attached (to a hypothesis or a project). Re-evaluate your hypothesis often; if it's no longer supported by data, no matter how perfect that hypothesis was, redraw the model and move on to the next hypothesis. The same concept also applies to selecting research projects. To stay competitive and keep moving forward, you need to be ready to give up your "baby project" that is no

longer important. Everyone has a limited amount of time to devote to doing science; make sure you are using your valuable time on something scientifically important, not just emotionally attached to you.

What has been your biggest accomplishment in your career so far? And your biggest challenge?

Scientifically, the biggest accomplishment is seeing a basic science discovery from a mouse model we developed in the laboratory moving into a clinical trial that could potentially benefit the affected patients (7; clinicaltrials.gov identifier: NCT02723448). This process usually takes decades but can be drastically shortened for rare diseases with drug repurposing and compassionate use. Personally, watching trainees getting excited about science and making discoveries of their own are also priceless.

Moving into a new field is always challenging and scary. I love innate immunity for its simplicity, and I had never imagined myself dipping my toes in glycobiology, metabolism, neuroscience that I thought were too complex. However, when an inborn error disease of innate immunity we study clearly affects glycobiology or causes disease in the brain, I must follow the science. Sometimes being naive or a newcomer has its advantages: You have a different perspective and don't fall into the conventional thinking of the new field. You also don't worry about (or aren't aware of) the dogma or the main players in the field. There are plenty of opportunities for innovation (or sometimes stupidity, in hindsight), but as long as you use your best scientific judgement, it is always exciting and worthwhile!



On a road trip to West Texas. Photo courtesy of Nan Yan.

What has been your biggest accomplishment outside of the laboratory?

The biggest accomplishment outside of the laboratory is probably raising two boys with my wife. My oldest son was born 1 mo after I started my own group. Every time we celebrate his birthday, it reminds me of how long I've been running my laboratory. It certainly wasn't easy at the beginning, with a new laboratory and a newborn, although there is never a perfect time to have children. Besides family joy, an extra perk of having children is that it forces me to become more efficient at work, more selective about what I think is important science worth pursuing.

You're talented at photography. Would you be a photographer if you were not a scientist?

Photography is probably the number one hobby I have outside of the laboratory. I love taking pictures of landscapes during travel or just everyday objects from an interesting angle or composition. Before I came to the U.S., I had an extensive collection of *National Geographic* magazines. I also love the National Parks in the U.S.; I have not visited all of them yet, but that's on my bucket list. If science doesn't work out, yes, I'd love to be a freelance photographer working for *National Geographic*.

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