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PEOPLE & IDEAS

Dan Davis: Up close and personal with immune cells

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Davis uses microscopy and imaging approaches to study immune cell interactions.

Dan Davis was initially drawn to research by his ambition to pursue some of the biggest questions in science—those that deal with the fundamental laws of the universe. He began his scientific career as a physicist, but Davis' curiosity eventually shifted from the laws that govern the universe to the details of how life works. It was these evolving passions that compelled him to become both a biologist and a writer. Davis was raised in London, and although his parents remember his early aspirations of becoming a farmer, he tells us that he always wanted to be a scientist. After earning his PhD in physics, Davis delved headfirst into the world of immunology as a postdoc at Harvard University in the laboratory of Dr. Jack Strominger. Before he was thirty years old, Davis had established a laboratory of his own in the UK. Today, Davis and his team take a zoomed-in approach to immunology, harnessing his unique perspective as a physicist to implement sophisticated high-resolution imaging techniques and spy on the behavior of immune cells. In addition to his work in the laboratory, Davis is an accomplished author of two immunology-based books for the public, which are examples of his many efforts to bridge the gap between academia and the rest of the world.

We reached out to Davis to learn more about his scientific trajectory and current research pursuits.

Where and with whom have you studied?

I did my undergraduate degree in physics at the University of Manchester. I chose Manchester for the buzz of the music scene at the time. I obtained a PhD in physics at Strathclyde University, Glasgow, Scotland, working with Professor David Birch. After my PhD, I wanted to switch to study some aspect of human biology because it seemed to me that was where the action was. In 1995, I wrote to many different laboratory heads in the United States, including Ahmed Zewail (the Nobel laureate who studied femtosecond chemistry) and Franz-Ulrich Hartl (who studies protein folding). I was thrilled that so many eminent scientists replied to me, and I still have a file with all their letters and faxes. I ended up heading to Harvard University to work with immunologist Jack Strominger.

> "What makes microscopy fun is that it is so inherently explorative."

I remember arriving in Boston in the midst of a snow blizzard and staying in a youth hostel. The next day in the laboratory I was completely overwhelmed seeing racks of plastic tubes, countless bottles, and pipettes—the things that were worlds apart from anything I was used to working with in physics. I immersed myself in it all, reading textbooks and papers and working long hours made fun by the friendship and camaraderie of other postdocs. Within six months, working with postdocs Ofer Mandelboim and Hugh Reyburn, we found that T cells express cell surface receptors previously associated with Natural Killer (NK) cells (1). This was an early example of an interesting theme in immune cell biology: protein expression once thought to be specific for one type of immune cell also turns out to be important for other immune cells. We now know that it is hard to define the differences between types of immune cells because the variability is enormous. Single cell sequencing and other technologies have shown that, at some level, every cell has its own uniqueness. It was at this time early in my postdoc position that I began to gain some confidence in my ability to contribute, while also realizing how much of one's life has to be dedicated to science to do so.

Dan Davis. PHOTO COURTESY OF NEVILLE MILES.

What first drew you to study NK cells?

I arrived in Jack Strominger's laboratory at Harvard University at a time when our understanding of molecular recognition by human NK cells was opening up. These cells were identified in 1975 as immune cells potent at attacking cancer cells. I realized that while the important receptors and ligands were being identified (and from crystal structures and site-directed mutagenesis, their interaction could be pinned down with atomic resolution) there was still a gap in understanding what actually happened over the few minutes that NK cells took to make a decision about the state of health of other cells. I wanted to visualize human immune cell interactions, to directly watch what happens over the few minutes that an NK cell discerns the state of health of another cell it is in contact with. So I tagged one of the vital proteins in this interaction, class I MHC protein, with GFP and watched cells interact. From this, I discovered the NK cell immune synapse (2), an unexpected dynamic molecular choreography at

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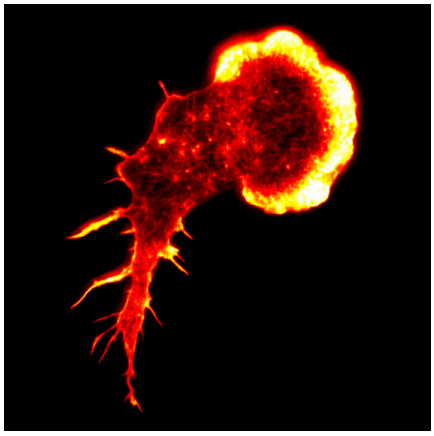

A super-resolution microscopy image of filamentous actin in a migrating human NK cell. IMAGE COURTESY OF ASHLEY AMBROSE AND DANIEL M. DAVIS.

the contact immune cells make with other cells, reminiscent of what had very recently been discovered for T cells by Avi Kupfer, Mike Dustin, and their colleagues. At 28, I left Harvard to set up my own laboratory at Imperial College London focused on imaging immune cell biology. In between jobs, my girlfriend and I traveled around Mexico, where faxes chased me across hotels and youth hostels, each a new iteration of our response to reviewers for our paper describing the immune synapse.

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

Building on my background in physics, my laboratory has always strived to use novel fluorescence microscopy techniques to visualize key molecular components of the immune response with ever-increasing precision. For some years now, we have been using super-resolution microscopes to study the integration of signals from immune cell surface receptors. An emergent theme across the work of many laboratories is that the classic Singer-Nicholson fluid mosaic model of unstructured cell membrane organization is too simplistic because many cell surface proteins are organized on a nanoscale. We have recently shown, for example, that clusters of inhibitory (SIRPα) and activating (FcγRI) receptors coalesce at the surface of human macrophages but segregate upon Fc receptor activation of macrophages (3). This raises new questions about how and why different receptors are organized into nanoscale clusters at cell surfaces and how the proximity of different receptors impacts signal integration.

What kind of approach do you bring to your work?

What makes microscopy fun is that it is so inherently explorative. Some lines of research in my laboratory address specific mechanistic problems, such as how cytoskeletal dynamics allow secretion of lytic granules out of an immune cell to kill a cancer cell. But many of our discoveries have come from seeing something unexpected down the microscope and following it up. Just by watching cells move around, for example, we discovered long thin strands of membrane that we called membrane nanotubes, which can keep immune cells and other cells connected over long distances. We then found that membrane nanotubes can provide a route for HIV to spread from one T cell to another (4). More recently, although we never set out to specifically understand how immune cells detach from a target cell after immune surveillance, by watching this happen and digging into the details, we stumbled across a process for this that involves shedding the activating receptors from the immune synapse. This is important for how immune cells sequentially move from one target cell to another so that one immune cell can serially kill several diseased cells where appropriate (5).

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

A great challenge for me has been to not take on too many things, but to focus on trying to do a few things well. As an academic, there are so many things one could be doing: research, teaching, reviewing, supervising, committee work, public talks, school talks, attending conferences, organizing conferences, and so on. I find it hard to say no, but I think sometimes you just have to.

What is the best advice you have been given?

One piece of advice that often plays in my mind is something a physician once said to me: You have to set out boundaries between you and your work because otherwise things will get out of hand and feel overwhelming. You have to be careful, for example, to not let feelings that come from experiments not working in the laboratory spill over into other parts of your life. And imagine if you discovered something really big, say a new cure for HIV. Everyone would want a piece of you for all different reasons and the only way to survive and stay sane would be to have boundaries.

What do you enjoy doing outside of the laboratory?

I have written two popular-level books and presented them on TV, on the radio, and at many science and literary festivals. Writing doesn't quite feel like a hobby though, as it's a big part of my life. My first book, *The Compatibility Gene*, told the story of the human leukocyte antigen system and how these few genes impact our health and individuality (6). One of the great joys in writing that book was interviewing many of the inspiring scientists who were involved in the discoveries, some of whom are no longer with us. My most recent book, *The Beautiful Cure*, more broadly describes the scientific quest to understand the immune system and how this knowledge unlocks new ideas for medicine (7). I know this might come across as boasting, but one of my own favorite writers, Bill Bryson, said he enjoyed both of my books. Whenever I remember that, it always makes me smile.

Any tips for a successful research career?

I like Kurt Vonnegut's advice best of all: "There's only one rule that I know of, babies—God damn it, you've got to be kind."

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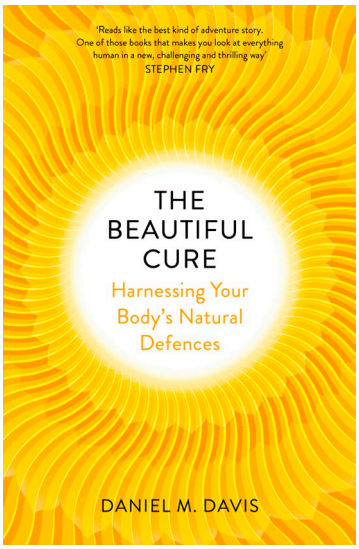

More than a hobby: *The Beautiful Cure.* PHOTO COURTESY OF JULIA CONNOLLY, PENGUIN RANDOM HOUSE.