Don Kirkpatrick

Kristin Elise Phillips, Health and Science writer at the University of Texas at Austin

November 2019

Chasing ubiquitin from coast to coast

It all started with a conference. It was 1997, and Don Kirkpatrick, now a Principal Scientist and Associate Director at Genentech in San Francisco, was an undergraduate at the University of Oklahoma (OU) when he received an invitation to attend a Society of Toxicology (SoT) conference. There, as part of the Minority Undergraduate Education Program, he met mentors who set him up with a summer internship at Searle Pharmaceuticals and encouraged him to pursue a doctorate degree.

"That first conference played a formative role in my career development, as I had never considered pursuing a Ph.D. In fact, I was headed toward a career away from laboratory-based research," says Kirkpatrick. "Starting from the early days of my career, mentors have played a crucial role in shaping my path."

After his internship, Kirkpatrick honed his research skills first as a doctoral student in Pharmacology and Toxicology with Jay Gandolfi at the University of Arizona and later as a postdoctoral research fellow at Harvard Medical School with the world-renowned mass spectrometrist Steven Gygi. By 2007, he was working full-time for Genentech; he now heads a lab that utilizes mass spectrometry based proteomics to untangle the many questions affiliated with basic research with a focus on drug discovery. His primary research interests center on understanding the complexities of disease mechanisms including cancer and neurodegeneration through the lens of a single protein, ubiquitin.

What was your path to mass spectrometry?

I was a graduate student when I started working on ubiquitin, which has since emerged as a central regulator of the proteome. I think it's fair to say that it controls nearly every protein inside a eukaryotic cell. At the time—around 2001 or 2002—it was very difficult to identify which proteins were being post-translationally modified by ubiquitin. Dan Liebler, a long-time mentor who at the time was on my thesis committee, said "You know, Don… mass spectrometry proteomics is a technology that you should really consider for your project." So at Dan's prompting I jumped on it [Kirkpatrick, D.S., *et al., Proteomics* **5** 2104-2111 (2005)], and I've continued to be mesmerized by this molecule for nearly 20 years.

When starting as a postdoc, I got the chance to continue some beautiful work initiated by Junmin Peng to study polyubiquitin chains with mass spectrometry [Peng, J., *et al., Nature Biotech*. **21**, 921-6 (2003)], and another postdoc in the group, Scott Gerber, nucleated my project with the idea to use stable isotope labeled peptides in a mass spec assay to quantify the different forms of ubiquitin [Kirkpatrick, D.S., *et al., Methods* **35** 265-7 (2005)]. Together with a number of terrific collaborators, we used this approach to dissect what a ubiquitin signal looked like on several interesting proteins including cyclin B [Kirkpatrick, D.S., *et. al., Nat. Cell Biol.* **8**, 700-10 (2006)] and the EGF receptor [Huang, F., *et al., Mol. Cell* **21**, 737-748 (2006)]. Mass spectrometry provided a window into the complex ubiquitin branching patterns that occur within biological samples. This approach allowed us and others to interrogate how ubiquitin signals become assembled, what enzymes take them apart, and how they control cellular functions [Phu, L., *et al., Mol. Cell. Proteomics* **10**, M110.003756 (2011); Cunningham, C.N., *et al., Nat. Cell Biol.* **17**, 160-9 (2015); Newton, K., *et al., Cell* **134**, 668-78 (2008)].

Did you have an early interest in science?

No, actually. While I was a biochemistry major as an undergraduate, I was reticent about the laboratory. That changed after getting the opportunity to attend the Society of Toxicology conference. That first summer in the lab with Julio Davila and Peter Smith really propelled my career. It was there that I came to appreciate how experiments could directly impact the development of a medicine. The questions being asked—even those down in the details of the biology—had a direct connection to whether the molecules under development were going to work.

The MPL department at Genentech that includes the Discovery Proteomics team led by Kirkpatrick

> *Starting from the early days of my career, mentors have played a crucial role in shaping my path.*

Can you tell us a bit about your background?

I grew up in Northridge, California, just outside of Los Angeles. Soon after the Northridge earthquake in 1994, I got a letter indicating that I had been awarded a scholarship to attend the University of Oklahoma as part of their National Scholars Program. Oklahoma was a big change, and in almost every way it was terrific. During that time I met people coming from places different than where I had grown up. Many of my close friends originate from that time of my life, and OU certainly had an important influence on my development, both personally and professionally. As I moved on to Tucson for my Ph.D., and later to Boston for a postdoc, I tried to immerse myself in each of those communities as well.

What are you working on now?

One of the long term goals within our field was to try and identify the full repertoire of proteins within cells and understand how they respond to perturbations in their environment. The emergence of multiplexing gives us an opportunity to do just that – to watch how the entire proteome changes as a function of time after a gene is knocked out, or when the cell is treated with a drug or noxious agent [Samie, M., *et al., Nat. Immunol*. **19**, 246-254 (2018)]. We are now routinely using isobaric multiplexing to watch thousands of proteins change as a function of time, treatment, genotype, etc.

What do you think about working in drug development?

At Genentech, we are passionate about understanding the biology that lies beneath devastating diseases. To do that well, you have to care deeply about science and be invested in research. Genentech encourages us to follow our nose, to chase the important questions and to look for breakthroughs that will really allow us to understand basic biology before setting off to develop cutting edge therapeutics.

For a long time, it has been appreciated that many proteins inside cells could potentially make good drug targets. But many of these same intracellular proteins were deemed "undruggable": that is, they don't have a good pocket that could be targeted to inhibit their function. So, how do you drug the undruggable target? An emerging approach is to destroy those proteins in an inducible way – to effectively carve that one protein selectively out of the proteome [Scudellari, M., *Nature* **567**, 298-300 (2019)]. The exciting thing is that many of these approaches involve manipulating ubiquitin, its related machinery and its functionality within cells.

What do you enjoy doing when not in the lab?

There's actually too many things for the time! I love the outdoors: camping and fishing and spending time in the Sierra Nevada mountain range. Mammoth Lakes is one of my very favorite places in the world. I love sports, and, to this day, I enjoy getting together with a group of college friends each year to see our favorite team play. But, right now, the most important thing to me is that my wife and I have four happy children. There is just so much going on in our house, and this is where the majority of my free time goes: I coach t-ball, enjoy watching my sons play soccer and my daughter play tennis. It is a full time job just trying to live in the moment and appreciate all the little things in life.