People & Ideas

Laurie Glimcher: Merging cell biology and immune function

Glimcher pursues a cross-disciplinary understanding of how cell biology affects the immune system.

Trained in research by some of the giants of immunology, Laurie Glimcher is herself a major force in that field. Most of her career has focused on understanding how different subsets of immune cells develop and are regulated (1). However, Glimcher is known in cell biology circles for her discovery of XBP-1 (2), a transcription factor that turned out to be important in lipogenesis (3) and in the ER stress or unfolded protein response (UPR).

Determined to follow an interesting lead wherever it will take her, Glimcher devotes part of her time toward understanding the interplay of ER stress with immune function and neurodegeneration (4, 5). Meanwhile, she continues to explore the regulation of immune function, while also making waves in the field of osteobiology (6). We spoke with her about how she's driven her career across professional and disciplinary boundaries.

QUEST FOR KNOWLEDGE

As an MD, what made you want to pursue research on top of being a doctor?

It was the quest for knowledge, and the questions that went with it that drew me in. I became fascinated by immunology when I was a first-year medical student at Harvard. I was curious about how the immune system is regulated and why it is dysregulated in autoimmune diseases—when the cells of your immune system start attacking your own body. In my fourth year of medical school I spent basically all of my elective time—about nine months—in Harvey Cantor's lab. While I was there, we identified a protein that would later become known as Nk1.1, which ended up being pretty valuable in immunology circles, and for which I received the Soma Weiss Award. That was particularly meaningful to me because my father, who had done his own medical training and spent all of his career at Harvard, had won that award 26 years earlier, and because I was the first woman to win it. I guess you could call that a turning point for me.

> "What always fascinated me was figuring out why the patients had the disease."

You didn't abandon medicine for research right away, though?

No. I finished one year of internship and one year of residency because my husband, whom I met at medical school, was doing three years of residency at Harvard. By the time I was in my second year of residency, I was already casting around for research projects to do. It wasn't that I was bored, it was just that being a physician was not for me an intellectually creative endeavor. What always fascinated me was not so much treating patients with disease, but figuring out why they had the disease. That was really what I cared about. So, I sought and received a position at the NIH, where I continued my research in immunology with Bill Paul.

The three years I spent at NIH were wonderful. The atmosphere was so vibrant and the immunology field was really bustling. I got great training from Bill, who was a wonderful mentor to me, and who encouraged me to pursue research on my own afterwards. I wrote and was awarded my own RO1 grant before my husband and I returned to Harvard so we could both finish our medical training. I'd had four and a half years of postdoc—call it what you will—before I started my own lab back at Harvard.

Laurie Glimcher

JUGGLING ACT

You were starting up your own lab and doing your residency simultaneously?

You know, it was tough. I had my grant, and momentum from the work I'd started with Bill Paul. I had a hood and a small bench, but I didn't really have any mentorship or anything. There was nobody to provide me with intellectual, emotional, or financial support. Certainly for that first year and a half when I was simultaneously trying to do my research and be a rheumatology fellow, there were very few immunologists at MGH (Massachusetts General Hospital) that I could speak to, so I was really flying by the seat of my pants.

I've tried hard to not have that happen to the people I train. I want to make their transition from postdoc to faculty a much more mentored and supported road. I was able to do it on my own, but it was hard. I was trying to juggle residency and research and, by that time, two children! My husband was a surgery resident, and they are kept fantastically busy, so for a while we almost never saw each other.

How did you manage the competing demands of family and work?

I think I did it by becoming very well organized. I'm not smarter than anybody else;

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I'm just exceptionally efficient. If I wrote out a list of things that I had to do, they would all get done that day. The other thing I learned to do was to prioritize. I had to give up the idea of being a perfectionist with anything but the data. When writing reviews or grants or whatever, once you get it to a good stage, you have to call it done and let it go. You have to be willing to compromise on those things, and also about things being perfect at home. Does anybody care if the sheets are folded exactly right?

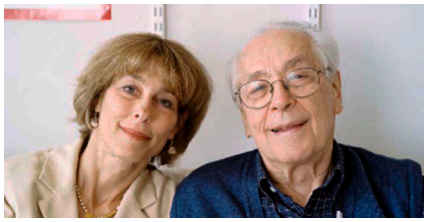
But I don't think you should ever have to choose between having kids and having a career. I always wanted to have kids, so I was going to make it work, and I am so glad I did, though I'd never have been able to manage it if my parents hadn't been around to help. Many people, women especially, struggle with this. I don't think it's fair, so I do whatever I can to support them. In my lab I make sure they have the support of a technician so they can get the most out of their training while still having a family, if they should so choose.

TAKE ALL ROADS

Do you have any other advice for young scientists?

Be a risk taker and don't be afraid to try new things. I have gone from one area of research to the next over the last 25 years, driven by the discoveries we've made, and with every shift I've had to learn a new field. You have to be willing to ask the experts for their help. Do lots of reading. Go to meetings. Make the leap.

For example, since the late 1980s my lab has been studying this transcription factor, XBP-1. We cloned XBP-1 because we'd been studying the regulation of MHC class II, a protein family central to immune surveillance. We'd identified a region, called the X-box, in the gene sequence of one MHC class II family member, which when mutated disrupted gene transcription. I remember I was in the hospital after having my third child when my graduate student brought me the film of a Southwestern blot she'd done to pull out a protein that bound the X-box sequence. That protein turned out to be XBP-1, so we went ahead and made XBP-1 knockout mice, fully expecting that they would have impaired MHC class II production. But lo and behold, when we finally got a mouse, the gene had nothing to do with MHC class II. We found it was involved in lipogenesis, and other groups later showed it to be a linchpin of the unfolded protein, or ER stress response—if you delete XBP-1, you activate the ER stress response. In fact, XBP-1 and ER stress turned out to regulate a completely different branch of the immune system: the differentiation of plasma cells, which are the cells that make protective antibodies.



Glimcher and her father collaborated on recent research.

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This work has spurred other kinds of questions, like whether XBP-1 functions in autoimmune diseases. When we deleted XBP-1 from gut epithelial cells, we found that it activated a pro-inflammatory response in the cells.

Over time, XBP-1 has led us in lots of different directions, so my students and I have had to get acquainted with these new fields. I've never felt myself to be an expert in any of them, even in immunology. I think some may accuse me of being a dilettante. But I wouldn't do anything differently because it's so much fun. You have the opportunity to make really new discoveries that are important in a new field. I love that. I don't want to just refine and extend what I've already been doing. The most exciting thing to me is to come up with a new idea, no matter what field it's in, and have it actually prove to be true.

What new directions are you headed in now?

My research interests are becoming increasingly cross-disciplinary. It can be really liberating to enter a new area, because you come into it without any prejudices, and you're able to take a fresh perspective. We're looking now at how the systems we've been studying in my lab all this time interrelate. For example, how does the immune system and the ER stress system in neurons impact neurodegenerative diseases? Recently I've also gotten interested in skeletal biology, which in some ways is simpler than immunobiology since there are fewer cell types to worry about. Now probably half my lab is working in osteobiology. This work was instigated by our discovery of an adapter protein called Schnurri-3 that controls adult bone mass, coauthored with my father, a bona fide skeletal biologist. But who knows where we'll go in the future?

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