People & Ideas

Valerie Weaver: Overcoming cancer's stiff resistance

Weaver investigates the mechanical properties of tumors and how changes in the tumor microenvironment influence cancer cell behavior.

PHOTO COURTESY OF LANE JOHNSON

Valerie Weaver

Each year in the United States alone, more than 200,000 cases of breast cancer are diagnosed. Most women find their tumors on their own, by feeling a lump in their breast. Tumors can be detected in this way because they are stiffer than normal tissue, explains Valerie Weaver, Director of UCSF's Center for Bioengineering and Tissue Regeneration. This stiffness is both a consequence and a cause of cancerous processes in solid tumors.

Weaver's work on cancer cells' interactions with the tumor microenvironment had its origins in her postdoctoral work with Mina Bissell at UC Berkeley, where she studied how integrin signaling affects the phenotypes of tumor cells (1, 2). Now, she is at the forefront of a burgeoning new field, mechanotransduction, which seeks a better understanding of how cells sense and respond to physical forces (3–5). When discussing her career, she says it hasn't always been easy getting to that position, but, even with all the challenges she's faced, it's been worth it.

RIGHT CHOICE

When did you decide on a career in science?

I come from a working-class background. Growing up, none of my friends were university bound. I think it was expected that I should learn how to type and get some kind of job with a nice pension, then get married and have a family. But I think I always knew I wanted something different for myself. I was a huge reader—I love books—and maybe that was why I decided to go to university. But I don't think I seriously considered a science career until well after that.

After college, I was working at Chalk River Nuclear Labs, and my supervisor there really encouraged me to try to go farther. She could see my potential even though I couldn't. So I went to graduate school at the University of Ottawa and started a postdoc at the Canadian Research Council. My horizons just opened up—there were so many possibilities. But I still didn't really know if I could or should pursue a research career.

Then I saw Mina Bissell give a presentation at the Canadian Federation of Biological Sciences meeting in Windsor. I somehow worked up the guts to run up to her at the end of the meeting and say, "Oh, I'd love to do a postdoc with you." To my surprise, she said, "Well, contact me."

So off you went to your postdoc?

Actually, no, not right away. I'd had a rough time during graduate school—my father died from a brain tumor, and I was in a really horrific car accident. And I wondered: do I have what it takes? Can I really do this? I needed time to think it through, so I just… took off.

I never told Mina my plans. I used the settlement money from my car accident and bought a plane ticket to Africa. I spent six months traveling around, ending up in India. It was an amazing experience, but, along the way, I had this revelation: I realized that I was really lucky that I had the opportunity to get an education and do reasonably well for myself in life. I had a certain capacity for doing research, and I had a passion for doing it.

> "I celebrate science and what it offers."

I ended up phoning Mina from a phone booth in Kathmandu and telling her that I wanted to come start my postdoc with her. It was a great choice: Mina is another person who really believed in me. Her belief gave me the power to think bigger and to expand my vision, to see where I needed to go.

RIGHT REASONS

And you never looked back?

I've met several students who seem confused about why they are pursuing a research career. They have all these external expectations put on them, and they put so much stock in whether they get a particular award or grade, as opposed to whether this is what they really want to do. I didn't have any expectations placed on me, so it was easier for me to decide that I was doing it for the right reasons.

As I tell my students, science is a tough job, but it's important to realize that nobody owes us this. We're lucky to do this! It's challenging and fun and interesting… I celebrate science and what it offers; hopefully that'll help draw people in for the right reasons.

What interests did you pursue in your postdoc?

Mina had recently published some papers with Nancy Boudreau where they showed that normal breast epithelial cells in 3D culture apoptose when they lose cell adhesion, but tumor cells are resistant to this kind of death. I wanted to look at how that pathway is altered in tumors and how tumors become resistant to apoptosis. So, after consulting Mina, I contacted Ole Petersen's group in Copenhagen, which had a bunch of human cell lines at different stages of tumor progression, and started trying to find out at what point during tumorigenesis they could no longer be killed by blocking cell adhesion.

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The really early lines died like crazy when you blocked β1 integrin, and, as the disease progressed, they died less, as expected. But when I got to fully progressed tumors, I remember looking at the cultures and thinking, "Okay, I must have mixed these up because they look just like normal cells." What was happening was that, by blocking β1 integrin, we were sending the tumor cells into phenotypic reversion; they were no longer invasive. This showed that signals from the environment are important for driving tumor cells' behavior.

RIGHT ENVIRONMENT

That's the subject you've chosen to pursue in your own lab?

I was hired at UPenn as part of what was going to be a big interdisciplinary cancer research group. But shortly after I got there the University had a funding crisis and stopped hiring. It ended up that I was the only cancer researcher in what was really an engineering and physics group. I couldn't get graduate students to come over because they were terrified by all the physics and engineering, and the lab was way on the other side of campus from the biological sciences labs. So I hired a technician, Nastaran Zahir, and trained her in lab work, hoping that she might stay to do grad school—and she did.

I was trying to think of a project for Nas that was relevant to my interests and to engineering. To make a long story short, I started wondering about things like viscoelasticity and whether that might impact tumor behavior in a 3D environment. We started thinking about when the mammary acinus expands during development or during tumor progression. Could there be some kind of physical force that's altered, and could we model it?

But I couldn't get any money for these studies. No one would take a chance on a grant for this; it just sounded too crazy. We ended up going around, collecting other peoples' extra mice—mice with myc- or ras-based tumors or whatever—to see if we could make force measurements on them. And what we found was that breast tumors are stiffer than normal tissue. We've been expanding on that ever since.

> "Signals from the environment are important for driving tumor cells' behavior."

How does stiffness in the tumor environment impact cancer cells' behavior?

Think of it this way. Mammals start off as one little egg, which is very soft and is not under tension. As an animal develops different tissue types, these different tissues have different properties of stiffness or softness, and the cells in them tune themselves to the stiffness of the extracellular matrix in their environment. They do this, in part, through ion channel activation but also through clustering of integrins. This changes the activation of Rho GTPases, which in turn alters actomyosin contractility and actin behavior. That then feeds back and changes how receptors function (by affecting their clustering or localization), which then drives reorientation of matrix bundles and more deposition, stiffening the local environment. You can therefore drive different configurations of cell surface receptors—literally reprogram the cell—simply by changing the stiffness of the cell's environment.

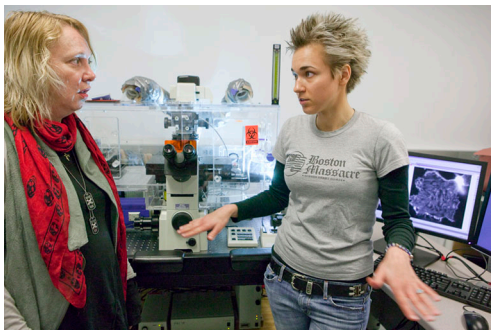

PHOTO COURTESY OF JANE JOHNSON

Weaver and graduate student Yekaterina Miroshnikova discuss new data.

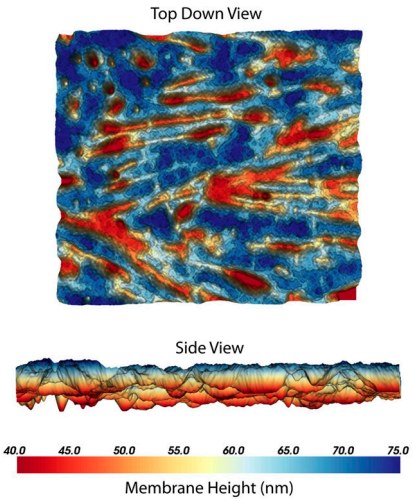

IMAGE COURTESY OF MATT PASZEK AND VALERIE WEAVER

A 3D reconstruction showing how membrane surface topology changes in cancerous cells.

When you talk about a breast tumor, or other tumors we work on like pancreatic or brain tumors, they don't have to stiffen very much to become a tumor. Tumor cells are hypersensitive to stiffness changes because many oncogenes change the cell's actomyosin contractility. We're also finding that oncogenes change things like the glycocalyx and cell surface glycoproteins, which can also affect the cell's mechanical characteristics. We can actually use atomic force microscopy and fluorescence image contrast (FLIC) microscopy to measure some of these changes.

I'm excited about how things are turning out. I love where our work is going, and I think people are finally starting to pick up on how interesting this stuff is. Of course, we have a long way to go. But I have a nice group and I feel extremely privileged to be part of this.

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