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People & Ideas

Mina Bissell: Context is everything

Bissell remains as passionate about science as ever.

Mina Bissell has never been afraid to challenge conventional wisdom, whether on a woman's role in the laboratory or on how a cell's context determines its function.

Bissell came to the US from Iran to study chemistry at Bryn Mawr and Radcliffe Colleges, before pursuing a PhD in bacteriology at Harvard Medical School. She moved to California for her postdoc in virology, before joining the Lawrence Berkeley National Laboratory in 1972, where she has remained ever since and was the Director of all Life Sciences until 2002.

Bissell investigates how the microenvironment—particularly the extracellular matrix (ECM)—influences cellular behavior. She proposed a "dynamic reciprocity" in signals between the ECM and the cell nucleus (1) and, to prove her model, she began to study mammary gland biology, devising 3D culture techniques that continue to reveal how differentiation is regulated by ECM proteins (2, 3). These cultures can readily distinguish between normal and malignant cells (4), and Bissell has shown how breast cancer cells can be reverted to nonmalignancy by correcting signaling through the ECM (5). Moreover, Bissell and collaborators have shown that destroying the ECM with metalloproteinases is sufficient to cause tumors (6, 7).

In a recent interview, Bissell helped put her own life and career into context.

GROWING UP IN IRAN

Where did your passion for science come from?

I was always very curious. I grew up in an intellectual and highly educated family, and my parents—especially my mother—were extremely ambitious for us. I read voraciously as a kid, and was the top student in the country at the end of high school. But science wasn't a passion that I grew up with or anybody encouraged me to do; it just happened.

Both of my mother's sisters were in the medical profession, and I had a brilliant uncle who was a professor at the medical school and another who was a math professor in the US. My father's family was religious aristocracy: my grandfather was an Ayatollah. And his father, grandfather, and so on were all Ayatollahs too.

My grandfather was a wonderful, scholarly man—I never saw him without a book. He had a magnificent library, and he wore beautiful long white robes and was totally in love with my grandmother all his life. He was also the most benevolent man I ever met. My father had no intention of becoming an Ayatollah; he called himself an atheist. But he and my grandfather were the best of friends. It was a very different attitude—and version—of Islam than people now associate with Iran and the current regime.

> "The idea that I would have a child and continue hadn't even occurred to my professors."

Do you ever return to Iran?

I haven't gone back since the Shah fell because I'm very outspoken and wouldn't tolerate it if someone said, "Put that thing on your head." Not once did I have to wear even a scarf, despite the fact I had an Ayatollah for a grandfather.

The curious thing is that even now, 54% of those studying engineering, medicine, and architecture at universities across Iran are women. And 52% of Tehran University faculty are women. Who hears about this? All you hear is Ahmadinejad!

CHALLENGING EXPECTATIONS

How did you end up in the US?

My father wanted me to go to England—he felt that America was too young a nation and couldn't train women well. But my grandfather said, "If she wants to go to the US, then she goes to the US." And I did!

I had my daughter in the first year of graduate school. It was difficult, no question about it, but the idea that I would have a child and continue hadn't even occurred to my professors—back then there were only three women students at Harvard Medical School and just one woman faculty. My mom, however, called and said, "You're not quitting, are you? Don't worry, we'll support you." I hadn't even thought once about giving up!

Mina Bissell

You enjoy challenging conventional wisdom in science. Has that always been the case?

As a child, I was encouraged to speak up. After four years of graduate school, I discovered that the whole basis of my project was wrong. When I told my professor, he replied "You won't make it as a scientist!" I went home and cried, but from then on I knew that I'd stay in science. He became a believer and a friend as soon as I showed him more proof.

I moved to California with my husband and after two years of postdoctoral work, I got a job in the empire of Melvin Calvin at UC Berkeley. He was a real dictator—I was being fired every week because I showed up pregnant with my second child. His associates always had to calm him down. One day I looked him in the eye and said, "I disagree with you sometimes, but not because I'm being difficult. You know so much more than I do, but I just know a bit more about biology, so why be so angry all the time?" He was totally surprised—nobody had ever said anything like that to him before—and we not only ended up being close colleagues, he also became one of my champions.

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How can the funding system help people develop unconventional ideas?
I always say, "If you have an original idea or you're really making a huge jump, you should expect not to get funded. If you do, it means people already largely understand it." But there has to be room for people to do long-term challenging work.

NIH is becoming more adventurous now, but I couldn't get NIH money for 15 years; thankfully I get funded now. NSF gave me my first grant, and without the DOE Office of Biological and Environmental Research, who decided early on I had something important to say, I would have had to give up some of my radical ideas. One needs alternative sources of funds: the breast cancer program in the Department of Defense has been creative and refreshing despite some initial criticism.

But finding these alternatives is becoming harder and harder because doing something novel in biology these days is so darn complex: You need lots of money and collaborations. One person with a microscope can rarely make a huge discovery now.

> "If people aren't passionate and a little nutty about science, they shouldn't continue."

How does that affect universities?
They need drastic reforms too. Decisions on tenure should assess the total impact of your work, and not whether you were the only one who intellectually contributed to it—you can't insist that people do it alone. Additionally, I think professors shouldn't keep their tenure after 65. Younger people need these jobs and we need to share resources. If you're still really passionate and capable of getting money after 65, then you should be given laboratory space and allowed to continue but, if not, you should work with and help younger group leaders instead.

So it's important for younger scientists to come through?
Yes, but we're all told in graduate school that everybody has to be a professor or they're a failure, which is nonsense. A few years ago there was a movement to limit the number of PhDs, but I think that was wrong. People who want to be educated should be, and then they can decide what to do with that education.

If people aren't passionate and a little nutty about science, they shouldn't continue with research. I agree with Bruce Alberts that PhDs can, and should, contribute to society and to science in many different ways.

UNDERSTANDING COMPLEXITY

You're involved with a new journal:* Integrative Biology. *What's the concept behind it?
I've always been enamored with technologies that push biology forward, and I've always known that we wouldn't understand complex biological questions without bringing different fields together. I was asked by the Royal Society of Chemistry to chair the journal's editorial board and I said, "Fine, but only if we insist on novel technologies that really answer important biological problems."

One of my current fellows developed a microenvironmental array to study the fate of breast progenitor cells. The reviewers lost sight of the importance of the technology and kept saying, "Why didn't you work in a mouse? You should make a mouse." So we put this beautiful paper in the first issue of *iBiology*. You can't answer every question in a mouse, especially when you want to work with human cells! Nature is so clever, if you knock a gene out, something different happens. It's not just redundancy—the complexity makes it very difficult for us to know what's going on. So you need a combination of model systems. This is why I appreciated early on that we needed to develop physiological assays.

Why are 3D approaches so important?
Studies with 3T3 and HeLa cells were useful in discovering new genes and processes. But you can't understand tissue specificity in 2D cultures, and you can't always do it in the mouse. 3D cultures are not always physiological either. To work outside the animal, you have to create a situation where the context tells the cell that it's a particular tissue and not something else. I always quote Gloria Heppner [from Wayne State University in Detroit]: "Don't ask what a cell *can* do, ask what it *does* do!"

We recently showed in 3D cultures that an ECM protein, laminin-111, must continuously signal to the chromatin for a mammary cell to express milk proteins. It would be really difficult to study this in vivo—you can't follow the kinetics. So we go back and forth between the mouse and physiological 3D cultures.

Finally, imaging is extremely important. Differentiation is dynamic and reciprocal; without imaging cells in 3D culture and in vivo, you won't learn what allows a mammary cell to be a mammary cell. I always say that there's no reason for arrogance because we still know so little. We've discovered a lot, but there's still so much to learn; and it's so much fun!

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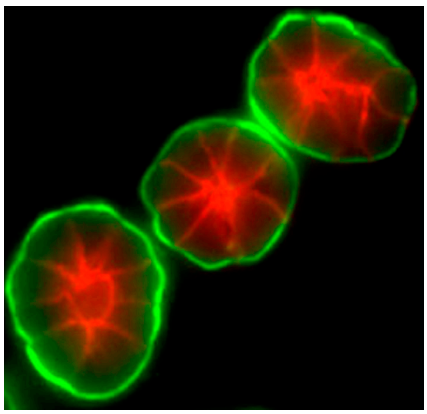

Breast cells cultured in 3D reproduce the structural units—acini—of human breast.