People & Ideas

Elaine Fuchs: A love for science that's more than skin deep

Fuchs is too passionate about her work to rest on her recently awarded laurels.

Elaine Fuchs has collected many awards in her 30 years researching mammalian skin development, but it's hard to beat the two prizes she received in late 2009. Shortly before winning the prestigious L'Oreál-UNESCO award for women in science, Fuchs was awarded the National Medal of Science—the US's highest honor for outstanding scientific contributions.

After studying bacterial sporulation as a PhD student with Charles Gilvarg at Princeton, Fuchs joined Howard Green's laboratory at MIT, where she investigated the expression of keratins in differentiating skin cells (1, 2). Fuchs then returned to her native Illinois to begin her own laboratory at the University of Chicago, and stayed for more than 20 years before moving to The Rockefeller University in New York in 2002. Fuchs' research has touched on many aspects of skin differentiation and function. Asked to pick her favorite work, she chooses her pioneering use of mouse genetics to identify mutant keratins as the cause of several human skin diseases (3, 4). She also mentions the generation of super furry mice by expressing a stabilized version of the transcription factor β-catenin (5) as well as the identification and characterization of a multipotent stem cell population in the hair follicle (6, 7). In a recent interview, Fuchs discussed her latest awards, and explained why the skin continues to hold her interest.

ASKING & ANSWERING QUESTIONS

Is it true that you refused to take the exam for graduate school entry?

Yes! [laughs] I was graduating near the top of my class from a very good university and I felt that the Graduate Record Examination wasn't testing my real knowledge, but rather how I could perform in a written exam. So I decided that perhaps they'd appreciate some creative writing instead. I wrote three pages explaining the reasons why I was not going to be taking my GRE, and I sent it along with my applications.

I got accepted everywhere, but it's quite unlikely that I would be admitted to any graduate program in the US today. I don't think professors are as open-minded toward rebellious students as they were during the Vietnam War era.

How did you decide to go to Howard Green's laboratory for your postdoc?

I had been working on bacterial sporulation and, in the course of that, I studied bacterial cell walls. Many antibiotics target the enzymes that synthesize cell walls, and that medical aspect was what I really liked about my science.

To maintain my interest in biomedical research, I decided to switch to the growth and differentiation of human cells, but I knew I was going to need a good culture system. Howard was a cell culture guru—he developed the use of human epidermal cells as well as the 3T3L1 line for adipocyte differentiation. Almost everyone else was using transformed mammalian cells at the time and I thought these were great systems to study—I still do.

And you've worked on skin ever since—what has captivated you for so long?

Skin is such a complex organ. We focus on the epithelium, but epithelial–mesenchymal interactions are very important in dictating whether keratinocyte stem cells will stratify to make an epidermis or differentiate into a sebaceous gland or hair follicle. How does that happen? How do you start with a stem cell and build a tissue? There are lots of facets to the problem, ranging from transcription to cell–cell and cell–substratum interactions. There's this endless array of signals from the environment that, in a sense, encompasses almost every aspect of biology.

So even though we still work on skin as a model system, we continue to ask different questions. We spent 10 years working on keratins, but if I'd stuck with that, I might have burned myself out. I learned early on in my career that it's important to choose a problem you're interested in, even if you don't yet know the technology you need to address it. I think people get into ruts when they become very good at something and do it over and over again. What we're doing now is very different to what we were doing several years ago, and we continue to try novel and original approaches.

Elaine Fuchs

PROGRESS ON MANY FRONTS

One of those original approaches was using transgenic mice to link keratins with human genetic diseases…

After cloning and sequencing the first keratins, we'd begun to hone in on the key residues that were critical for the assembly of keratin intermediate filaments, but we couldn't predict the disease we should be looking at from the disrupted keratin networks we saw in our cultured skin cells. We thought that engineering mice harboring our dominant-negative keratin gene might offer us better clues. We set up transgenic mouse technology, but when we got our mice expressing mutant keratin, they showed no phenotype at all. I thought, "We just wasted all this time learning this technology, and we're getting nowhere."

Then one day a technician said, "There's this dead mouse that's half eaten, and it looks like it's got a severe problem with its skin." We took a look and it was expressing whopping amounts of our transgene. We realized that the mom was eating every single phenotypic mutant while leaving behind all the nonphenotypic ones. I gave [laboratory members] Bob Vassar and Pierre Coulombe my office for the night, and they babysat until the moms delivered. After their preliminary analysis, we sat down with a dermatology textbook and it was pretty clear: the pathology matched

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perfectly with epidermolysis bullosa simplex, a blistering skin disorder in humans.

But not everyone believed you at first?
No. I don't blame people because diagnosing mice as having a particular human disease was unconventional at the time. I presented the work at a large meeting, and the chair took the microphone and said, "I don't know what you've got, but you certainly don't have EBS." It took a few moments for me to react—it was looking pretty bad. The audience listened to the chair, who continued to declare confidently that our findings were rubbish.

But at that point Mina Bissell stood up and said, "I don't know whether she's going to be right or wrong, but I just heard an interesting story, and I think we should give her the chance to find out." This broke the ice for UPenn's chair of dermatology, John Stanley, to stand up and say, "Actually, I would also diagnose the pathology as EBS." Eight months later, we published a paper documenting the human genetic basis of EBS, so it didn't take long to prove our hypothesis.

You were one of very few female group leaders when you began in Chicago. How was that?
A technician from another laboratory came down as I was setting up my laboratory, and said, "Are you Dr. Fuchs' new technician?" and I had to say, "I *am* Dr. Fuchs!" There were cases where I'd be introduced to the seminar speaker as the prettiest member of the department—things that would make me cringe. I didn't know what to make of these comments, and I'm not sure the men knew what to make of having me there.

I didn't care what my salary was—it was more than I'd got as a postdoc— until after I was a tenured faculty member, when I discovered that my salary was actually lower than what they were offering to starting assistant professors. It was only after I realized I'd been underpaid all those years that I got angry. So there were definitely gender issues that could've distracted me, but I was so thrilled to be able to do my science that nothing else seemed to matter so much.

You've been a strong advocate for women in science, which was recognized by your L'Oreál-UNESCO award. Do any significant challenges remain?
Things are enormously better, particularly in the US. In general, the door is open for women all the way up to being an associate professor but it's still difficult at the upper end of the scale—there are very few women in leadership positions. And there are still women at some universities who feel they are underpaid, have less space, and receive fewer privileges than their male colleagues. Most major universities have gotten the message, but I'm not sure all the smaller universities have followed suit.

> "There's this endless array of signals from the environment that encompasses almost every aspect of biology."

HOPE AND CHANGE

The other prize you won recently was the National Medal of Science. How was your trip to the White House?
Having the President of the United States shake my hand and place a medal around my neck was a moving experience. It was also nice to have not only my husband, but also my mother (who's close to 88 years old now), my sister, and eldest nephew present. It was particularly thrilling for me because President Obama recognizes the importance of basic research and science education to the future of our country.

Could scientists do a better job of communicating the importance of their work?
Yes—we need to educate politicians about the importance of basic research and increasing the budget for it. [Former congressman] John Porter, at a recent Howard Hughes meeting, asked us all, "When was the last time you contacted a politician and invited them to your laboratory? They need to see what scientists are doing." If politicians don't understand what we can learn from basic research and appreciate its importance, why should they support it?

How do you maintain your enthusiasm?
A professor's role is a combination of research and education. I empathize with the pain students feel as they initially struggle with scientific research, yet there's nothing more gratifying than watching a student's first experiment work. You see them think, "Well, it's really worth it after all. I *can* do it." As long as I'm passionate about the scientific questions we tackle, I don't think I'll ever get tired of being a professor. It's the best possible job in the world.

What can we expect next from the Fuchs laboratory?
New approaches, of course! We've identified lots of new genes that change their expression patterns as stem cells make epidermis and hair follicles. But we can't use classical genetics to figure out what all these changes mean—a conditional knockout mouse takes a couple of years to make, and there's a lot of redundancy in the genome. We're developing new strategies to make functional analyses of mouse skin development a more tractable process. There are many signaling pathways that must converge to build and maintain tissues during normal development and wound repair, and a lot of pathways go awry to generate the myriad of human skin disorders, including cancers. We know a little bit here and there, yet we still have a lot of pieces to fill in. But I love the puzzle!

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Fuchs receives the National Medal of Science from President Obama.