



A KALEIDOSCOPIIC VIEW

Elaine Fuchs brings an eye for the creative to the many-colored facets of her life and work.

by ROBIN MARANTZ HENIG | *photography by* PETER ROSS

WALKING THROUGH THE MUSEUM OF MODERN ART

arm-in-arm, Elaine Fuchs and her husband, David Hansen, look like any other New York couple: slim, elegant, dressed in black. But listen in on their conversation as they pause before a Picasso, as I was able to do one afternoon last winter, and you can hear something more: two fiercely intellectual people who look for inspiration for their creative work in almost everything they do, including museum-going.

This trait might be one reason that Fuchs, head of the Laboratory of Mammalian Cell Biology and Development at Rockefeller University in New York, has managed, in her nearly 30-year career, to pioneer new ways of studying skin and hair and to manipulate stem cell differentiation so deftly that she was able to turn a skin stem cell into a cloned adult mouse.

“I look immediately at the central figure,” Fuchs says to her husband as they gaze at Picasso’s *Three Women at the Spring*, “and I follow her hair.” Eventually, she tells him, she follows the folds of the woman’s robe and the stream of water she directs into a brown pitcher. “I get a sense of the river here, with the river as a part of the flow of life.” And over on the left side of the canvas, she says, “the exposed features of the women are tantalizing, in a way that suggests fertility.” Much of what

Fuchs sees in the paintings that inspire her carries back to biology.

Hansen, a professor of philosophy and education at Columbia University’s Teachers College, has a different interpretation, focusing instead on geometry, on the flatness of Picasso’s figures.

Trailing the couple on this museum outing is a film crew making a documentary on women in science. The crew is supported by L’Oréal, the French cosmetics company that partners with the UNESCO Foundation to fund the prestigious L’Oréal-UNESCO Awards in the Life Sciences, given every other year to five outstanding women scientists, one from each continent. Vignettes from this documentary will be presented at a ceremony in Paris in early March, celebrating Fuchs and the four other 2010 award recipients. It is the latest in a string of accolades for Fuchs, an HHMI investigator since 1988. She also received the National Medal of Science from President Barack Obama in a 2009 White House ceremony.

Fuchs’s stem cell work is among the discoveries that led to these honors. In the late 1990s, she and her students and post-docs generated mice with thick fur coats, suggesting that they might have stumbled on a clue about how hair follicle stem cells work. Several years later, her team

devised a method to test the hypothesis. They attached green fluorescent markers to infrequently dividing cells from adult mouse tissue, which they thought might be stem cells, and then purified, cultured, and grafted the cells onto hairless mice. When the mice grew green fluorescent hair and skin, the scientists knew the tagged cells were in fact stem cells.

With her colleague Peter Mombaerts, Fuchs later cloned healthy mice from these stem cells using a technique known as nuclear transfer. They removed the nucleus of a mouse oocyte and replaced it with the nucleus of a hair follicle stem cell. They then grew the hybrid cell *in vitro* to the blastocyst stage and implanted those cells into the uterus of a mouse. While only a few percent of the clones survived to become healthy mice, the experiment demonstrated that skin stem cells can be successfully reprogrammed to a pluripotent state with the capacity to generate all 220 different cell types in the body.

The reports of these experiments—published in 2007 in *Cell*, *Science*, and the *Proceedings of the National Academy of Sciences*—led to a flurry of media attention. Such attention, however, is not really what Fuchs is interested in. To her, the real questions about stem cells are much more basic than creating hair or cloned animals.

“What I really want to know is why embryonic stem cells can choose any tissue pathway, while adult stem cells are much more restricted in their options,” she says. Yes, she has shown that skin stem cells can be reprogrammed to generate a whole mouse. But more important is what happens in nature, when skin stem cells turn into skin, hair, or sebaceous glands, but never—without laboratory manipulation—a neuron or a kidney cell.

SEEING OPPORTUNITY

This kind of lifelong questioning began, in a way, with a butterfly net in a field behind Fuchs’s childhood home in Illinois.

“Early on, my mother made a butterfly net for my sister and me,” recalls Fuchs. Her sister Jannon is four years older, and the two girls spent long after-



ELAINE FUCHS'S STUDIES OF SKIN AND HAIR CELLS MAY EVENTUALLY LEAD TO A CURE FOR BALDNESS, BUT SHE MANIPULATES STEM CELLS TO ADDRESS LARGER HEALTH QUESTIONS.

noons in the fields behind their house in Downers Grove. Soon they were catching butterflies, insects, pollywogs, and the occasional crayfish from a nearby swamp. “We had butterfly nets and strainers and old kitchen utensils, and we started to ask for science books for Christmas,” she says.

When she was about eight years old, Fuchs read about using thyroid hormone to accelerate metamorphosis in pollywogs. She pleaded with her father, a geochemist at Argonne National Laboratory, to get her some so she could try it for herself. “I had

no concept of nanomolar concentration,” she says with a smile. “I just wanted to speed things up. So I dumped the entire contents into the water—and killed all of my tadpoles. That was my first real science experiment”—pretty much a complete failure.

It was Jannon who seemed destined to be a scientist, she says; Jannon was “the smart one” and Elaine was “the fun one.” Elaine admired her big sister, but Jannon Fuchs remembers it from a slightly different vantage point. “If given the choice,” Jannon told me by phone from her home

in Denton, Texas, where she is a professor of neuroscience at the University of North Texas, “I would have preferred to be the social one!”

Fuchs’s father assumed Elaine would become a teacher—it was Jannon whom he urged to go into science—and so Elaine headed down that path. When she entered the University of Illinois in 1968, she enrolled in chemistry, physics, and mathematics classes, but she still didn’t think of herself as an especially good student—until she looked around her.

In her science classes, Fuchs was one of just three women of some 200 students. She knew that meant a particular kind of scrutiny.

“I remember being in the physics class thinking, ‘If I were to get an A, the professor would think I cheated. But if I get the best grade in the class, the professor couldn’t think I cheated, since I would be doing better than everyone else.’ Boy, that really motivated me.” She made straight As in college, often at the top of her class.

But Fuchs wasn’t a total grind. She joked around with the science geeks, hung out with the graduate students, and in one class asked the TA to teach her how to juggle tennis balls. She intended to join the Peace Corps after graduation—a plan that changed when she was assigned to work in Uganda, then under the bloody rule of Idi Amin. She chose graduate school at Princeton University instead.

At Princeton, in 1972, Fuchs again felt the sting of being a woman in a man’s world. Fuchs recalls her advisor, Charles Gilvarg, saying on more than one occasion that he didn’t think there was a place for women in science. Fuchs took his dismissive attitude as a challenge. She worked hard, often staying in the lab until 10 p.m., studying spore formation in bacteria as she sought to acquire the skills of a bench scientist. But she also played hard, beginning what would become a lifelong love affair with travel. Even on a paltry \$3,000 a year stipend, Fuchs managed to travel to India, Nepal, Guatemala, Mexico, Peru, Bolivia, Ecuador, Turkey, Greece, and Egypt during her five years at Princeton.

Eager to tackle human biological problems, Fuchs pursued a postdoc in the Massachusetts Institute of Technology (MIT) lab of Howard Green, a pioneer in culturing human cells—specifically, skin cells derived from newborn foreskins. “I learned cell culture from a master,” she says. “Howard really paid attention to the kind of detail that, even now, very few people have the capacity to do.” He recognized, for instance, that to grow human epidermal cells, you have to co-culture them with fibroblast cells from the dermis, located just beneath the epidermis, thus reproducing the “cross talk” between cell types that occurs in nature.

At MIT, Fuchs started wearing makeup and nice clothes, partly to annoy a female colleague who said women scientists should avoid looking too feminine. Today she still dresses carefully and elegantly, and her long blonde hair is always permed. With bright blue eyes, a long oval-shaped face, and a dazzling smile, she has skin so wrinkle-free that it makes you wonder whether studying skin cells is its own fountain of youth.

CREATING NEW DYNAMICS

In 1980, Fuchs became an assistant professor of biochemistry at the University of Chicago and once again found herself in a man’s world. As she was setting up equipment on the first day in her lab, the department chairman’s lab technician dropped by. “Are you Dr. Fuchs’s new lab technician?” he asked.

“Umm ... I *am* Dr. Fuchs,” she replied.

Things got better a few years later when a departmental reorganization brought a cohort of three strong female biologists together into the new Department of Molecular Genetics and Cell Biology: Fuchs; Janet Rowley, already a member of the National Academy of Sciences; and another assistant professor, Susan Lindquist, now a lifelong friend and fellow HHMI investigator. Fuchs and Lindquist designed and co-taught a course called Gene Expression in Cell Biology, which they continued until Lindquist left for MIT and the Whitehead Institute for Biomedical Research. And their friendship went beyond the classroom.

They were neighbors in Hyde Park, and their husbands were also good friends—in fact, Lindquist introduced Fuchs and Hansen—so the two couples got together often for dinner and conversation.

“Every New Year’s Eve we would go out together to a restaurant, and then to a dance party sponsored by the Chicago Symphony,” says Lindquist. Getting to know her professionally and socially, Lindquist says, showed her that Fuchs is “both a phenomenally good scientist and a phenomenally good human being.”

One of Fuchs’s goals when she got to Chicago was to make a cDNA library (a collection of DNA fragments used to help identify genes and the proteins they produce) of the major structural proteins she’d been characterizing at MIT. In those early days of recombinant DNA technology, such a goal was ambitious. Eventually, Fuchs and her colleagues not only determined the DNA sequences encoding these proteins but also defined the two basic subunits required for the most important structural protein, keratin,

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to self-assemble into filaments. And they discovered that the filaments, in turn, were essential for the skin's protective and hydrating functions, forming an elaborate cytoskeletal network that provides mechanical integrity to the cells at the skin surface.

By the mid-1980s, Fuchs moved on to investigate what happens when the genes involved in making keratin proteins are damaged. At the time, geneticists approached such a question using a technique known as positional cloning. An investigator would choose a disease of interest and then find a large family with affected members. Then the scientist would collect DNA samples from everyone in the family and study the differences in DNA sequences between the affected and the unaffected, hoping to find the relevant mutation.

"This strategy did not divulge how or why the defect in the protein caused the tissue abnormality, which was what I was interested in," Fuchs says. "So we started at the reverse end and worked our way back." This process involved a relatively new kind of laboratory model, developed in the early 1980s: the transgenic mouse. It was a backward approach, since the idea was first to create a mouse with a specific mutation of interest, then analyze the pathology of the tissue defects, and finally find a resemblance to a human genetic disorder.

Not many scientists were making transgenic mice in 1986. Fuchs contacted one of the few in the Midwest—Susan Ross at the University of Illinois—and asked about sending a graduate student, Robert Vassar, to train in the Ross lab.

With this training, Vassar created a transgenic mouse expressing a mutation in the *K14* gene, which is responsible for building a keratin network in the innermost layer of the epidermis. But the transgenic mouse with the *K14* mutation seemed to be normal in appearance, health, and behavior—in other words, the mutation showed no distinct phenotype. "We were very disappointed," Fuchs recalls. "We thought it was a complete failure, a good idea but bad luck."

After a few litters of *K14* mutants were born with no apparent defects, Fuchs's lab manager, Linda Degenstein, noticed a mother mouse eating a newborn pup with an apparent skin defect. Might Degenstein have stumbled on nature's way of taking care of deformed offspring—and also an explanation for why all the transgenic pups in the litter appeared normal? Clearly, they thought, close observation of the mice in the immediate hours after delivery was needed.

"We essentially had a stakeout all night long," recalls Vassar, now a professor of cell and molecular biology at Northwestern University in Chicago. "We would bring the mice into the lab, and then camp out the entire evening waiting for them to give birth." The stakeout revealed that some of the *K14* mutations were so severe that the very act of birthing stripped the epidermis off the newborn. The mouse pups were unlikely to survive in this way, so the mother was instinctively cutting her losses, eating the doomed mutants so she didn't have to waste energy caring for them. A less attentive team would have missed it altogether.

Vassar and a postdoc, Pierre Coulombe, now chairman of biochemistry and molecular biology at the Bloomberg School of Public Health at Johns Hopkins University in Baltimore, managed to remove the mutant newborns from the cage in time to assess the damage. "The severe blistering was due to mechanical fragility in these mice," Vassar says. Without a proper keratin network, the skin cells were as fragile as eggshells, ready to break under the mildest strain.

After a trip to the medical library, Fuchs and Vassar uncovered two rare human diseases that looked much like the mouse disease: epidermolysis bullosa simplex (EBS), which involves blistering of the inner epidermal layer, and epidermolytic hyperkeratosis (EH), which manifests in the outer layers. Within a year, they had worked out the genetic basis for both EBS and EH, building on a discovery Fuchs had made as a postdoc, that as epidermal stem cells differentiate, they switch off two

keratin genes, *K5* and *K14*, and switch on two others, *K1* and *K10*.

These studies established a paradigm for what are now 89 distinct genetic disorders of intermediate filament proteins. This work also led to a greater understanding of normal skin. When Fuchs moved her lab to Rockefeller in 2002, she continued to focus on skin stem cell differentiation.

Fuchs's research today looks at the signaling pathways that help a skin stem cell decide whether to become an epidermal cell or a hair follicle. For a stem cell to become a hair follicle, at the right moment, the pathway known as Wnt must be turned on, and another, known as BMP, must be switched off. In the absence of these opposing signals, the stem cell becomes skin. While such research at some point could lead to the elusive cure for baldness, Fuchs is focused on its less commercial, more profound implications for human health. She and her colleagues are now investigating the relationship between the process of stem cell activation and defects that cause cell proliferation and cancer.

MAINTAINING FOCUS

Fuchs and Hansen spend most weekends exploring New York, often ending up at one of the city's many art museums, standing for long stretches at a time in front of their favorite paintings. A few in particular at the Metropolitan Museum of Art—*Virgin and Child* by Murillo, Vermeer's *Young Woman with a Water Pitcher*—really hold their attention, as well as several Picassos at the Museum of Modern Art. "We can stand in front of a painting for an hour," Hansen told me, "and even though we've seen it dozens of times before, we see something new in it."

The same is true, it seems, of the way Fuchs looks at a skin cell—like a work of art that reveals new insights every time she studies it, no matter how many times she's looked at it before. Like Picasso in his cubist period, she continues to focus her kaleidoscopic view on familiar questions in search of surprising answers. ■