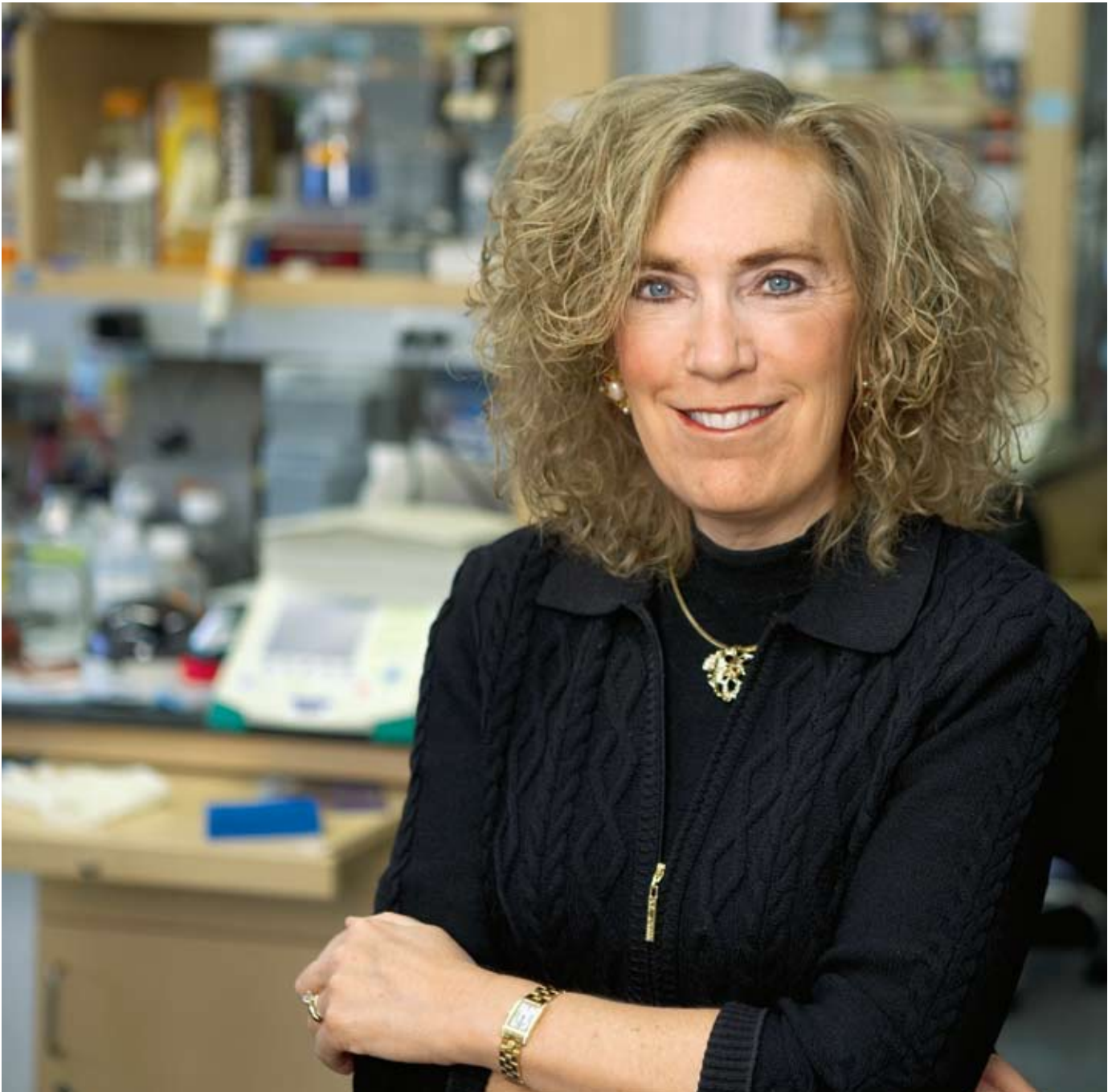


# More than Skin Deep

*Adult skin stem cells can be used to produce embryonic stem cells, and thus any other tissue of the body.*



*Elaine Fuchs explores the mechanisms governing skin stem cells and their remarkable ability to both self-renew and to commit to a particular tissue, such as sebaceous glands. She turned that journey into the first mouse successfully cloned from adult skin stem cells.*

Matthew Septimus

ELAINE FUCHS USED TO DO CROSSWORD PUZZLES AS A DIVERSION FROM HER undergraduate studies. With crosswords, every solved clue creates new hints to help solve neighboring clues. Fuchs, an HHMI investigator at The Rockefeller University, has followed a similar approach throughout her professional life. By honing each experimental finding into a new set of tools, she has probed deeper into the question that first piqued her curiosity three decades ago: How does mammalian skin grow and produce complex tissues such as hair follicles and sebaceous glands?

Fuchs' recent work focuses on the stem cells, sprinkled throughout adult skin, from which all new skin tissues arise, and her latest findings are considerably more than skin deep. With a technique known as "nuclear transfer," she and Rockefeller colleague Peter Mombaerts have demonstrated that adult skin stem cells can be used to produce a complete cloned organism.

Early in her career, Fuchs set out to understand how cell growth and differentiation influence human disease. Using cultured cells as her experimental model, she learned all she could about key skin proteins, their genes, and the developmental pathways they control. "I felt that if you want to understand the basis of human diseases, you need to understand what's normal before you can attempt to understand what's *abnormal*." Shifting between cultured cells and transgenic mice as model systems, Fuchs' team discovered the genetic bases of two key classes of skin blistering diseases, epidermolysis bullosa simplex and epidermolytic hyperkeratosis, and their various subtypes. Fuchs extended this work to elucidate the gene responsible for a related muscle degenerative disorder and set the paradigm for more than a dozen disorders involving a cytoskeletal structure called the intermediate filament.

Three years ago, researchers in Fuchs' lab learned how to fluorescently mark stem cells in skin, a technique she says "helps us monitor different types of stem cells, including those of skin, within the living mouse." The researchers purified the glowing cells and used gene-chip technology to determine their

gene-expression profiles. After identifying genes preferentially expressed in skin stem cells, they turned to mouse genetics to reveal some of the genes' functions. In a series of three papers published last year, Fuchs' team reported on three different transcription factors that they learned have profound roles in the respective differentiation of stem cells into hair follicles, sebaceous glands, or epidermis. The findings, she says, revealed that the developmental pathways adult skin stem cells use to build tissues are strikingly similar to those used by embryonic skin stem cells.

That realization led Fuchs and Mombaerts to wonder whether the skin stem cells they studied could be reprogrammed to generate other tissues. In the February 20, 2007, issue of the *Proceedings of the National Academy of Sciences*, the scientists reported the first successful cloning of healthy mice from adult stem cells. They achieved that goal by using the technique of nuclear transfer: replacing the nucleus of an unfertilized oocyte with the nucleus of an adult skin stem cell (see "A Visual Primer on Cloning," page 56). After transfer to a mouse's uterus, such hybrid cells were capable of developing into healthy adult

mice, showing that the adult skin stem-cell nuclei could be reprogrammed to produce all tissues in the adult mouse.

Mouse cloning from other somatic stem cells has been attempted before, but the few cloned mice that resulted were not normal and almost always died soon after birth. Fuchs' and Mombaerts' cloning experiments had success rates as high as 5.4 percent, and half of their cloned mice lived out normal life spans.

Instead of introducing a mouse hybrid embryo into a mother to produce a cloned offspring, Fuchs points out, the embryo could be grown in a culture dish with the goal of producing embryonic stem cells. If scientists are able to adapt this strategy to human skin stem cells, she says, this technology might prove to be clinically important in the future. "You might then be able to tailor-make embryonic stem cells to a particular patient and thereby avoid rejection by the immune system," she says. "Additionally, you might be able to study a patient's neurodegenerative disease by creating neurons from the embryonic stem cells generated from a skin biopsy."

Does Fuchs still do crossword puzzles as a diversion? She says they no longer interest her. "What I used to like about crossword puzzles is that you knew when you had solved the problem. In biology, you can never solve the problem. But that's what I now find fascinating. With the results of each new experiment comes the next question to address." ■ — PAUL MUHLRAD

"I felt that if you want to understand the basis of human diseases, you need to understand what's normal before you can attempt to understand what's *abnormal*."

ELAINE FUCHS