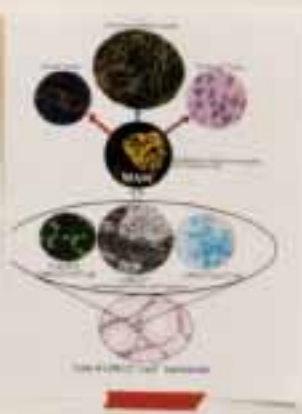
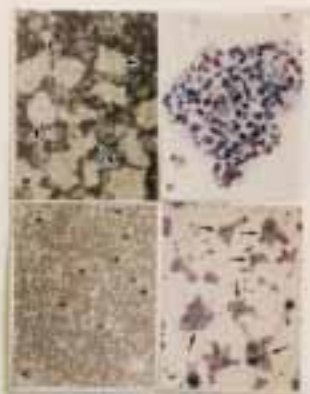




Handwritten notes and a yellow tag on the wall.



Handwritten notes and a purple tag on the wall.

Shahin Rafii's team has already shared their resources, sending mice with genetically labeled GPR125 cells, spermatogonial stem cells, and multi-potent adult stem cells derived from spermatogonial stem cells to several other laboratories.

From Sperm to Stem Cells

Adult stem cells derived from mouse testes appear to match the capabilities of embryonic stem cells.

WHEN SHAHIN RAFII WAS A TEENAGER IN TEHRAN, IRAN, EAGER TO CONTINUE the family tradition of becoming a physician-scientist, the country and its universities were in turmoil that culminated in the Iranian revolution of 1977. ¶ “It wasn’t just the American hostages,” Rafii says about that difficult time. A cousin was arrested and executed. The family feared a knock on the door. It was a difficult time to get an education, yet Rafii

had already become fascinated by tumor biology and the possibility of regenerative medicine. His brother, Shahrokh Rafii, a cardiologist in the United States, urged Rafii to join him and to apply to medical school. It felt like a big risk, but the dangers at home were greater. Rafii left just before the revolution began. Eventually he earned his M.D. from Albert Einstein College of Medicine.

Now an HHMI investigator at Weill Cornell College of Medicine in New York, Rafii’s fascination with tumorigenesis has paid off in unexpected ways, thanks to an astute observation he made about a particularly unusual type of tumor.

In the September 20, 2007, issue of *Nature*, Rafii and his collaborators described how cells from the testes of adult male mice can be turned into stem cells. Moreover, the researchers demonstrated that these reprogrammed sperm-cell precursors (spermatogonia) in living mice could develop into working blood-vessel tissue as well as contractile cardiac tissue, brain cells, and a host of other cell types. If they can do the same in humans, the stem cells could potentially be used to develop treatments for men with heart and blood vessel diseases, Alzheimer’s disease, Parkinson’s disease, stroke, diabetes, and even cancer.

These findings have been a decade in the works, beginning when Rafii was a fellow in hematology and oncology at Weill Cornell. There, he became intrigued by teratomas—bizarre, but curable, tumors that develop primarily in the testes and ovaries. They resemble disorganized embryos with many kinds of cells—skin cells, heart cells, brain cells—and even teeth. The curious composition suggested to him that the testes might be a reprogrammable source of adult stem cells for treating patients.

Adult stem cells are self-renewing and can in principle be redirected to become multipotent—able to differentiate into, among other things, organ-specific tissues, such as cardiac cells and blood vessels, that are essential for organ regeneration. Researchers typically turn to bone marrow and sometimes to the heart or brain for adult stem cells. But these cells are rarer than diamonds. “I would probably have to remove the majority of a patient’s bone marrow to get enough stem cells to eventually regenerate just a small piece of the heart,” says Rafii. In addition, the technology to grow enough adult stem cells to use in regenerating human organs simply doesn’t exist.

Instead, Rafii and his team turned to spermatogonial progenitor stem cells in the testes.

Usually, these cells make only sperm. But Rafii’s experience with teratomas suggested to him that maybe the cells could be directed toward tissue repair or regeneration.

The researchers began with mice. “The challenge was to isolate the spermatogonial stem cells and then to reprogram them from making sperm only to making various tissues,” Rafii says.

The cells were not easy to identify. But in collaboration with researchers at Regeneron Pharmaceuticals, the team discovered a marker, called GPR125, on the surface of spermatogonial stem cells. Next came finding the right “feeder” cells to encourage the growth, reproduction, and conversion from spermatogonial stem cells to adult stem cells. Marco Seandel, a senior postdoctoral fellow in Rafii’s laboratory and first author of the *Nature* paper, developed unique feeder cells from adult mouse testicular stroma cells (a type of connective tissue cell that supports the proliferation and differentiation of stem cells).

Something about the culture medium with the new type of feeder cells made it work. The challenge now, says Rafii, is “to identify the switch and find out how to turn it on. We feel we are very close.”

The ultimate challenge will be to determine whether the methods work with human spermatogonial stem cells. The team has already begun studies with testes tissue from a human organ donation program as well as tissue isolated from monkeys. They have also begun exploring whether a similar approach might work in reprogramming putative stem cells in ovaries, although that may be “a long shot,” Rafii says, because similar stem and progenitor cells are scarce and difficult to biopsy.

Yet, he’s willing to make that gamble, he says. As he has learned through his experiences in life and in the lab, taking chances can pay off. ■ —JANICE HOPKINS TANNE

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SHAHIN RAFII