



RESEARCHERS BELIEVE THERE'S ENORMOUS  
 POTENTIAL IN STEM CELLS FROM A PLENTIFUL  
 SOURCE: FAT BY MICHAEL FITZGERALD

# LIQUID GOLD

**I**nside the bright, spacious operating room lies a 40-year-old woman, anesthetized, with her arms spread wide. Her side is being pierced by an aspirating tube used in liposuction.

The surgeon pumps the tube into the fat over her oblique muscles. Hard work. He breaks out in a sweat, and after a few minutes, the thin plastic visor attached to his surgical mask is clouded with steam, and he has to take a break to replace it with goggles. The procedure yields a stream of golden, aspirated fat mixed with blood, which flows out into a sterile container.

There's gold in them there hills, believes plastic surgeon J. Peter Rubin, who helps people establish normal lives after severe obesity. Stem cells from fat can build all kinds of body tissue for therapeutic purposes, he says.

ILLUSTRATION | JULIETTE BORDA

The atmosphere in the operating room is genial. Pop and alternative music streams from a computer at the back wall. J. Peter Rubin, the attending surgeon, talks casually with the surgical fellow assisting him, Jeffrey Gusenoff.

Later, Rubin will focus intently on the precision work needed during the operation. (This is a routine operation, but Rubin accepts the axiom that “you cannot operate without complications,” particularly in an operation where the surgeon is acting as a tailor, altering the human body.) But during the liposuction, things remain chatty until there are 800 milliliters of fat in the container. Then Rubin starts peppering the nurses with questions and instructions. “Is that stable?” he asks about the container. “We don’t want it to tip over. Is the lid sealed? We can’t lose that. I need to call Dan [his lab technician]—we’re earlier than I thought we’d be.”

If the fat gets contaminated, it can’t be used in research.

“We have to be careful with that—it’s mission critical!” he says, referring to the role the lipid plays in his experiments. “That’s liquid gold.”

(Rubin later notes that, of course, all fat tissue used for research work is done

with consent from patients and approval from the University’s Institutional Review Board.)

After a few minutes in the container, the fat floats on top of saline solution in a thick golden layer. Uncontaminated human fat is incredibly valuable to Rubin, because it supplies his research. He believes it will one day be invaluable to many patients, as well. He and others have found that stem cells from fat can be coaxed to become different kinds of tissue. The first paper establishing that fat tissue, technically adipose tissue, held stem cells with such promise was published in 2001, by collaborators at Pitt and UCLA.

“To think about where the field is now is just mind-boggling to me,” says Adam Katz (Res ’01), an author on that 2001 paper who did his research while a resident at Pitt.

Katz, now an associate professor of plastic surgery at the University of Virginia, started his research in 1996. He remembers, “People scoffed at the concept and were incredulous that there would be stem cells in waste tissue like fat.”

Questions remain about the unique aspects of different types of stem cells, including fat stem cells. But researchers have shown that

these cells, once called pre-adipocytes, can turn not just into new fat tissue, but bone, cartilage, nerves.

Generally, stem cells have generated more hype than hard facts, more questions than answers. For instance, under certain circumstances, some think adult stem cells (Rubin and Katz study such cells) could become a source of cancer—as suggested by experiments where a stem cell was used to build too many generations of cells. And when scientists recently wowed the research community by manipulating normal skin cells to act like embryonic stem cells, concerns were raised regarding whether a certain retrovirus used to implant the cells could cause cancer. Research published in *Science* in February found otherwise regarding the retrovirus, but more work needs to be done on even this basic question.

On the other hand, researchers have used fat stem cells to kill cancer cells in mice.

One thing is clear to Rubin: Fat stem cells, which lie between the cells that actually store fat in our bodies, have promise. While no clinical trials using these cells have yet been sanctioned in the United States, other

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countries with less stringent and less glacial requirements for approvals have seen exciting developments. In Japan, a group has started a clinical trial to use fat stem cells to engineer tissue for breast reconstruction. In Germany, researchers used fat stem cells to help regenerate the skull of an injured child. In Spain, fat stem cells were used to help repair bowel fistulas in patients with Crohn’s disease. In Finland, fat stem cells were grown into a human jawbone, trumping a German group that had used bone marrow stem cells to grow a jawbone, but could not prove that the stem cells had actually done anything.

In this country, investigators have suggested that fat stem cells can create bone and cartilage.

Because fat stem cells are adult stem cells (found in adults, not a developing embryo), they skirt the ethical minefield of embryonic stem cells. They appear to have some advantages over other types of adult stem cells, as well. For one thing, they’re easy to get (one Texas doctor demonstrated this by doing a liposuction on himself in front of journalists), so they can be taken from any potential patient, eliminating the risk of the body

rejecting them. They also are hardy cells, and plentiful.

Very plentiful. America, a nation used to throwing its weight around, now has problems getting out of its chair. More than two-thirds of Americans are overweight, and one-third are officially obese. Gastric bypass operations, which shrink the stomach and let food move more quickly into the small intestine, have become more common: In 2004, American doctors performed 140,000 such procedures. But what does a morbidly obese person do once he’s lost two-thirds of his body weight?

Extreme weight loss can leave people with enough excess flesh to make an elephant look taut. Rubin, who has become known for resculpting such patients, might remove more than 10 pounds of skin and fat from just one person. (His record is 136 pounds; that was from a patient with a giant apron of skin. Such cases are unusual.) Each pound might have 200 million stem cells in it.

Rubin takes some of that extra fat and invests it in what he hopes will become a gold mine of research breakthroughs. Investigators

he’s working with at Pitt are exploring whether fat stem cells can help regenerate nerves and blood cells. At the moment, his primary interest is in using fat stem cells to regenerate breast tissue for cancer patients who’ve had mastectomies. That could replace the use of implants, or today’s state of the art, using tissue from other parts of the body, which involves extensive surgery.

With Kacey Marra, who is a PhD polymer chemist and assistant professor of surgery at Pitt, Rubin codirects the Adipose Stem Cell Center in the school’s Division of Plastic and Reconstructive Surgery. The two researchers have nine grants between them, five of which support the exploration of various aspects of stem cells in tissue regeneration.

One such grant is examining how to use tiny scaffolds to which stem cells will attach and then grow into mounds of tissue.

Rubin says their collaboration has helped create approaches like using these scaffolds.

“We come at it with different angles and skills. It’s a wonderful synergy between a surgeon scientist and a pure basic scientist,” he says.

Marra also is exploring how the stem cells

can grow into nerves and repair injuries.

Katz says that Rubin's work helped establish that fat stem cells derived from different parts of the body behave differently, and in particular, that stem cells from the abdominal area seem to be the most effective.

His work targeted toward breast reconstruction is one reason why Rubin won the Presidential Early Career Award for Science and Engineering (PECASE) for 2006, one of fewer than a dozen National Institutes of Health-funded researchers so honored. The awards are given to scientists beginning their independent careers and are based on criteria like the quality of research, academic and clinical records, potential to make significant scientific contributions, and community service. Federal agencies such as the National Science Foundation and NIH forward names to President Bush for the honor. The National Cancer Institute recommended Rubin.

"Dr. Rubin excelled in all areas of evaluation," said Suresh Mohla, associate director, Division of Cancer Biology at the NCI, in an e-mail.

Rubin method, but Rubin himself will have none of that.

On a recent Wednesday—after a two-day stint as a visiting professor at a medical school in Georgia—Rubin starts at 8 a.m. with a PhD student's two-hour preliminary thesis examination. Then he's off to the clinic, where he has 16 patient appointments scheduled. He wears a pinstriped blue suit, a red tie with a red paisley pattern, and a white shirt with red pinstripes and his initials on one of the French cuffs.

He checks his Blackberry at a stoplight. He has an e-mail from a collaborator, Vera Donnenberg, discussing plans for an experiment. She needs, to be blunt, some fresh fat. Rubin thinks he can help—he has an operation scheduled for the next day.

Even in clinic, Rubin thinks research. A patient asks him about having a fat injection, a technique plastic surgeons use to do things like fill in facial wrinkles. He tells her that as much as 40 to 50 percent of the fat could be resorbed—but research he's doing into how to recreate tissue might change that. (On a day this writer tagged along, he talked patients

working with other scientists.

"I need to collaborate with people who have a skill set I don't have," he says. "Collaboration is incredibly important. If you bring the right people together, really cool things happen."

One of the nurses comes up to him and reminds him, gently, of the patient. He waits a few moments after she enters the room then follows her in.

By 10 o'clock Thursday morning, the liposuction is done, and the tummy tuck is under way. For tummy tucks, Rubin favors a Number 22 scalpel, a blade that looks like it was designed by Hollywood, tapered like a shark ready to bite flesh.

When Rubin gets ready to sew his patient's belly back together, he stops and says, "Now I'm going to show you something really innovative." He holds up a bit of suture thread. The thread has odd little bumps on it but looks otherwise unremarkable.

The bumps, it turns out, are small barbs. "It will hold in place when you put it in. That's much better than tying knots." He starts sewing the thread into one of the

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Rubin, who is 42, is like a perpetual motion machine, fueled alternately by the energy soda Vault Zero and coffee.

Last year, he was a named author on 11 research papers. He performed more than 350 operations. And his first textbook appeared. With a coauthor, he wrote *Aesthetic Surgery After Massive Weight Loss*, one of the first textbooks in the emerging field of post-bariatric body contouring. Also in 2007, his wife gave birth to their third child; they now have three kids younger than 4.

He travels frequently to give lectures on various aspects of reconstructive surgery or to attend meetings like that of the International Federation of Adipose Therapeutics and Science (IFATS), of which he is a founder and past president.

Besides pursuing stem cell research, he also publishes on new techniques in plastic surgery.

His most notable surgical innovation is a breast reconstruction technique that takes advantage of natural tissue. Rubin calls it dermal suspension with total parenchymal reshaping—he takes breast tissue to create an internal brassiere. Gusenoff calls it the

out of at least two elective surgeries he felt would not meet their goals.)

Between patient meetings during clinic hours, he checks e-mail while he's talking with the nurses and scribbling notes on an article for a journal he's guest-editing. By late afternoon, Rubin has switched to Diet Mountain Dew (less caffeine than Vault). He's about to go in and see a patient who is considering a lower body lift in the wake of a gastric bypass operation.

His phone vibrates. It's another e-mail from Donnenberg. She and her husband, Albert Donnenberg, are collaborating with Rubin on research exploring whether stem cells from fat could be used to create new blood cells. She wants to know whether there will definitely be more fat tomorrow. There will, and he goes into action.

"I just need to make a couple of quick calls," he says.

He calls Dan O'Donnell, the lab technician he and Marra share, and then calls the lab tech for the Donnenbergs to make sure that what will happen with the samples is clear to everyone involved. Three phone calls later, he begins to talk about the value of

triangles of belly cut off the patient, to demonstrate how it won't budge if pulled in one direction, because of the barbs, but pulls easily out the other way. The technology had been around a while, he says, but it hadn't been applied in plastic surgery broadly until a surgeon at Duke University used it to suspend the skin in a minimally invasive face-lift. The technique seemed to work well, initially, and got a lot of attention. Rubin remembers attending a session at a conference that was standing room only. Senior-level plastic surgeons there were skeptical.

"They were right. The procedure didn't have the longevity people hoped for," he says, speaking from experience. He tried the technique himself.

That does not diminish his enthusiasm for the thread for other plastic surgery procedures. "It's perfect for wound closure."

The surgeon is a student of innovation. On a shelf in his office sits a book on Robert Oppenheimer.

"They picked him to run the Manhattan Project because he was still young enough to be open-minded about what approach to take," says Rubin. "There were better-

established people in the field, but they had already made up their minds which way to go,” he says.

Also on the shelf is Charles C. Thompson’s *What a Great Idea!* Rubin likes Ira Flatow’s *They All Laughed*, which is about discoveries in science, and a book by Evan Schwartz called *Juice: The Creative Fuel That Drives World-Class Inventors*.

Rubin has tried some of the techniques he has read about. He’s attempted to create a specific place or time to let the creative juices flow, for instance, but that didn’t work so well for him. What does seem to work is talking to scientists with different perspectives, he says.

**I**n weeks when Rubin is in town, he typically blocks out five hours each Tuesday for lab meetings and related activities. Thursday is operating day. But because he only had one operation today, and he was in Georgia on Tuesday, a somewhat impromptu lab meeting is scheduled for this Thursday afternoon.

When Rubin breezes in, still dressed in his operating scrubs, he says, “Where is Han Solo?” a reference to Han Li, who is both

to Li, who is investigating whether fat stem cells could more easily yield the kind of pluripotency that scientists recently derived from normal skin cells.

This work, they hope, will build on the jaw-dropping breakthroughs made in 2006 and 2007 by James Thompson of Wisconsin and Shinya Yamanaka of Kyoto University, who both led teams that were able to take run-of-the-mill skin cells and, by adding four genes to the cells, produce what acted like embryonic stem cells. Li is exploring the ability of adult stem cells to do this more easily. His experiments look promising, and he has anticipated several of Rubin’s questions already.

Despite his obvious excitement, Rubin still checks an e-mail on his phone while they talk—he’s monitoring the status of the day’s experiment. Then he shifts back to focusing on the potential for a paper to be done by late spring.

Rubin says, “Have you decided yet on *Science* or *Nature*?”

Li laughs and says, “I haven’t confirmed it yet!”

Rubin suggests he move quickly. “Someone else is probably thinking about it right now.”

father. In college, he considered writing or anthropology, but he wound up on track for medical school.

Once there, he found that he loved surgery. And while he strongly considered cardiothoracic surgery, he felt drawn to plastic surgery. At the time, postbariatric surgery was just emerging as a field. Plus, it had a dramatic impact on patients.

“Not only were these cases very technically challenging and very fertile ground for innovating new techniques, but you were also helping people through a truly amazing transition in their lives. People who, a couple of years ago, could hardly walk up a flight of stairs, and now their lives were completely different,” he says.

Rubin links his research with his clinical and operating room time. That combination is an important one, says Adam Katz.

“Peter has been a visionary pioneer in the ‘life after weight loss’ concept.

“He’s pioneered the way to organize it into a clinic and practice and research setting. He’s intertwined a significant health problem with significant clinical challenges with novel basic science research, and he’s

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a surgeon and a molecular biologist. Han comes in a few moments later, and Rubin starts the meeting by asking Huaping Tan to talk about his “great news.” Tan is working on developing a biodegradable gel that could be an injectable carrier for the fat stem cells in work that might someday provide an alternative to silicone implants. Tan, who came over from China in January, has achieved ... something. It’s not clear at first, but with Li translating between Mandarin and English, Rubin and Tan converse. Rubin is excited by what he hears. Tan has developed a compound that won’t solidify too quickly, a major step forward for the project.

“As soon as you can, make some modifications. Maybe in a week or 10 days, maybe we can test some cells,” he says. Rubin thinks this work will certainly yield a meaningful paper, and he’s almost bubbly.

“This is great. This is goodgoodgood!”

Rubin also talks to the other two researchers at the meeting and makes suggestions for both of them to consider. He then turns

The two talk more about the progress of the research and what questions remain open. When they’re done, Rubin says, “Good, Han. Goodgoodgood! You’ll be famous!”

“No, you’ll be famous!” Han says, and they both laugh.

Marra says this kind of give-and-take is powerful—there is an exchange of expertise between her fellows, who know how to do chemical engineering, and Rubin’s fellows, who know what they’d like to do for patients.

“In graduate school, you make a polymer and you put it on the shelf,” she says. “Here, we put it in an animal to see if it works.

“The surgeons are really driven to help patients. It’s very motivating.”

**R**ubin didn’t start out wanting to be a plastic surgeon, in part because his father, Leonard Rubin, was an accomplished plastic surgeon who had done groundbreaking work on soldiers during World War II. Like many children, Rubin wanted to do something different than his

tied it all together well.”

Rubin’s main research goal this year is to get the data he needs to apply for a clinical trial using fat stem cells for regenerating soft tissue in reconstructive surgery. (He’d like to see that approach used for breast reconstruction someday.) He is fairly certain that the FDA will approve such a trial within five years, and he’s hopeful that it will happen sooner.

He’s a little frustrated at the breakthroughs happening elsewhere, even as they excite him. The lab in Finland that used fat stem cells to create a human jawbone has invited him to visit, and he’s looking for an open spot in his calendar. The truth is, there remains plenty of work to do before fat stem cells go from promise to widespread practice.

But right now, after a full Thursday, he has to change out of his scrubs. It’s back into a suit and then over to the North Side to speak at a meeting of postbariatric surgery patients.

He’s still chasing his twin goals of helping them build normal lives and using their liquid gold to brighten the lives of many others. ■