Mastering Stem

AGAPITO SANCHEZ, JR.

BY EMILY CARLSON

Like many people turning 40, Peggy Goodell had hoped the monumental day would come and go quietly.

Goodell treated it like any other Wednesday: She got up, rallied her girls to school, and headed to work.

Laying low didn't last. Later that day, a man wearing a gold suit studded with rhinestones sashayed into her office, took her by the hands, and crooned, "Don't Be Cruel."

Turns out the singing Elvis was a "gift" from her dad, and Goodell, now 42, wasn't all that surprised. Her father, she laughs, has a knack for teasing her and her sisters.

That sense of humor must run in the family, because Goodell always enjoys a practical joke, even if it's on her.

Cells

“I encourage people to poke a little fun at things,” she says.

Her job, though, is no laughing matter. A molecular biologist at Baylor College of Medicine in Houston, Texas, Goodell works in one of the hottest areas of science: stem cell biology.

She’s studying how cells that all start out alike can turn into any of about a dozen different types of blood cells. Her findings could help improve treatments for leukemia, lead to new insights about aging, and advance a field in which so much remains unknown.

All-Purpose Cells

Stem cell scientists have worked with two types of cells: embryonic stem cells and adult stem cells. Both varieties seem to live forever, dividing indefinitely to give birth to even more cells just like themselves. Some of them will mature, or differentiate, into a specific type of cell.

Embryonic stem cells are particularly talented since they have the potential to become just about anything—cells of the heart, brain, stomach, you name it.

Adult stem cells, on the other hand, have already specialized and don’t change careers.

“Adult stem cells from the skin can make skin cells, but they can’t make blood cells,” Goodell explains.

If you want to know the latest on stem cells, you’d better pay attention to the news. Scientists report new developments and discoveries about them all the time.

In fact, researchers recently announced that they had reprogrammed ordinary skin cells to function just like embryonic ones. The advance could offer a way to study stem cells without using human embryos, which have been the only source for isolating the embryonic master cells.

Goodell works mostly with adult blood stem cells called hematopoietic stem cells. (Their abbreviated name, HSC, is much easier to say!)

Scientists have been researching these cells for more than 40 years. Found mainly in the spongy marrow filling the hollows of our bones, HSC manufacture all our blood cells—from the red ones that carry oxygen to the white ones that fight infection.

HSC are extremely important since they constantly replenish sick or dying blood cells.

When people with leukemia or other blood cancers receive bone marrow transplants, what they’re really getting is a supply of HSC that can produce healthy blood cells inside the body.

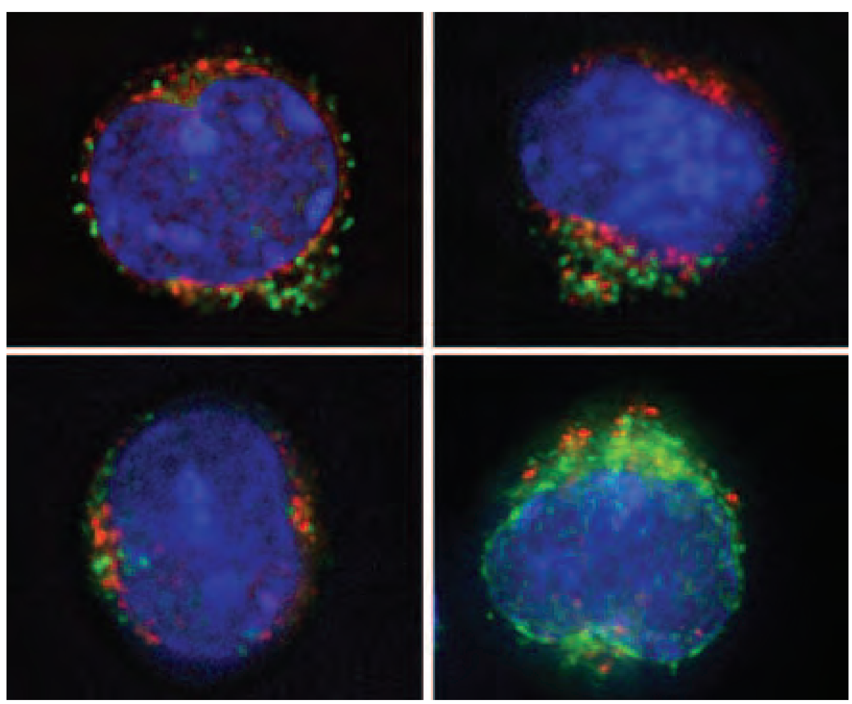
But HSC make up less than 1 percent of the cells in a quart of bone marrow—the amount typically donated.

While bone marrow transplants are life-saving therapies, they carry significant risks. Giving a higher proportion of stem cells in the transplanted cell mixture would help make this a safer procedure, Goodell explains.

To up the dose of the blood-making stem cells, Goodell is trying to coax HSC to make more of themselves in a lab dish.

Describing this process, Goodell conjures up an image of strawberry jam. Like the jam, bone marrow is a thick, jelly-like concoction stocked with seeds—stem cells.

“What I’d like to do is find a way to select out the ‘seeds’ from just a teaspoon [of marrow] and grow them,” Goodell says.



KUAN LIN

▲ Hematopoietic stem cells (HSC, shown in this photo from a microscope) manufacture all our blood cells. A huge nucleus (blue) nearly fills each of these four HSC.

Major Players

Goodell and her lab group have figured out how to isolate HSC from bone marrow, and now they're looking for methods to grow them in a controlled way. One tactic is to study the mechanisms involved in the constant division of HSC and their decision to specialize.

The researchers have identified a handful of genes that they think play a role. Now, they're trying to figure out what each one does. In time, they're hoping to see the big picture of how hundreds of genes work together to instruct a cell to stay young, or to grow up.

Each person in Goodell's lab works on a small piece of the puzzle. Graduate student David Weksberg, for instance, is examining an HSC gene that helps the cells divide but also plays a role in triggering immune responses to bacteria.

Weksberg, who's finishing a combined M.D.-Ph.D. program (see "Dual Doctors," page 13), had tried out many labs before he settled on working in Goodell's.

"It was the best fit," says Weksberg, who attributes the lab's hard-working but laid-back vibe to its boss.

"The lab's personality comes from Peggy," he says.

Levity in the Lab

Goodell might not have experience hiring Elvis impersonators, but she does know how to mix work with fun. Like her dad, Goodell endorses humor as a key part of life. Laughter helps Goodell's lab members stay close while they work on the serious business of figuring out stem cells.

For example, when Weksberg was away at a scientific meeting, his lab friends neatly wrapped everything in his work area—notebooks, storage trays, canisters—in foil.

Another time, jokesters stuffed shredded paper in the ceiling and created a trapdoor so the confetti rained down on one of Weksberg's unsuspecting friends.

One Halloween, Goodell's students surprised her by each showing up in "Pregnant Peggy" costumes complete with black wigs, scarves, and bulging bellies. Undeterred, the boss—who was pregnant with her third daughter—joined her look-alikes for group photos.

GOODELL LAB, DAVID WEKSBERG

Lab pranks and costume fun lighten the mood of doing serious lab work.

DAVID WEKSBERG

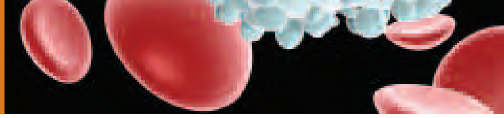
Watch a Goodell lab video featuring the department chairman-superhero "Super-Art": http://video.google.com/videoplay?docid=-8512151439908280785.

Other lab Halloween themes have included the "Ballad of Peggy Bobby" race car costumes and the Simpsons (Goodell was Marge).

With Goodell's encouragement, Weksberg directs video skits about lab life for an annual competition sponsored by the Baylor genetics department. The top prize nets up to $3,000—enough to cover lunch for all the lab members at weekly meetings for 3 months.

The videos make working in the lab seem like a day at *The Office*, full of the characters and crazy situations familiar to fans of this TV show.

The 2007 entry tackles the topic of lab space—and spoofs the constant need for more of it. When the next-door neighbor of the Goodell lab



moves out in the fictional video, her students claim the vacated area for their research—and relaxation between experiments!

They turn blank walls into movie screens, abandoned desks into ping-pong tables, and an empty room into a dance club booming with hip hop by the rapper 50 Cent. Goodell, looking cool in red leather and black sunglasses, waits for the bouncer to let her in.

Alas, any permanent plans are thwarted when a new professor gets the space.

An earlier flick shows the department chairman as a fast-changing superhero flying through the sky with his laptop, ready to help students zero in on important data or simply get to hard-to-reach lab equipment.

Students typically spend a weekend filming the parodies, which they brainstormed earlier over pizza provided by Goodell.

Although hands-off with the production, Goodell herself was the mastermind behind the whole video competition. She got the idea from some British colleagues, who performed skits poking fun at lab life during their holiday parties.

She admits that she loved the British researchers' ability to laugh at themselves. She volunteered to set up the Baylor competition, establish the ground rules, and run the audience-voting system. So far, Goodell's lab has won about $8,000 in prize money.

"I love it because not only are the skits funny, they are a good team-building exercise," says Goodell, who has cameo appearances in almost all of the videos.

"The students really have a great time and are very proud," she says.

Making Connections

Along the way to studying the genes controlling HSC function, the Goodell lab has discovered many interesting things about the role of the stem cells in other biological processes.

For example, stem cells grow old.

Goodell says this shouldn't be too much of a surprise.

"As you age, most aspects of your body simply stop working as effectively as they did when you were younger," she says.

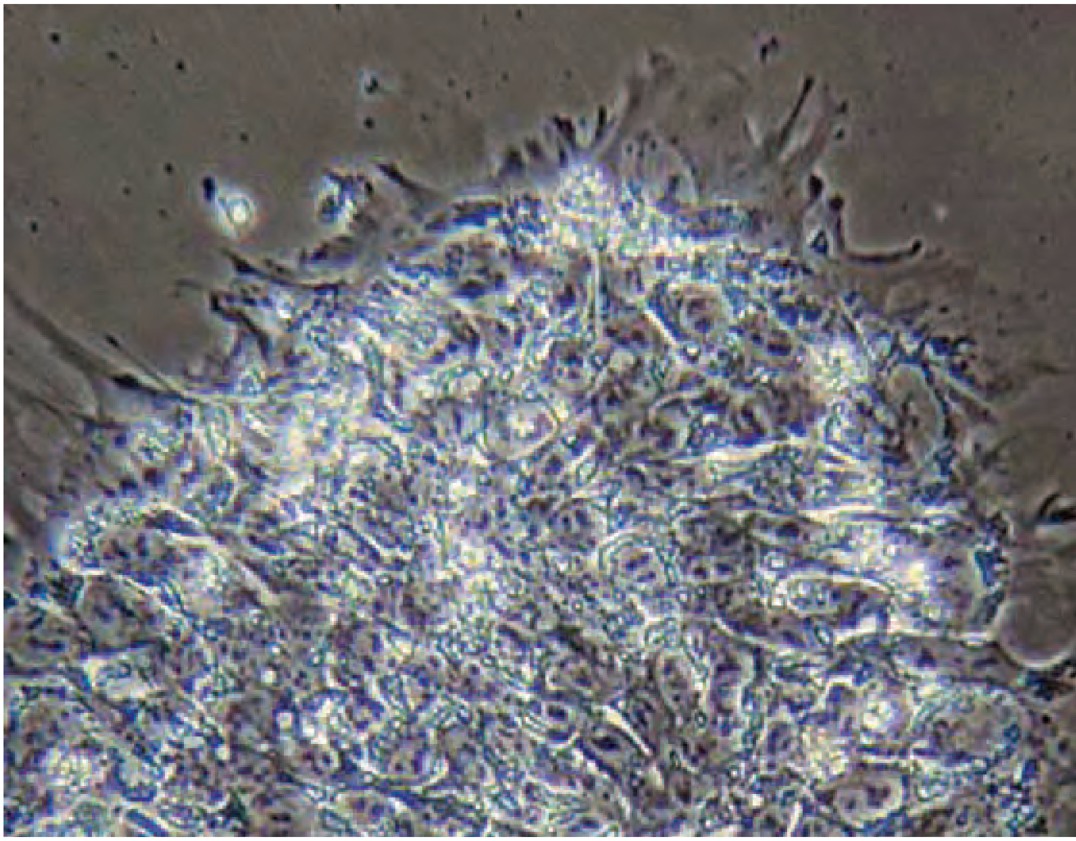
"If your blood stem cells are really just as good when they're old, then your immune system should be just as good. Obviously, we know that's not the case," Goodell adds.

But determining stem cell age isn't simple. And, it's not as exact as carbon dating or counting tree rings.

To show that HSC age, Goodell transplanted mice with stem cells from either young or old relatives. She found that the aged stem cells made fewer new blood cells, suggesting that they didn't work as well.

"Now what we're interested in," says Goodell, "is how we could improve stem cell function with age." Doing so could rev up immune function in older adults and lower their chances of developing blood cancers, for example.

Goodell has also found that stem cells and cancer cells have similar patterns of gene activity. This may explain why



JEFF MILLER

These human embryonic stem cells are "blank slate" cells that can differentiate into any of the 220 cell types in the human body.

they share something else—their ability to divide endlessly.

Finding the genes that can control how stem cells grow could help other scientists find ways to *stop* cancer cells from growing.

Following Suit

Getting HSC to make more of themselves would be one way to produce a hardy supply of the blood-making stem cells for transplants.

Another way draws on the innate talent of human embryonic stem cells. Since these cells can make any kind of cell, Goodell is trying to cajole them into becoming HSC.

Goodell and other researchers don't yet have a good handle on how to tell embryonic stem cells to turn into nerve cells or skin or bone, for example. That's partly because the field is so young: Scientists first learned to isolate and cultivate the cells less than 10 years ago—not very long in the world of medical research.

"I love the work, and it's really important for health."

While some researchers are trying to guide the stem cells' differentiation by changing the environment in which they grow, Goodell is changing their genes.

All the cells in our bodies contain the same genes, but the genes differ widely in their activity. For example, skin cells sense heat, cold, and pain, whereas heart cells beat. That's because different genes are switched on and off in different cells, triggering a range of outcomes.

The same goes for stem cells: The genes in embryonic and adult stem cells differ in their activity. Goodell knows which ones are "on" in HSC, and she wonders if turning on those genes in embryonic stem cells could change the cells from wild cards that can be anything to cards that have to follow a particular suit.

"We still have a long way to go," admits Goodell. "But I love the work, and it's really important for health."

One More Hour...

The possibility of a breakthrough on the horizon keeps Goodell going—just like it did when she joined her sister Maryellen in Tanzania to hike Mt. Kilimanjaro.

At the time, Goodell had plenty else to do and many reasons not to go. She had just started her job at Baylor and still needed to set up her lab. Plus, she didn't even like to hike.

None of that mattered.

"Family is very important to me," says Goodell, who saw the trip as an adventure to share with her sister.

Just after midnight on the fourth morning of the 20,000-foot mountain climb, the guides woke up the Goodell sisters and the other hikers. They needed to reach the top before sunrise, otherwise clouds could block the panoramic views...and, more problematically, the path back down the mountain!

PEGGY GOODELL

Peggy Goodell (left) and her sister Maryellen climbed to the peak of Mt. Kilimanjaro in Tanzania.

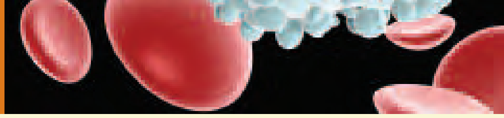
The group trudged on, clambering over giant rocks, scaling steep slopes, and growing even more exhausted.

"I wanted to quit," Goodell recalls. "But I thought, 'There's only one more hour of this. I can make it.' That's become a metaphor for my life."

Reaching that summit helped Goodell sustain her stamina when she returned to Texas to start and run a research lab.

As a student, she had learned how to do science, but now she had to basically manage a business. She had to hire people, fill out forms, get lab equipment, and apply for grants to fund her research.

"It's like you've never been taught to juggle and someone hands you 10 balls and says you have to get them all up in the air!" says Goodell.



Unlimited Potential

Now operating at full speed, the Goodell lab in its quest to grow HSC offers just one example of how scientists can use human embryonic stem cells. Goodell says that others could use them to study normal human cells, understand the causes of birth defects, and test the safety and effectiveness of medicines.

Scientists also see the cells as a potential source of replacements for diseased or injured cells in people.

Imagine curing diabetes by coaxing the master cells to produce insulin.

Or getting them to make the neurotransmitter dopamine to fix the brains of people with Parkinson's disease.

But a lot more progress needs to happen, says Goodell. Currently, only adult stem cells—mainly HSC and skin stem cells—are used to treat illnesses in people.

To teach more researchers how to work with human embryonic stem cells, which are notoriously finicky, Goodell has set up a training facility. There, researchers can explore the best conditions in which to grow and study the cells, ultimately advancing our understanding of the cells and realizing their potential.

"I think these cells are an important technology, and we want to encourage other scientists to learn how to work with them," says Goodell.

As for her own research, Goodell is still looking for the answers. She knows that she might find the key to growing HSC tomorrow, or she may spend the next 10 years looking.

"You never really know with science!" she says. ■

Dual Doctors

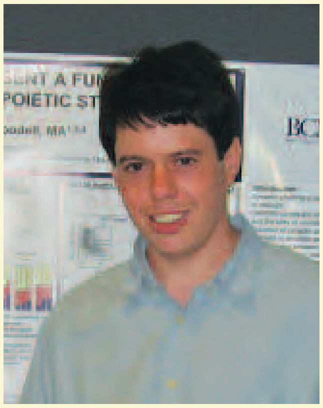
Want to be a doctor? What kind? One who sees patients (an M.D.), or one who does lab research (a Ph.D.)?

How about doing both?

Today, more than 40 medical schools offer joint degree programs that train students to treat patients *and* do research.

David Weksberg is one of them. In college, Weksberg liked asking questions and testing different ideas through experiments. But during his senior year, he realized that he also was interested in how that research could help people.

Physician-scientists bring special skills to research. They ask medically related questions that can help turn basic experiments into improved patient therapies.



ALLAN WEKSBERG

Dual doctors spend about 8 years completing both advanced degrees. They are in short supply and high demand.

Many types of financial support are available for this kind of training. Some programs pay tuition and offer stipends for living expenses. Loan repayment programs can offset debt if a student does research after he or she graduates.

Most M.D.-Ph.D.s work for universities or hospitals and split their time between the lab and clinic (see "Dr. Data," page 2). They do many different kinds of research: biochemistry, neuroscience, pharmacology, computer science, epidemiology, and bioethics.

Weksberg, who in his spare time shoots videos about lab life (see main story), is searching for genes that control how stem cells grow and divide. When he graduates in 2009 with both degrees, he plans to do a medical residency in radiation oncology. His career goal, he says, is to use stem cells to boost radiation-based cancer treatments.—*E.C.*