STANFORD
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# Cell Division

**Stanford has launched an ambitious stem-cell institute, hoping to cure or treat cancer and other diseases. But moral qualms about using embryonic cells have polarized scientists, ethicists, Congress and the public. The outcome of the debate could determine the future of U.S. medical science.**

**by Christopher Vaughan and Kevin Cool**

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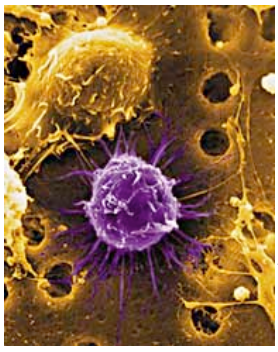

**WORKER CELL: An adult stem cell, collected from human bone marrow. It can replace blood cells killed by cancer or by cancer treatments like radiation and chemotherapy.**

Andrew Leonard

**AS A PEDIATRIC ONCOLOGIST** for more than 30 years, Philip Pizzo has treated hundreds of kids with cancer. He takes heart in the medical advances that have resulted in today's 80 percent to 90 percent cure rate for pediatric cancer patients. But he also knows the torture endured by children fighting the disease, the sores that form in their mouths, the constant nausea and the possible brain damage that radiation or chemotherapy can leave behind.

Watch this cycle of pain long enough and you might understand why finding a cure for kids with cancer isn't enough. Finding a cure that doesn't hurt them seems like a moral imperative, too.

That's where Philip Pizzo is coming from when he talks about stem-cell research. Despite the remarkable progress he has seen, no current therapy comes close to the promise suggested by the extraordinary properties of stem cells, says Pizzo, dean of Stanford Medical School. Unlike treatments that kill cancer as it proliferates—and produce horrible side effects—stem-cell applications could be the silver bullet researchers have long sought, a way to kill cancer at its source. "We now have an opportunity to learn a lot more about the root cause of cancer," he says. "There is good evidence that there may be cancer stem cells. We could look within existing cancers and identify the stem cells and, over time, create a laboratory-based study to learn what makes them malignant."

Adult stem cells already have produced innovative cancer therapies. Irving Weissman, professor of pathology and cancer biology, has used stem cells drawn from bone marrow to effectively treat women with advanced metastasized breast cancer. Doctors at a Michigan hospital recently used stem cells to repair a child's diseased heart, and new evidence emerges virtually every week suggesting that stem cells may be useful in treating genetic diseases ranging from Alzheimer's to Lou Gehrig's disease.

So when Pizzo announced last December that Stanford had established a cancer/stem cell institute, it seemed a landmark event worthy of celebration. An anonymous $12 million gift had provided seed funding for a program that would study adult and embryonic stem cells, bringing together basic and clinical scientists to, as Pizzo put it, "translate the fruits of laboratory research into therapies that will directly benefit patients."

But the euphoria was short-lived. Initial press reports focused on Stanford's desire to develop new embryonic stem-cell lines using "nuclear transplantation," a clinical description of a procedure also known as cloning. Suddenly, instead of being hailed for its vision, Stanford was accused of disregarding public debate about the moral and ethical consequences of embryonic stem-cell research. Leon Kass, chair of the President's Council on Bioethics, blasted Stanford's decision to avoid the word cloning as disingenuous. "Stanford has decided to proceed with cloning research without public scrutiny and deliberation, and has hurt the cause of public understanding of this subject by its confusion of the issue," said Kass, a conservative medical ethicist at the University of Chicago.

Pizzo and Weissman, director of the new institute, countered that Stanford had no plans to clone human babies and that they used scientific terminology to be precise, not evasive. "We want to translate the advances in embryonic stem-cell research to create [cell] lines that represent genetically determined diseases and make these lines available to investigators who want to understand and treat these diseases," Weissman said.

The backlash is a hard lesson in the realities of the stem-cell debate. Science, religion, politics and ideology swirl in a stew of competing arguments about the possibilities and the dangers of using embryonic stem cells. For Weissman, MD '65, and many biomedical scientists, abandoning research that might save the lives of desperately ill people is morally repugnant. Critics, including the president of the United States, worry that obtaining and manipulating embryonic stem cells will lead to terrible moral consequences, including the reduction of the human genome to a scientific tool kit. The controversy has polarized scientists, including scientists at Stanford, and spawned competing legislation.

Ultimately, the debate is about what it means to be human—whether we are talking about the single-celled speck we all once were or the debilitated, dying animal we are destined to become.

## WHAT IS A STEM CELL?

Under the microscope, there is little to distinguish a stem cell from most of the others that Amy Wagers, a pathology graduate student in Weissman's laboratory, has looked at over the years. Drawn from mouse bone marrow in the basement of the Beckman Center for Molecular and Genetic Medicine, sorted from tens of thousands of other cells and spun down onto a microscope slide, the stem cell appears as a slightly lumpy, bluish blob.

"My friends ask me if I can show them a movie of stem cells or something," Wagers says. "But they are really pretty boring to look at."

In fact, there is nothing controversial about the stem cells Wagers and other Stanford researchers are working with today. They come not from embryos but from adult mice and humans. Such stem cells were discovered more than 40 years ago by a team of researchers at the University of Toronto, and the first scientist to isolate and culture them was Stanford's Weissman.

Though outwardly unremarkable, adult stem cells are special. They make the many different kinds of blood and immune cells in bone marrow. Nerve stem cells make new nerve cells. When you get a cut on your arm, skin stem cells create new skin cells to fill the gap and heal the wound. They are constantly at work, maintaining our bodies.

Stem cells are the only cells that can produce exact replicas of themselves, and that gives them great therapeutic potential. A few blood-forming stem cells transplanted to a cancer patient who has undergone whole body radiation can completely repopulate the red and white blood cells in the bone marrow. We may eventually be able to irradiate whole organs safely, killing the cancer that has invaded them, and rebuild the organs with stem cells.

As powerful as adult stem-cell therapies may prove, Weissman is convinced that embryonic stem-cell research will yield even greater results. Embryonic, or pluripotent, stem cells are the master cells of human development, capable of producing any kind of human tissue. But they are present only in the very earliest stages of embryonic development, before they differentiate into specific cell types. They appear four or five days after fertilization, part of a mass of some 200 cells called a blastocyst. However, harvesting these stem cells destroys the blastocyst. And here is where science and ethics converge in a profound dilemma. So far, blastocysts used for experiments have been obtained from in vitro fertilization clinics whose donor couples had an excess supply. Stem cells extracted from these embryos and cultured in laboratories produced stem-cell lines, and estimates of how many are available to researchers range from 10 to 70. President Bush has said federal funding cannot be used to create more embryonic stem-cell lines.

Stanford is not involved in human embryonic stem-cell research, but it would like to be. To get these über cells, the new center's researchers would transplant the nucleus of a somatic human cell (somatic refers to any differentiated cell in the body) into an unfertilized human egg, prod it into dividing, and extract the stem cells a few days later at the blastocyst stage. (Stanford describes this procedure as nuclear transplantation as opposed to therapeutic cloning or research cloning, and different attitudes about the use of these terms helped fuel the controversy surrounding the University's new institute.)

The developing blastocyst and the stem cells extracted from it contain the same set of genes as the person donating the somatic cell. As a result, if the donor carries a gene for a particular disease, so will the stem cell. "If we could make pluripotent stem cells from an individual patient, we could analyze what genes went wrong in a particular inherited disorder," says Weissman. "Then we might be able to develop therapies for everyone with that disease."

Because there are so few of them, existing cell lines will not shed light on any given disorder, says Weissman. They generally come from white, upper- and middle-class patients, providing a very limited sample of a genetically diverse population. For example, he says, a stem-cell line carrying genes for sickle-cell anemia, a disease that predominantly affects people of color, probably doesn't exist.

Theoretically, the list of diseases that might be vanquished with pluripotent stem cells is quite long, says Weissman. "We could treat the 'bubble children,' people with diabetes, autoimmune disorders, Lou Gehrig's disease—the list goes on and on."

At Stanford, the focus is on cancer. The rationale for bringing together cancer and stem-cell biology in one institute is based in part on Stanford's existing strengths in both areas and in part on the important relationship between the two fields, says Weissman. "What we're doing is examining these two fields that we thought were separate and looking at the overlap between them." (See sidebar.)

Physicians have long used the tissue-building capability of adult stem cells to treat certain kinds of cancer through bone-marrow transplants. Stem cells are only a small part of whole bone marrow, but they are responsible for replenishing the marrow with red and white blood cells killed by cancer treatments such as radiation or chemotherapy.

Weissman revolutionized this therapy by isolating the stem cells that perform this blood-building service and developing techniques to cull large numbers of them from bone marrow. He has formed two companies to make those techniques useful clinically.

More recently, Weissman discovered that isolating and transplanting only "purified" (cancer-free) stem cells instead of whole bone marrow could obtain far better results. The reason: the bone marrow itself contains cancer cells. In his study, 35 to 40 percent of patients with advanced breast cancer who received bone-marrow transplants after radiation or chemotherapy suffered a recurrence of the cancer. "With just a stem-cell transplant, there is no recurrence of cancer from the transplant itself, allowing us for the first time to find out how effective the therapy regimen was in eliminating the cancer cells in the body," Weissman says. The results speak for themselves: 37 percent of his patients who got the stem-cell treatment were alive, cancer-free, five years later. The five-year survival rate for all late-stage breast cancer patients is 16 percent.

If pluripotent stem cells could be coaxed to replace organ tissue as well as blood cells, or if stem cells for each organ could be isolated, cancer therapy could change dramatically. "One problem with liver cancer is that if you give it enough radiation to kill the cancer, you also kill the liver," Weissman says. But because it takes two to three weeks for the cells to die, he adds: "If you could irradiate the liver and then infuse it with liver

stem cells, you could replace every liver cell," essentially rebuilding the organ. The same technique might be used to treat cancer in the lungs, he says.

Weissman also has isolated a stem cell responsible for leukemia in mice. His experiments have shown that leukemia will recur (after radiation therapy) "only if you transplant the leukemia stem cells," not the many other blood-borne cells associated with leukemia, he says. Isolating stem cells for other cancers would likely help scientists study what makes these cells malignant, he believes.

Some of Weissman's recent mouse experiments with Stanford colleague Judy Shizuru, PhD '86, MD '92, have gone beyond investigating cancer therapies to understanding how stem-cell transplants can cure autoimmune diseases like Type I diabetes and lupus. In these diseases, the patient's immune system attacks the body. When the rogue immune cells and their stem-cell precursors are eliminated through radiation or chemotherapy and then stem cells are transplanted from a donor, the immune attack ceases, he says. Organ transplants can also be given without the risk of rejection if the recipient also gets a stem-cell transplant from the donor, Weissman says.

**WHEN STANFORD ANNOUNCED** its plans to form the new Stanford Institute for Cancer/Stem Cell Biology, it distributed a press release, expecting limited notice. Instead, it ended up on the front pages of newspapers across the nation, but for the wrong reasons.

The controversy centered on an Associated Press story that reported Stanford's institute planned to clone human embryos, and a subsequent flare-up over a Stanford website item that suggested the University's initiative had the blessing of the President's Council on Bioethics. Soon after the AP story appeared on December 10, Stanford issued a statement attempting to clarify the terms it was using—"nuclear transplantation for the production of pluripotent stem cells"—and noting that this was "not equivalent to reproductive cloning." The AP story was revised and redistributed a few hours after the original and changed its characterization of Stanford's plans from "cloning embryos" to "developing human stem cells." However, a few days later, Leon Kass, chair of the president's bioethics panel, demanded an apology from Stanford for claiming that the panel supported both the research and the nuclear transplantation technique. And he accused the University of trying to conceal its plans beneath scientific jargon. "It's absolutely critical that we call things by the right name so we don't kid ourselves about what the moral issues are," Kass said.

Stanford officials apologized for the website error, but insisted that they were not obfuscating or inventing words but merely using terms that a National Academy of Sciences panel had deemed a more accurate and precise description of embryonic stem-cell procedures. Weissman himself chaired the NAS group that studied stem-cell research and issued a report last year. "We have adopted the NAS terminology 'nuclear transplantation for the production of pluripotent stem cells' because when the public hears 'cloning' and 'embryo' they think of something different from the reality," Weissman says. "When people are asked to draw an embryo they usually draw a fetus. People don't realize that scientists have long used the term to describe what they do to replicate bacteria, viruses or adult cells and only recently and rarely to describe reproductive cloning." Indeed, the word "clone," which comes from the Greek word for twig, was first used in its modern sense 100 years ago by scientists describing the reproduction of a plant by grafting a stem onto another plant's roots.

William Hurlbut, a member of the President's Council on Bioethics and a consulting professor in Stanford's program in human biology, agrees with Kass. "To substitute 'nuclear transplantation for the production of pluripotent stem cells' for the term 'cloning' is simply to distance the description from the moral arena," he says. "While Irv may be right about a general misperception [regarding cloning], it seems to me this is not a justification for changing medical terminology, but a compelling argument for the need to educate our democratic society so they can think clearly about this important issue."

**According to Hurlbut, it's important to acknowledge that the developing cells are "an early stage of a human life in progress."**

Linda Cicero

The first few steps of the nuclear transplantation method Stanford researchers want to use are the same ones scientists have employed to clone the sheep "Dolly" and other animals—but the process diverges thereafter. Weissman and other members of the NAS panel differentiate "reproductive cloning," in which the dividing cell is implanted in a womb to create a full-fledged being, and the nuclear transplantation method, in which the process is halted after a few rounds of cell division and the embryo is a ball of a couple of hundred cells in a petri dish.

The NAS panel called the potential practice of human reproductive cloning "dangerous and likely to fail," and Weissman adamantly agrees. He estimates that about 17,500 experiments with reproductive cloning have been performed on animals and more than 99 percent resulted in deaths, often accompanied by grisly malformations. In some cases, the mother died along with the fetus. "Human reproductive cloning should not be allowed," he says.

While there is broad agreement on the dangers of reproductive cloning, a wide gulf exists about the desirability and moral acceptability of creating stem-cell lines using nuclear transplantation. This issue quickly distills to the question at the heart of embryonic stem-cell research: at what point does an embryo deserve protection?

Scientists generally agree that the 200 or so cells that compose a blastocyst can be considered an early-stage embryo. President Bush has described it as "nascent human life." However, supporters of nuclear transplantation point out that the embryos would never develop beyond a few hundred undifferentiated cells unless implanted into a woman's uterus, which Stanford has no plans to do.

But according to Hurlbut, it's important to acknowledge that the developing cells are "an early stage of a human life in progress, with a drive in the direction of the full development of a distinct individual human person."

Hurlbut, '68, MD '74, says a national dialogue is needed to bridge a polarized, difficult debate on the issue, and that he joined with the majority on the president's council in calling for a four-year moratorium on therapeutic-cloning research to provide time for such a dialogue. He sees a moral imperative for finding new treatments for disease, but is troubled by the lack of a "clear, bright line" for deciding when embryos deserve protection. He says a bill sponsored by Utah Sen. Orrin Hatch, which would allow nuclear transplantation if the embryos were destroyed after 14 days, fails to resolve the sticky moral issue of what constitutes human life.

"If we say it's okay to harvest stem cells up to 14 days after conception because it's at such an early stage of development, then some will argue for 16, 18 or 22 days. Strong scientific and medical arguments can be made for research on embryos beyond the 14th day, and efforts to create artificial wombs are already under way."

Stanford law professor Henry Greely has written extensively on bioethics and was on the panel charged with advising the state of California on stem-cell research. (California allows state funding for developing new embryonic stem-cell lines.) Greely, '74, feels that the earliest forms of human life deserve some measure of respect, but that this is trumped by the needs of sick people. "The embryo is more than just a clump of human cells, but the interests of the early embryo are overwhelmed by the interests of living, breathing people" who are ill, he says.

As for the difficulty of fixing an appropriate point for protecting the embryo, Greely says we make such decisions all the time. "We live on slippery slopes; they define our lives. The first time you tell a white lie, you are on a slippery slope to perjury. The first time you roll through a stop sign, you are on a slippery slope to mass murder. The point is to hold our place on slippery slopes."

Advocates for therapeutic cloning/nuclear transplantation say that embryos produced in a laboratory for research purposes are not much different from the millions of "extra" embryos created at in vitro fertilization clinics and subsequently destroyed or loaned to researchers. But Hurlbut, while emphasizing that he supports stem-cell research, is concerned with the morality of "creating embryos with the express purpose of using them for medical research." He adds: "The intent here is quite different; an instrumental approach is taken. We must not come to see human life at any stage, even the earliest stages, as a mere utility, even for good purposes of scientific research."

Which leads to another question: is it possible logically to reconcile legal abortion with a law that prohibits therapeutic cloning to protect the rights of a developing embryo? Perhaps not, and some have suggested that the real agenda in their opponents' desire to ban cloning is to eventually reverse *Roe v. Wade.* "If you can get a blastocyst classified as a full human being with all the rights of a newborn, you have won the abortion debate," Weissman says.

Hurlbut feels this position cuts both ways. "If we say that human life gains its moral standing from implantation, then wouldn't we have to say that abortion is morally wrong? But if we say that moral status is an accrued or accumulated quality, then some will challenge our designated developmental date and use the same argument for the right to gestate a clone. They will say, 'Get your laws off my body. If I can have an abortion with no reason given, as the law allows, then why not for a good reason? Why can I not create a clone, implant it and harvest its fetal tissues or organs to save the life of my dying child?' "

President Bush has said he would only sign a bill that bans all cloning procedures. According to Bush, a law banning reproductive cloning but allowing nuclear transplantation would open the door to cloning babies. "Anything other than a total ban on human cloning would be virtually impossible to enforce," he said in a policy speech at the White House last year. "Once cloned embryos were available, implantation would take place. Even the tightest regulation and strict policing would not prevent or detect the birth of cloned babies."

A Justice Department report issued last May appeared to agree, saying that enforcement of a partial ban poses "certain law-enforcement challenges that would be lessened with an outright ban...." The report noted that whereas nuclear transplantation entails "visible steps" easily distinguished from in vitro fertilization, the introduction of an embryo into a woman's body is a private matter and there would be no easy way to tell whether the embryos were derived from a fertilized egg or a cloning procedure. "Entrusted with enforcing such a limited ban, law-enforcement would be in an unenviable position of having to impose new and unprecedented scrutiny over doctors in infertility clinics and/or research facilities to ensure that only fertilized embryos were being transferred to would-be mothers," the report said.

**IN FEBRUARY, THE HOUSE PASSED A BILL** that would bar taking part in any cloning procedure resulting in a human embryo. (Work with adult stem cells would not be affected.) The bill calls for up to 10 years in prison and a $1 million fine.

"The House bill represents the view of a small number of individuals who have a perspective that is highly religiously grounded and is not supported by logic or reason," says Pizzo. "Not all spiritual or religious people draw the same conclusions [about what constitutes human life]. I would like to see myself as a highly spiritual person, and I would like to think that I can support this research and still be true to my ethical and moral principles."

Hurlbut disputes the view that religion drives opposition to therapeutic cloning. "This is recognized worldwide as a 'species issue' of great importance, and good people can disagree on such issues for reasons that reach beyond personal religious beliefs. I sat on the president's council for six months of difficult debate and I never heard a single argument from a religious perspective."

Supporters of the House bill say they're also worried that allowing nuclear transplantation would create a commodity market for women's eggs, large numbers of which would be needed to develop and sustain new stem-cell lines. "Therapeutic cloning will require 50 to 100 eggs to create enough cloned embryos just to develop a few stem-cell lines," says Florida Rep. David Weldon, a chief sponsor of the bill. "Donating eggs is an invasive procedure" that has been linked to ovarian cancer, and is likely to be most attractive to poor women who need the money, he adds.

Moreover, says Weldon, stem-cell therapies may not be scalable to large numbers of patients. About 16 million Americans suffer from Parkinson's disease. How many eggs would be needed to produce enough stem cells to treat them all? Would the high price of treatment mean that only wealthy patients could benefit?

Weissman says there may be a solution to the potential egg shortage. "What I would like to see is the development of methods to get eggs from pre-oocytes" in the ovaries, Weissman says. If scientists knew how to chemically turn pre-oocytes into oocytes, excess ovaries from gynecologic surgeries could supply all the eggs physicians need.

The anticloning bill now under consideration faces an uphill climb in the Senate, where Hatch helped defeat similar legislation last year. The fact that Hatch, a conservative Republican and a strong abortion foe, is leading the charge to protect stem-cell research points out the paradoxical nature of the debate. Historic allegiances are all mixed up. And how one feels about the importance of the research may depend on how

personally one might experience the payoff. Nancy Reagan favors aggressive federal support for stem-cell studies, hoping to find a treatment or cure for Alzheimer's, even while former political allies of her husband line up to halt it.

Weissman pointed out in *Stanford Medicine* that he has been here before: he and his colleagues were intimately involved in a similar debate 25 years ago over the ethics of DNA research. "There were the critics then, the same people saying, 'You're playing God, you're creating life.' But today there are hundreds of thousands of people who are alive" because of drugs created with recombinant DNA, he said. "Those who would ban this [embryonic stem-cell] research must take responsibility for the lives that would be lost because they banned it."

"Serious disease is a fight against time," says Pizzo. "The longer we wait, the more lives are lost."

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*Christopher Vaughan* is a science writer living in Menlo Park.

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## Inside the Institute

Linda Cicero

The Stanford Cancer/Stem Cell Institute is barely off the ground, but the kind of work it will foster is already going on in laboratories throughout the Medical Center. For example, assistant professor of developmental biology Seung Kim, MD '92, has kept diabetic mice alive using insulin produced from embryonic stem cells.

Institute director **Irving Weissman** (right), MD '65, says the new center will provide funding and support for those efforts while seeking to attract internationally recognized scientists in stem-cell and cancer biology. He is especially interested in exploring similarities in how stem cells and cancer cells proliferate, which could lead to a dramatic new understanding of the origin of cancer and how to treat it. Research at the institute will be integrated into the educational program of the School of Medicine, allowing students to opt for a five-year medical degree program in cancer and/or stem-cell research.

The institute will have two deputy directors: Karl Blume, professor of medicine and former head of the bone-marrow transplantation program, will lead the clinical investigation unit; a director of scientific affairs has yet to be named. Stanford also will recruit a medical director for the Clinical Cancer Center now under construction, a facility designed to promote collaboration between clinicians and researchers.

Medical School dean **Philip Pizzo** (left) sees the stem-cell institute as a prototype for future interdisciplinary research programs at Stanford. "In the plotting and planning of the future of Stanford medicine, I felt it was important to identify targets of opportunity that will bring knowledge from the lab to the bedside," he says. "There are a handful of areas—cancer and stem cells, neurosciences, cardiovascular medicine, immunology and infectious diseases—where there are significant medical problems and we have significant research strengths."

Established with an anonymous $12 million gift, the institute will seek additional funds from public and private sources.

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## Can They Really Do That?

Rod Searcey

One of the compelling reasons scientists have given for pursuing embryonic stem-cell research is that these cells are capable of producing all kinds of human tissue, whereas adult stem cells may be limited to a specific type, such as blood or skin. But recent findings by professor of pharmacology **Helen Blau** indicate that adult stem cells may be more versatile than originally thought.

"We have been excited to find that some cells in bone marrow seem to be able to perform as a backup squad for repairing tissues unrelated to blood," says Blau. Marrow was previously thought only to harbor stem cells destined to give rise to blood and immune cells.

In mouse experiments, Blau and graduate student Mark LaBarge observed that a few transplanted bone marrow cells gravitated to injured muscle and then became new muscle cells to repair the damage. These marrow-associated stem cells (MASCs) provided up to 4 percent of the muscle fibers in mice subjected to strenuous exercise followed by a stem-cell transplant.

This was the first study showing supposedly tissue-specific cells being recruited to build another kind of tissue. Future studies may try to determine how MASCs migrate out of the bone marrow, find their way to where they are needed and know what to do when they get there, Blau says. "We would love to know what signals they are responding to."

Blau also has found evidence of stem-cell plasticity in humans. "We looked through tissue in a brain bank, looking for women who had received bone-marrow transplants from men," she says. Surprisingly, specialized nerve cells with male genes were found in this female brain tissue. Something in the donor's bone marrow had traveled to the brain, taken up residence and gone native, becoming indistinguishable from original brain cells —except for the telltale Y chromosome.

Blau says that even though MASCs may turn out to have some of the same therapeutic applications as embryonic stem cells, research on embryonic cells remains important. "We don't know which cells will work the best, so we have to pursue both pathways," she says.