

By Katie Sweeney

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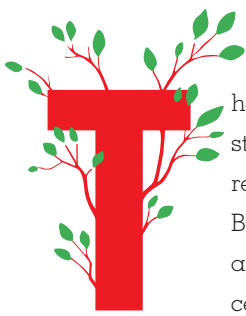


# HEART HEAL THYSELF

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Scientists are on the threshold of something astonishing: A revolutionary discovery that could help a failing heart regrow into a new, healthy organ.





The human heart holds a reservoir of cardiac stem cells. It is small, it is hidden, and until recently, doctors didn't even know it existed. But one day—if Eduardo Marbán, MD, PhD, and his colleagues are successful—stem cells will enable the heart to heal itself.

A clinical trial under way at Cedars-Sinai aims to fuel the hopes of millions who battle heart disease. It is an experimental treatment that has all the makings of a coming revolution in cardiac medicine—one in which a diseased heart can regrow new, healthy tissue.

Just five years ago, the idea was unthinkable. Scientists believed the heart had no ability to repair itself. If a heart cell died, it was never replaced. If massive numbers of heart cells were lost in a heart attack, they were lost forever.

This view was shattered by a single discovery: The heart undergoes a slow but constant process of cell repair and replacement. Any given heart cell, it is now believed, may be replaced at least three times over a lifetime. The mechanics responsible for this ongoing maintenance? Cardiac stem cells.

This uncovers an electrifying possibility: since the heart has a supply of stem cells that repair normal wear and tear, can we use these cells to jump-start the heart's regenerative process after a heart attack?

"It opens a completely new avenue for treatment because we can focus on not just minimizing injury to the heart, but also on maximizing repair," says Eduardo Marbán, MD, PhD, director of the Cedars-Sinai Heart Institute at Cedars-Sinai Medical Center. "If we can do that, we might be able to spare the sickest patients drastic treatments such as heart transplant. Patients whose hearts are less impaired could even become normal. It's a heady prospect."

Just how powerful are adult stem cells? Researchers at the University of Minnesota used them to grow a beating rat heart—right in the laboratory. "It didn't beat very strongly, but it did beat," Dr. Marbán says. "Can you grow a human heart? We don't know. But it speaks to the tremendous potential of regenerative therapies."

Soft-spoken and silver-haired, Dr. Marbán is leading Cedars-Sinai into the new frontier of cell-based heart therapies. In 2007, he left a 26-year career at Johns Hopkins University School of Medicine, where he was chief of

cardiology. He came to Los Angeles with a plethora of research and the Specialized Center for Cell-Based Therapies, a program focused on developing new stem cell-based treatments for heart patients. Funded by the National Institutes of Health, it's one of only three such centers in the country. The program was infused with a dramatic, \$20 million commitment from the Board of Governors to support "lab-to-patient" heart stem cell research.

"There's already a lot of work going on in California and nationally on the basic mechanisms of stem cell biology," Dr. Marbán explains. What we're doing is taking new discoveries and converting them into practical treatments for heart patients."

That's important because heart disease is still the nation's number one killer. Every year, 1.1 million people in the United States have a heart attack, and another 550,000 people are diagnosed with heart failure—a chronic, progressive illness in which the heart's pumping power becomes ineffective. Caused by the loss or dysfunction of heart muscle cells, heart failure is the number one cause of hospital admissions in the nation and leads to 250,000 deaths annually.

"Heart failure is a huge problem, and while we can treat its symptoms, we can't cure the disease," says Ernst R. Schwarz, MD, PhD, medical director of the Cardiac Support Program and co-director of Cardiac Transplantation at Cedars-Sinai Medical Center. "Not only is it expensive in dollars, but it's incredibly costly to quality of life."

### Straight from the Heart

The road to new treatments will take trailblazers.

One of them is W. Dibblee Hoyt.

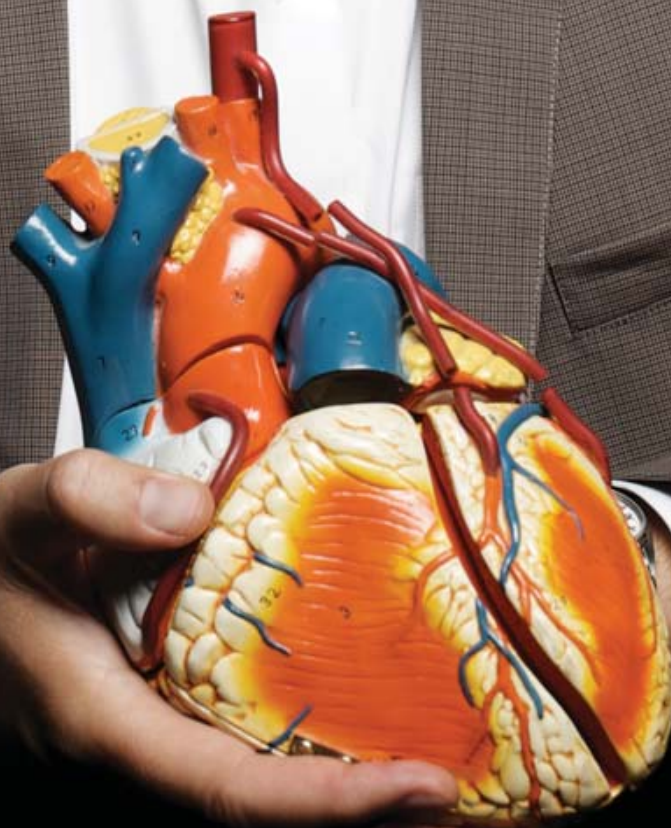
There is a summit near Hoyt's Lompoc, California farmhouse where he can watch the tranquil expanse of rolling hills and trees that stretch down below.

Several months ago, Dibblee hiked to the top of the mountain with his 30-pound camera backpack in tow. The 20-minute climb was strenuous. It was sunset in early June. The view was the perfect cover photo for his *Living Cowboy Ethics* magazine assignment. After snapping several pictures, the 58-year-old photojournalist and photography teacher headed home.

He was on the highway when the symptoms started—

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—Dr. Eduardo Marbán



profuse sweating at first and then an intense, squeezing pressure in the middle of his chest. Dibblee waited for the pain to go away. It didn't. He made it to the hospital in time to have three blocked arteries cleared and opened with small mesh tubes called stents. "The cardiologist told me that I'd had a 'widow-maker,'" he says. "I just feel happy to be alive."

Today, less than a year later, Dibblee Hoyt is on medication and going through a cardiac rehabilitation program. But there's something more. Shortly after his heart attack, the survivor became a pioneer.

It had been just ten days since his heart attack when Dibblee Hoyt arrived at Cedars-Sinai for a bone marrow aspiration—a procedure normally associated with cancer patients. He had signed up for and been accepted into a leading-edge clinical trial that's studying a very different therapy: transplanting bone marrow stem cells into his heart to regenerate it.

Treated with a local anesthetic and with his girlfriend Sherrie at his side, he lay face down as Michael Lill, MD, expertly extracted a sample of bone marrow from his back. Stem cells were isolated from the sample. Later that day, Raj Makkar, MD, used a catheter procedure to deliver those same stem cells directly to Hoyt's damaged arteries.

### The Stem Cell Plan

**D**r. Lill is medical director of the Blood and Marrow Transplant Program and the Cedars-Sinai Outpatient Cancer Center. Dr. Makkar is the co-director of the Cardiovascular Intervention Center. Their Phase I clinical trial for heart attack patients like Dibblee is nicknamed "Revitalize."

"The goal is to see if the bone marrow stem cells can help the heart regrow healthy tissue and restore heart function," Dr. Makkar explains. "Basically, we're trying to regenerate the tissue that was lost in the heart attack."

Results are tracked by performing an MRI of the patient's heart function before the procedure and again four months later. Although the study is not complete, similar studies around the world have found that the procedure is safe and has modest benefits.

Do the bone marrow stem cells turn into heart tissue? "There may be different mechanisms in how cell therapy

can actually help the heart," Dr. Makkar adds. "The cells we inject may become heart muscle cells, or they may release certain chemicals that prevent cell death. We don't yet know for sure."

Still, bone marrow-derived stem cells may not be the best-suited cells for regenerating heart tissue. The race is already on to improve on these currently available cell types and find a better stem cell to do the job.

Dr. Marbán and Dr. Makkar are already collaborating on a new Phase I clinical trial to study a logical candidate: that small reservoir of stem cells found in every heart. Unlike bone marrow stem cells, these cardiac stem cells are already programmed to become heart cells and blood vessels—theoretically making it easier to coax them into making heart tissue.

The study is set to begin this year at the Board of Governors Heart Stem Cell Center. It will involve patients who have heart failure or have had a recent heart attack. They will undergo a tiny biopsy of heart tissue using a minimally invasive catheter procedure. Cardiac stem cells will be removed from the sample and grown in the lab over several weeks, using specialized methods developed by Dr. Marbán and his team. This much larger population of stem cells will then be injected by a catheter into the arteries that feed the damaged region of the heart.

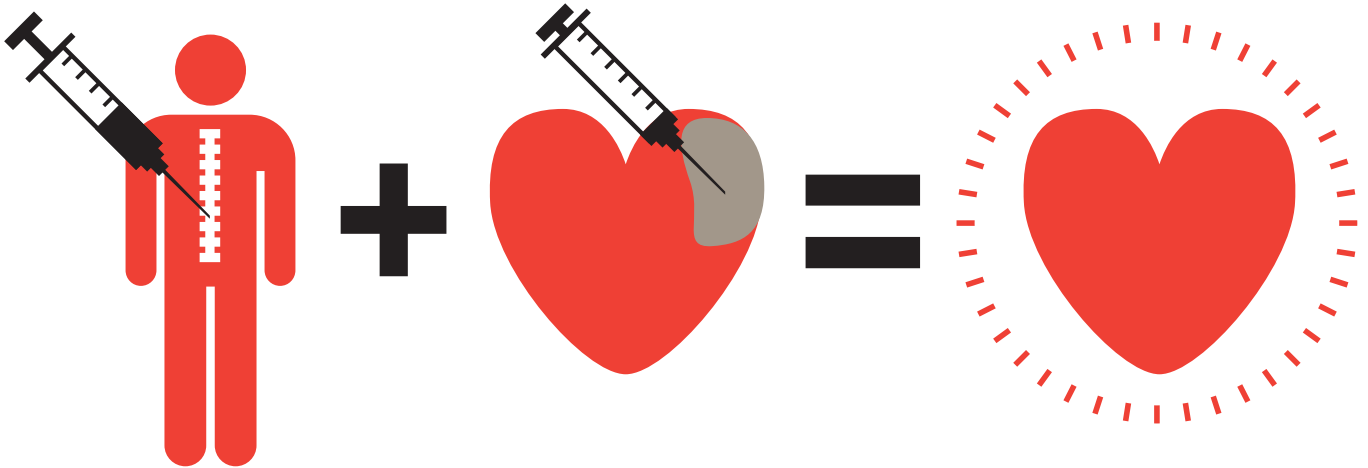
Introducing a much larger number of stem cells may increase the chances that they'll take root and grow. The trial will be the first of its kind in humans, but preclinical studies in mice and pigs are promising, both in terms of regenerating heart muscle and improving heart function.

### Searching for Answers

**T**he field of tissue engineering and regeneration goes far beyond cardiac medicine. Successfully growing new organs is thought to be years away, but engineered skin is already being used in burn patients, and engineered cartilage is being used for certain joint repairs. Researchers around the world are studying whether it is possible to regenerate brain cells after a stroke or to grow new bladders, heart valves, and even teeth.

Research into heart stem cell therapies is just beginning and obstacles abound. Scientists are watching carefully for adverse effects, such as tumor formation and arrhythmias

## Bone Marrow Stem Cells



### Not Your Everyday Cell

Why do researchers believe that stem cells hold such vast potential for heart patients? Often called the body's "master cells," stem cells have the ability to develop into any cell type, from skin and nerve cells to blood and organ cells. They are also the only cell type that

has the ability to self-renew.

Much of the media coverage about stem cells has focused on embryonic stem cells—highly primitive and dynamic cells derived from a blastocyst, a days-old embryo consisting of a handful of cells. Those cells' embryonic origin is at the center of the ethical controversy surrounding stem cell research. While promising, embryonic stem

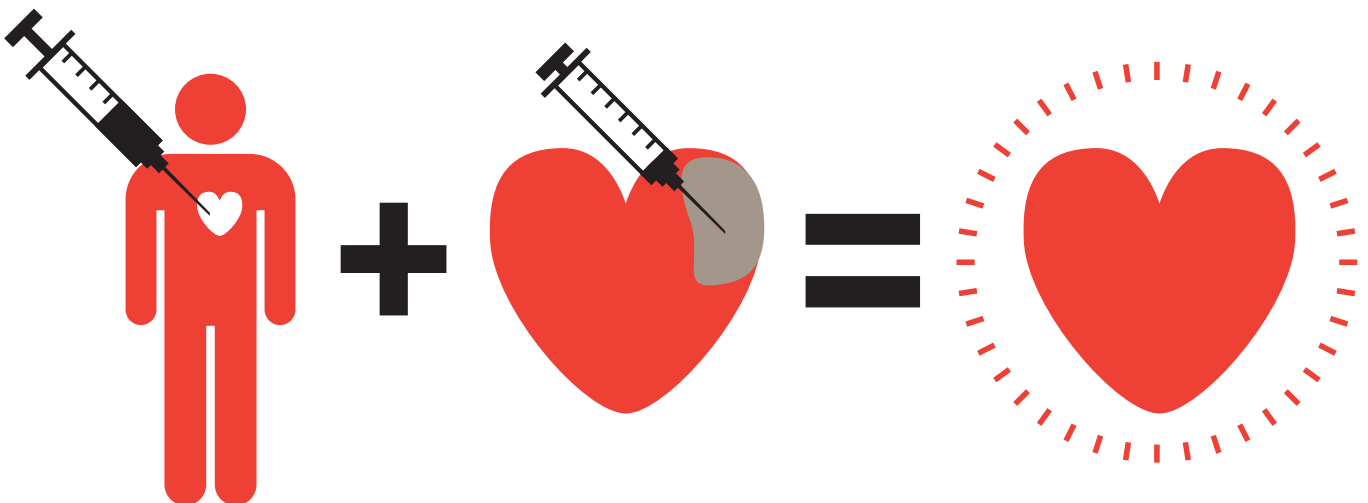
cells face other hurdles besides controversy. Their extremely primitive nature means they can develop into anything—including tumors. And they are not a perfect genetic match for recipients.

But there is a second type of stem cell that has garnered less attention: adult stem cells. Found in the blood and other tissues of adults, infants and children, these cells hold

vast potential for helping the heart and other organs to regenerate.

Although embryonic stem cell research is ongoing elsewhere at Cedars-Sinai, it is these adult stem cells that are the star players in the Heart Institute's research. Since they are derived from a patient's own body, they're controversy-free—and there's no risk of rejection.

## Cardiac Stem Cells



(irregular heartbeats). While neither have been encountered in animal heart stem cell studies (or the bone marrow stem cell human trials), they remain a potential concern.

Even if safety is proven, large challenges remain, such as how to increase the likelihood that injected stem cells will survive. The humbling reality? More than 95 percent of stem cells injected into a heart die within the first 24 hours.

"The survivors can still take root and have functional benefit," Dr. Marbán adds. "But if we could reduce that cell death from 95 percent to 40 percent or 20 percent, it stands to reason that we could boost the overall effectiveness."

**B**one marrow-derived stem cells may not be the best-suited cells for regenerating heart tissue. The race is already on to improve on these currently available cell types and find a better stem cell to do the job.

Just quantifying how many stem cells survive has proven challenging. While an MRI can show whether heart function has improved after stem cell therapy, it does not show how many—if any—stem cells actually survived, explains John Terrovitis, MD, post-doctoral research fellow at the Cedars-Sinai Heart Institute.

Dr. Terrovitis is leading efforts to develop innovative ways to track stem cell survival through imaging. One solution: attaching a gene normally expressed in the thyroid to the stem cells, and then tracing that gene through widely available and safe nuclear medicine scans, such as SPECT and PET scans.

To trace the gene, researchers inject a radioactive isotope designed to temporarily accumulate in the thyroid. The isotope then "lights up" on a nuclear medicine scan wherever it accumulates in the body—just as an airplane's

location lights up on a radar screen. Because the stem cells have been attached to a thyroid gene, any surviving stem cells in the heart will attract the isotope and light up on the scan.

Scientists are also studying the best delivery methods for stem cells. The current theory is that many stem cells are simply being washed away in the bloodstream after delivery. Using special biomaterials or tissue glues could help prevent some of that loss.

A deeper challenge, though, will be figuring out the optimum number of cells to deliver without overcrowding—and how to make those cells feel at home after they are delivered to the heart.


"Many stem cells probably initiate cell death because they suddenly do not know where they are," Dr. Terrovitis explains. "We're looking at ways to either pre-treat them with chemicals or somehow give them signals to let them know that they are back inside the heart."

On the other hand, future treatments may not involve transplanting cells at all. Scientists may one day be able to simply administer a drug that could direct stem cells already residing in the heart to rapidly accelerate their activity and move to an area of injury.

"I look at what we're doing now as version 1.0 of something where, ultimately, version 6.2 may be the one that's really successful," Dr. Marbán says. "It's challenging, but the potential avenues for therapies are unlimited."

### Back on the Hill

**A**lthough he does not have the stamina he once had, Dibblee Hoyt is feeling better and is back hiking up the hill behind his farmhouse. The study he participated in is almost fully enrolled and Dibblee will be followed for a full year by researchers. Once the study is complete, data will be presented to the Food and Drug Administration, and if results prove encouraging, a larger, randomized Phase II clinical trial will be conducted.

The revolution in treating heart disease has begun. 

**MORE ONLINE:** for an audio slideshow narrated and photographed by Dibblee Hoyt go to [discoveringforlife.org/hoyt](http://discoveringforlife.org/hoyt)

## Is there Life After Life?

With regenerative medicine, there is.

Scientists point to the Greek god Prometheus as a fitting symbol for the growing field of regenerative medicine. Zeus punished Prometheus by chaining him to a rock and sending an eagle each day to tear out and eat his liver. The organ, however, was able to renew itself each night, allowing Prometheus to survive.

Today, medical facilities around the world are getting closer to making the once-mythical concept of regeneration a reality by developing therapies to restore lost, damaged, or aging cells and tissues in the human body. Also known as tissue engineering, regenerative medicine uses tissue and cells to replace permanently damaged organs such as the liver, heart, or kidney without the risk of rejection. This method could someday improve the treatment of dozens of chronic diseases, from diabetes and Hepatitis C to Parkinson's.

The concept of tissue engineering has been at the medical forefront for more than a decade, but it was not until several years ago that real breakthroughs were made in the under-

standing of stem cell biology and the development of sources of cells for transplantation in laboratories worldwide.

At Cedars-Sinai, transplant surgeon Jeffrey H. Fair, MD, is among those making advances in tissue engineering, specifically in the area of liver stem-cell therapies. In 2008, Dr. Fair won the Winnick Clinical Scholars Award, a private endowment at Cedars-Sinai that supports cutting-edge clinical investigation. Fair's research involves the use of advanced grafting techniques of embryonic stem cells as a replacement therapy for liver-based genetic defects, such as hemophilia A and B.

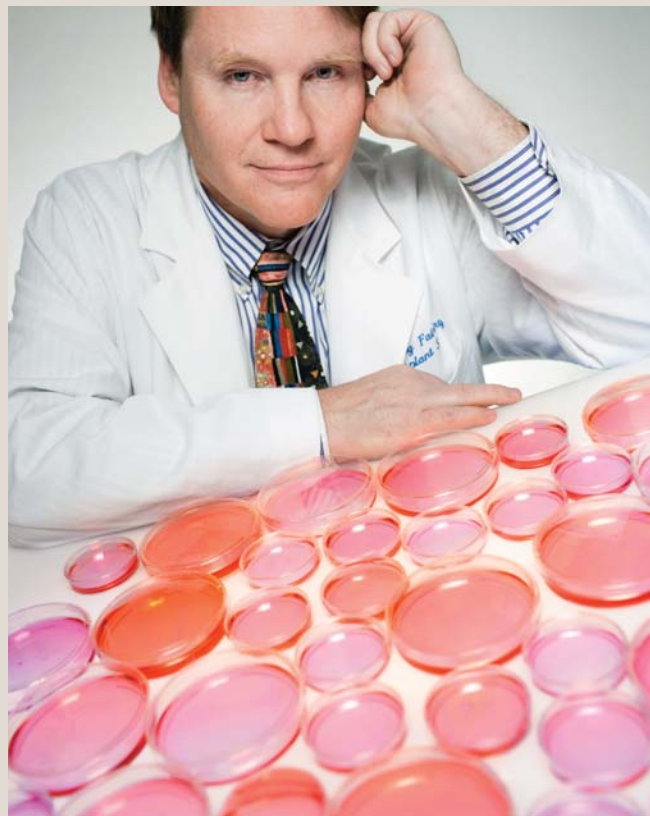
In the long term, Dr. Fair expects his work, which is also supported by funding from the NIH, to reduce

costs and improve quality of life for organ-transplant patients currently at the mercy of long waiting lists or resigned to a post-surgery life of toxic drugs.

"As a transplant surgeon,

you see that what you do is helpful but enormously limited," he notes. Through tissue-engineering advances, he continues, "we'd like someone to keep the liver that they originally had but fix it, essentially."

The biggest challenge for regenerative medicine, notes Dr. Fair, is to obtain funding to move things forward at a pace that matches ideas that are "pouring out of everybody." The field "is so wide open right now," he says. "I think the combination of gene therapy, cell therapy, and bioengineering will all interface in almost unimaginable ways over the next decade." ●



Dr. Jeffrey H. Fair