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Doris Taylor views aging as a failure of stem cells. Taylor says not only do stem cells decrease in numbers as we age, but their function declines as well.

Photo by Bill Kelley

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FACE TO FACE

Heart Maker

By Carmen Peota

Build a heart out of stem cells? It's not a crazy idea to University of Minnesota researcher Doris Taylor.

When you meet Doris Taylor, Ph.D., director of the University of Minnesota's Center for Cardiac Repair, she seems sensible enough. She looks you in the eye and speaks calmly with a slight southern drawl. Her corner office on the seventh floor of the University of Minnesota's Nils Hasselmo Hall is tidy and pleasant.

Go behind the locked doors of her lab and see the sinew-like remnant of a rat aorta that her lab team has stripped of living cells but is trying to revive with an infusion of stem cells, and you realize she has some pretty crazy ideas. In fact, she says, she swears by them. ("Trust your crazy ideas" is printed on a card hanging above her desk.)

In 1995, when the pioneer in cardiac regeneration first suggested using stem cells to treat cardiovascular disease, others called her crazy. In the foreword to a focused issue of the journal *Basic Research in Cardiology* published in 2005, Roberto Bolli, M.D., of the University of Louisville wrote that it was so widely believed that it was impossible for the heart to form new myocytes after birth that anyone who dared to suggest otherwise was regarded as "extravagant, stupid, misguided, heretic, or an outright lunatic." Fortunately, he went on, "a small group of undaunted investigators dared to challenge the establishment and for several years provided evidence supporting the concept."

Taylor acknowledges that many were skeptical that heart muscle could be regenerated. "When we first put forth the idea in 1995, it was a crazy idea," she says. "Now it's not a question of if this is going to happen, it's a question of *when* it's going to happen."

Dream Job

The opportunity to pursue her ideas—even the wild ones—is what lured Taylor to Minnesota in 2003. When offered the Medtronic-Bakken Chair in Cardiac Repair, she saw an opportunity to continue in the tradition of one of her heroes, Earl Bakken. "Talk about somebody who thinks outside the box," she says of the Medtronic founder who built the first implantable pacemaker. "I figured that if a chair was named after Earl Bakken, you really had a chance to innovate."

Taylor's charge in Minnesota would be to create the Center for Cardiovascular Repair, an interdisciplinary group under the umbrella of the university's Biomedical Engineering Institute. The mission of the center would be to develop novel ways to treat and cure heart ailments using molecules and cells rather than mechanical devices. It was a dream job for someone with the stated goal of one day building a heart out of stem cells.

So even though Minnesota was a long way from Duke University in Durham, North Carolina, where over a dozen years Taylor had

Doris Taylor at a Glance

Education

B.S. Biology, Mississippi University for Women, 1977
Ph.D., Pharmacology, Southwestern Medical School, Dallas, 1988

Current Position

Medtronic-Bakken Chair in Cardiac Repair and director of the Center for Cardiac Repair, University of Minnesota

Roots

Doris Taylor claims she always wanted to change the world. And she thinks that stems from growing up in Mississippi during the 1960s and '70s in the midst of the changes brought by the civil rights movement. "How can you not [want to] change the world?" she asks.

She also thinks her family has much to do with her drive. "I grew up in a family where we were taught to ask the next question." That family included a twin brother who had cerebral palsy and a father who died of cancer when Taylor was only 6. "If that doesn't make you want to change the way your world is, I don't know what does," she says.

established herself at the forefront of cardiac regeneration, she accepted the job. "The hardest thing I ever did was leave my friends and colleagues at Duke," she says. "I think about them all the time, especially when the azaleas are in bloom [there] and it's 16 degrees here." She tips her head toward a window on a frigid April afternoon.

More Logic than Leap

Taylor did not set out to study, let alone upend, paradigms in cardiology. When she started her Ph.D. work at Southwestern Medical School in Dallas during the 1980s, she was more interested in the head than the heart. She wanted to study mind-body interactions, specifically, the connections between the physical and mental aspects of pain and chemical dependency. But she was advised that neuroscience hadn't yet advanced to the point where she could find answers to the kinds of questions she was asking. So she chose instead to focus on cell-cell interactions.

Later, as a post-doc at Albert Einstein College of Medicine in the Bronx, she became interested in cardiac cells. She learned the dogma of that time—that heart muscle couldn't heal on its own because it was incapable of either cellular turnover or cellular repair. She first experimented with gene therapy, then started looking at the possibility of coaxing heart cells to divide.

It didn't take her long to realize this was not what she wanted to do. "There were people who were a whole lot smarter than me who were trying to make it work and couldn't," she says of the latter approach. She began to wonder, Was there something that could be transplanted into the heart that might replace damaged cells?

During the late 1980s, when Taylor was first asking such questions, stem cells were not yet on the radar screens of very many researchers. It was understood that bone marrow and blood cells could generate more bone marrow and blood. But few scientists were thinking that immature cells could make other kinds of tissues as well.

Taylor was interested in how satellite cells or myoblasts repaired skeletal muscles after injury. Then she was struck with a crazy thought: "We said, 'OK, heart's a muscle. Skeletal muscle is a muscle. Maybe we can use those [skeletal muscle] cells and let them grow up in the heart environment, and they'll learn how to behave more like heart cells.'"

Taylor moved to Duke University Medical School, where for the better part of the next decade she worked on that idea. "It took us from 1989 to 1998 to pull the pieces together," she says, explaining that her team had to figure out how to grow muscle cells in a dish, test whether the cells were functioning, measure function in the heart, transplant the cells, and see if they made a difference in an animal model.

Promising Trials

Doris Taylor, Ph.D., director of the Center for Cardiac Repair at the University of Minnesota, says only a handful of researchers were talking about cell therapy at the cardiology meetings she attended five years ago. Now, she estimates, at least one-quarter of the talks are on cell therapies.

One of those at the March meeting of the American College of Cardiology in New Orleans focused on results of a study

Their efforts worked. Cells from the thigh of a rabbit were injected into scar tissue in the animal's heart and repaired the damaged muscle. "I'll never forget—ever—the day that we took one of those hearts that we'd harvested from an animal and sliced it open, and you could see this chunk of muscle in the middle of that scar," Taylor says. "I ran all over the building, saying, 'You've got to see this! You've got to see this!'"

In 1998, a paper on the research was published in *Nature Medicine* and Taylor found herself at the forefront of a brand new field—cardiac

involving physicians with whom Taylor regularly works: Tim Henry, M.D., and Jay Traverse, M.D., of the Minneapolis Heart Institute at Abbott Northwestern Hospital. Both have studied stem cell treatments for several years.

The phase I trial of a drug called Provacel, a mesenchymal stem cell product derived from donated bone marrow, began in 2005 and was completed last year. Fifty-three first-time heart-attack patients at 10 medical centers were given the treatment intravenously within 10 days of their attack. The treated patients were followed for six months and showed low rates of side effects such as cardiac arrhythmias and significant improvements in heart, lung, and overall function.

Traverse says that the research was encouraging for a number of reasons, including the fact that the cells came from a single 20-year-old donor from Baltimore. "So this young, healthy person can supply cells for the whole trial—that's sort of exciting," he says, noting that the cells appear not to induce rejection.

Traverse also says that it was the first cardiac stem cell therapy to be given intravenously. "It means that any place in the country, any small hospital could potentially give this therapy to a heart attack patient," he says. "You don't need a specialized center with special equipment or cell-processing facilities." He notes that the Provacel trial was encouraging. "It was a little bit different. It's a breath of fresh air."

Abbott physicians have been involved in five different trials of cell therapies for cardiac patients. "In fact, we've probably done more cardiac stem cell patients than any center in the United States," Traverse says.

The number of cardiovascular cell therapy trials is likely to increase in Minnesota. Last year, the Minneapolis Heart Institute Foundation, Hennepin County Medical Center, the Veterans Affairs Medical Center, and the University of Minnesota received a $1.5 million grant from the National Institutes of Health to form the Minnesota Cardiovascular Cell Therapy Clinical Research Network**.—C.P.**

regeneration. "Nobody was doing this kind of stuff," she says.

Shortly after Taylor's paper appeared, French researchers transplanted muscle cells into a human heart. Two years later, clinical trials were taking place in Europe. In 2002, Taylor herself witnessed in Rotterdam the first patient in the world to get stem cells injected through a catheter into the wall of the heart. Encouraging results began to come in—improved ejection fractions, reduced diameters, thicker muscle tissue.

But Taylor says a "huge number" of questions remained: Which cells worked best and in which patients? What was the best method of delivery? When should cells be given? How many should be given? Where should they be given? How did they work?

Complicated Endeavor

During a recent lecture to students at the university, Taylor explained the problems researchers continue to encounter in working with stem cell therapies. The first consideration is whether to use embryonic or adult cells. The next is where you're going to derive them from. Most commonly, stem cells are derived from blood, bone marrow, and umbilical cord blood. But now muscle, many organs, and even fat have been shown to contain stem cells. Then, there's the issue of the patient population. Do you want to attempt the trial in patients who have had their first myocardial infarction or in those who have been sick for years? How old should they be? "It becomes difficult to look at the literature and sort this out," she told the class.

Taylor also said that the literature is beginning to show that some cells are not as effective as had been thought, nor as safe. "So we have to go back to the bench. That's where we come in," she said of basic scientists such as herself, who can attempt to understand the mechanisms behind stem cell therapies.

Assisting Nature

Despite the many unanswered questions, Taylor has an ever-expanding vision for the potential of stem cells to help the 450,000 Americans who have a heart attack each year and the millions around the globe who are living with heart disease. She initially thought cell therapy would be a treatment for cardiac injury that prevented heart failure. Then she thought that it could also be used to treat people who already had heart failure. Then she realized it could be used for patients with atherosclerosis in order to prevent a heart attack from ever happening.

Now, her goal is a cure for heart disease—to regenerate the injured tissue. In a field that is moving as quickly as stem cell therapy, Taylor adds, that seems less crazy than it once did. "In the last couple of years, we've made remarkable progress. We've got something now that beats and pumps in the lab

like a heart," she says of a very heart-like structure that she and her team grew from stem cells and transplanted into an animal.

The greatest technical challenge Taylor had to overcome to achieve this was to create a scaffold on which the stem cells could arrange themselves. To do this, they removed a heart from a rabbit, stripped it of living cells using a resin they concocted, then implanted endothelial, smooth muscle, and cardiac muscle stem cells on the scaffold. Taylor describes the approach as giving nature the tools and getting out of the way.

"We're not smart enough to figure out how to regenerate that scaffold," she says. "And I would argue that all the tissue engineers in the world aren't smart enough to figure out that scaffold. But nature knows how to do it."

It's an approach Taylor believes is novel, and she's working feverishly to publish the results. But not so feverishly as to get it wrong.

She says her team is committed to going as slowly as needed with research on stem cell therapies and tissue regeneration to convince themselves and the world that their approaches are safe and effective.

In the end, Taylor believes researchers working with stem cells need to under promise and over deliver. "All new therapies," she says, "need to pass the 'Sure, use it on my mother' test." **MM**

Carmen Peota is managing editor of Minnesota Medicine.