Subject: NPR interview on using stem cells to repair damaged hearts

Using stem cells to repair damaged hearts National Public Radio (NPR) July 8, 2005 Friday

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HEADLINE: Using **stem cells** to repair damaged hearts

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BODY:

JOE PALCA, host:

We're going to switch gears here. For the rest of the hour, we'll take a look at the growing field of cardiac regenerative medicine or, to put it in more poetic terms, how can you mend a broken heart? When someone suffers a heart attack, blood supply to the muscle of the heart is interrupted. Depending on the severity of the attack, the heart may lose function. If enough damage is done, you might end up with heart failure. Unlike some other organs, such as the liver, the heart can't fix itself. Dama ge from heart attacks is permanent, at least for now--but at least for now. But researchers are hoping to fix that by coaxing **stem cells** to turn into heart muscle cells that can essentially repair an ailing heart.

Joining me now to talk more about that work is my guest, Chuck Murry. He is a pathologist and the director of the Center for Cardiovascular Biology and Regenerative Medicine at the University of Washington in Seattle. He joins us by phone. Thanks for talking with us today, Dr. Murry.

Dr. CHARLES MURRY (Center for Cardiovascular Biology and Regenerative Medicine, University of Washington): I'm glad to be here.

PALCA: So I wonder, first of all, did I get that right? Can the heart not regenerate itself after an attack?

Dr. MURRY: Not significantly. The heart is perhaps the least regenerative organ in the

body, and so after a patient has damage to the heart, say , from a heart attack, the heart heals by forming scar tissue instead of forming new muscle tissue.

PALCA: And why do you suppose it's different between the heart and the liver? Or are we asking one of those, you know, grand questions here?

Dr. MURRY: Well, it's a grand question at one level. Let me start with the trivial answer to it to begin with. The liver is perhaps the best organ in the body in terms of its ability to regenerate, and this may be the basis for the old Greek myth of Prometheus, who regenerated his liver nightly after the vulture would gnaw it out. And the liver, the cells that are left over after some liver damage, are able to go back into the cell cycle and start dividing once again. And so in very short order, even after a patient, for example, has a resection of part of their liver as a result of--for a surgical procedure like removal of cancer, the patient can regenerate almost all of their liver mass within a w eek or two.

The heart, on the other hand, the muscle cells that survive a heart attack are not able significantly to divide. And as a result, there's not a reparative response. And while people argue about whether there is any kind of resident **stem cell** population in the heart, it's clear that if they're there, they're still not able to mount a physiologically significant response. So there's really very little new muscle that's generated in the heart after a heart attack.

PALCA: All right. That--I just wonder what you mean by a resident population of **stem cells.** What's that all about?

Dr. MURRY: Well, we used to think that the heart had no ability to generate new muscle cells. And the notion was that you were born with essentially all the heart muscle cells that you were ever going to have in your body, and if you died at age 100, your heart muscle cells were going to be 10 0 years old. There has been some increasing evidence over the last five years or so that maybe it's not quite that simple, that perhaps there may be a process of slow turnover in the heart, that, like most things in our body, that the cells in the heart may actually turn over. And there may be some **stem cells** that live in the heart that are capable of repopulating muscle cells, but at a very slow rate. And they would not be sufficient to meet the demand in case of a large-scale loss of muscle like might happen in the case of a heart attack.

PALCA: We're talking with Dr. Chuck Murry from the University of Washington about the potential of using **stem cells** to repair broken hearts. You can give us a call. Our number is 1 (800) 989-8255.

I'm Joe Palca and this is TALK OF THE NATION from NPR News.

So, when people talk about using **stem cells** to repair the heart, a re they talking about getting those heart **stem cells** out of the heart and then somehow expanding them and putting them back into the heart, or are they talking about something else altogether?

Dr. MURRY: Well, that's one of several strategies that are under way at the moment, Joe. Would you be interested in hearing a little bit about what's going on in the clinic?

PALCA: I think I thought--I'm sure my listeners would even if I've heard it before. Yes...

Dr. MURRY: OK.

PALCA: ...I'd be very interested.

Dr. MURRY: So, let me, just by way of background--10 years ago, this was a radical concept, that one might be able to use cells to rebuild the heart from its component parts. And in the ensuing decade, there's really been a revolution in **stem-cell** biology and people have now--it's now moved to be a mainstream experimental concept And the first clinical trials have actually begun. We have a couple of cell types that people have begun doing clinical trials with to see if there's promise for repairing patients' hearts after a heart attack. The cell type with which we have the most experience actually comes from skeletal muscle. Now this is the type of muscle that's in our arms and legs and so forth--it's, you know, standard voluntary muscle. And what we've known from this is that you can take a biopsy of a patient's skeletal muscle, grow cells up in a dish--and this is a specialized kind of **stem cell** that's not multipotent. In other words, it can only form more skeletal-muscle cells. But they can be expanded in a dish and then reimplanted into a patient's heart on an elective basis. And so this has been most commonly done at the time when a patient would have coronary artery bypass grafting. But groups have also been working on putting these cells in with catheters in the coronary catheterizati on laboratory.

And their initial--so what we know about this at the moment is it's certainly feasible, reasonably safe, though there have been some problems with rhythm disturbances in some of the patients that have raised concerns. And there are hints that this might be effective, but of course it's going to take larger-scale trials to answer the question of whether it's an effective therapy or not.

PALCA: Right. And I guess the difference is that a skeletal muscle, as you say, comes from, you know, the things you use to move your arm and flex your arm, and the heart's a very different kind of muscle. And the question is, can they talk to each other and work together to help the heart pump?

Dr. MURRY: That's the critical question. And the biology of skeletal muscle is intrinsically different from that of the heart. Heart-muscle cells are all electrically connected to one another by special cell junctions. And this allows--when a single cell fires, it lets the electrical excitation to sweep through the whole heart so that you get coordinated mechanical contractions, so the heart beats in synchrony. Skeletal muscle is very different. The cells are electrically insulated from one another, and that's the basis for getting fine motor control so that nerves can fire and stimulate contraction of just enough skeletal muscle to do the job.

PALCA: Got it. So you say--but there are other clinical trials besides these skeletal-muscle cells that...

Dr. MURRY: That's right. So the next type to hit the scene was bone-marrow cells. And this was based on some provocative trials that suggested **stem cells** from bone marrow might actually be able to regenerate a substantial amount of the heart after a heart attack in studies that were done in mice in 2001, I guess. And so people very quickly moved to working with bone-marrow cells because bone marrow is already a standard clinical therapy. And so while it took about a decade to go from animal experiments to human experiments with skeletal muscle...

PALCA: Dr. Murry, I have to interrupt you because, again, we need to take a short break, but we'll come back to that topic in just a minute. So please stay with us.

I'm Joe Palca and this is TALK OF THE NATION from NPR News.

(Announcements)

PALCA: From NPR News, this is TALK OF THE NATION/SCIENCE FRIDAY. I'm Joe Palca.

We're talking this hour about new **stem-cell** research, particularly as it pertains to the heart. My guest is Chuck Murry; he's a pathologist and the director of the Center for Cardiovascular Biology and Regenerative Medicine at the University of Washington in Seattle. We'd love to hear your calls and questions about this. Our number is (800) 989-8255, 1 (800) 989-TALK. Maybe you have heard of some new technique of using **stem cells** to treat the heart that you'd like to inquire about. Dr. Murry is the right person to task.

And as we were heading to the break, Dr. Murry was telling us about some techniques using bone marrow perhaps for therapy. So why don't you go back and pick that up where we left off.

Dr. MURRY: Right. So, basically, bone marrow has shown significant promise for treating the damaged heart as well. We originally thought that bone marrow might be a good candidate to grow back new muscle. It looks like that's probably not the case. But what bone marrow may be very good at doing is growing new blood vessels, and so sort of a natural bypass mechanism, like growing your own coronary bypass vessels to restore blood flow to tissue that's not been getting enough flow.

So the clinical trials have begun in Germany and in other countries. They're just gettin g going in the United States at this point. And once again, we know that this is feasible. We know that it seems to be pretty safe. And there are hints in the early trials that this might have some benefit to the function of the heart as well. But that's going to need to await, you know, more detailed Phase II trials.

PALCA: So why are bone-marrow **stem cells** making new blood vessels?

Dr. MURRY: One of the surprises over the last decade that we learned is that one of the key cell types to form new blood vessels, the endothelial cell, actually has a precursor, a progenitor cell that is formed in the bone marrow and circulates and homes to areas of injury. And part of the body's natural mechanism to repair itself seems to be involving sending these progenitor cells to areas of injury and growth of new blood vessels.

PALCA: OK. Well, let's hear what our listeners are curious about. And we'll star t with Vickie in Burke, New York. Vickie, welcome to SCIENCE FRIDAY.

VICKIE (Caller): Hi. Thanks for taking my call.

PALCA: Sure.

VICKIE: I had a question about the research using **stem cells.** Has there been any research using them for congenital heart defects in infants or young children? I'll take my answer off the air. Thank you.

PALCA: OK. Thanks, Vickie.

What about that, Dr. Murry?

Dr. MURRY: Oh, that's an interesting question. One of the--that's probably not going to be the place that we start in doing these kinds of research because there are already reasonably good surgical approaches for treating children with congenital heart disease. And so I think we're going to start in patients who have fewer options, people who have heart failure and no other good medical means of treatment.

But wh at we would like to be doing, for example, is creating patches of new muscle tissue perhaps by tissue-engineering approaches where muscle cells or their precursors are seeded onto a biomaterial, a scaffold of some sort. And you could imagine using this to repair common heart defects like holes in the septum between the atria or between the ventricles.

PALCA: Interesting.

Let's take another call now. What about Walter from Atlanta, Georgia? Walter, welcome to the program.

WALTER (Caller): Yes, thank you. Yeah, I was wondering, supposing someone has already had a myocardial infarction and they have a fair amount of scar tissue, how do you get around that scar tissue to actually replace it with functional cells? It would seem like that, you know, there's no way to remove the scar tissue short of surgery.

PALCA: Interesting. What about that, Dr. Murry?

Dr. MURRY: Th at's a good question. That's going to be one of the hardest things that we face at the moment. I think it's going to be easier to treat patients in the early phase of their disease before they've made significant scar tissue. That said, we have many more patients in the country who have old scar tissue than those who are in the process of healing it. And I think our first clinical trials are actually going to begin in patients who have old scar tissue. One of the hopes is that the cells--that if we're able to establish a good cell population, that they will make enzymes that will remodel the connective tissue of the heart and actually may be able to convert some of this scar tissue into new muscle tissue. But I don't want to make it seem like we've got this figured out. This is very much a current experimental challenge for us.

PALCA: OK. Well...

WALTER: Could I ask a quick follow-up question?

PALCA: Oh, sure, go ahead, Walter.

WALTER: Have any animal trials been done along those lines?

PALCA: Any animal trials. OK, thanks for that.

Dr. Murray, animal trials on this?

Dr. MURRY: Yeah, so everything has been done in animal trials virtually. And very little has been done in human beings at the moment. But what we know at present is that even in people or in animals it's possible to put new cells into the old damaged region of the heart that's full of scar tissue. And some of these cells will take and establish new muscle tissue. So I think there's reason to be optimistic that even patients who have old scar tissue might actually derive benefit from **stem-cell** therapies.

PALCA: OK. Dr. Murry, do you think there's enough evidence from animal studies now to go forward in humans?

Dr. MURRY: I think to go forward with the cell types t hat we've discussed, the time is right to go into the clinic because one can only get so many--you can only get so much information from an animal trial, and then it's time to simply see whether or not this actually works in patients. So for bone marrow or skeletal muscle cells, I think it's good. There's a specialized cell type that resides in bone marrow called the mesenchymal **stem cell.** This has been well-tried in animal models and is just getting going for experimental trials as well--in clinical trials, I mean to say. So I think for these, it's good. I think for other more novel cell types, we need to do more of our homework in the animal laboratory.

PALCA: Now we've been talking about the class of **stem cells** that are mostly referred to as adult **stem cells** in the sense that, for example, bone marrow you can get from bone

marrow to form the **stem cells.** What about the possibility of fin ding cells that you would only be able to get from embryonic **stem cells** that would be useful in the heart?

Dr. MURRY: I think that's a really important thing to bring up, Joe. And my laboratory has looked very hard at trying to derive cardiac muscle cells from adult **stem cells,** and we've been unable to do it with bone marrow. We've been unable to do it with skeletal muscle. And the only way that we've reliably been able to do it in my own laboratory is through embryonic **stem cells.** And if one takes embryonic **stem cells,** whether they're from mice or from human lines that exist, it's possible to differentiate them in a culture dish, in a petri dish and get areas of spontaneously beating heart muscle.

PALCA: And I mean, but if you can do that, then what's the issue, what's the hurdle in terms of getting them into mice for testing and into patients for therapy?

Dr. MURRY: Right. So--you know, I tell you, when you sit and look through the microscope and you see areas of spontaneously beating human heart muscle in a dish, it's not farfetched to imagine trying to take these cells and grow back human heart muscle in a patient who's suffered a heart attack or has heart failure from other causes. People in multiple laboratories, including my own, are working on this. Most recently my own group has been able to take human embryonic **stem cells,** differentiate them in a dish, get the heart-muscle cells from that cell population, and implant them into the hearts of experimental animals and grow new human heart muscle.

PALCA: And I gather quite a number of labs around the--I know there's a lab in New York here that's working on similar things. How far off do you think this is?

Dr. MURRY: Well, it--we haven't shown--this is for the human embryonic **stem cel l**-based approach as you're talking, correct?

PALCA: Yeah, primarily.

Dr. MURRY: Yeah, we haven't yet demonstrated that this results in improved function of the heart. So I think what we would have to--the next step is in small-animal models like mice and rats to demonstrate that this works. Then, before going to patients, I think we probably need to scale it up to an intermediate animal like a pig or something. And then presuming that that continues to show effectiveness, one could hope to see the first clinical trials beginning in perhaps three years or so, optimistically.

PALCA: OK. Why don't we take another call here? Let's go to Jim in Philadelphia, Pennsylvania. Jim, welcome to SCIENCE FRIDAY.

JIM (Caller): Hi. Thank you for taking my call. I'm very interested to know--I'm actually a first-year medical student, so I just got through studying the heart. Once the transplanted tis sue, the **stem-cell** transplanted tissue is put into the damaged heart, how will that implant make connections, you know, form the little synapses and gap junctions that function, you know, in a syncytium instead of just separate from, you know, the

heart?

PALCA: In other words, how do they know how to stay put?

JIM: Yeah, like, what's your research going to--like, how do you even begin to answer that question? Like, how does the implanted tissue connect and sort of, you know, communicate with the, you know, native tissue or the tissue that's already there?

PALCA: Jim, thanks for that call.

Dr. Murry, what do you think?

Dr. MURRY: That's a really good question. That's one of the big challenges at the moment. What we know is that if we take heart-muscle cells and we implant them into normal areas of heart muscle, these can form those normal electr ical junctions and mechanical junctions so that the cells will contract in synchrony with the rest of the heart. So that's very encouraging. It really gets back to Walter's question, previously. The biggest enemy we have in this regard is scar tissue. And scar tissue can serve as an electrical insulator and it can physically isolate the graft cells from the host cells. And it may prevent them from making these connections that allow for spontaneous transmission of electrical impulses to them. And if that proves to be too thorny of an issue, we may have to actually put in a pacemaker to try to pace the graft cells directly.

PALCA: Interesting point.

Let's go now to Sarah in Portland, Oregon. Sarah, welcome to the program.

SARAH (Caller): Hi. Nice to speak with you.

PALCA: Good to talk to you. What's your question?

SARAH: Well, a little bit related to heart muscl es--I was wondering if this technology translates to repairing regular muscles in the body. I have a stomach muscle--part of my stomach muscle had to be removed a few years ago because of a tumor that was growing on it, and they replaced it with mesh. And it, of course, impairs my function somewhat. And I was wondering if eventually someday that muscle can be regrown.

PALCA: Interesting question. Thanks for that, Sarah.

What do you think, Dr. Murry?

Dr. MURRY: I think that skeletal muscle--so what Sarah's talking about is skeletal muscle or voluntary muscle that is present in our body wall and arms and legs and so forth. It's probably going to be easier to regrow skeletal muscle than it is to regrow cardiac muscle. I think many of the techniques are already in place. And there are a number of groups that are working--the University of Washington and elsewhere--to

regrow skeletal muscle for applications just li ke that. I think the kind of approach I described earlier where a tissue-engineering strategy is taken using a biomaterial scaffold, seed the cells that you want onto it, and then use that to repair a defect could be very promising for a case like Sarah describes.

PALCA: Now we were talking earlier about the possibility of using **stem cells** derived from embryonic **stem cells.** What about the possibility that these cells, once they were implanted, could suddenly turn into a tumor of some sort?

Dr. MURRY: Well...

PALCA: Yeah.

Dr. MURRY: ...there are two things, Joe, that keep me up at night worrying about complications of the kind of work that we're doing. One is that we would create electrical disturbances that would perhaps result in lethal arrhythmias in the heart. And the second is that somehow the cells that we would introduce might not grow the way w e want and that they would create a tumor.

What we know is at the moment with adult **stem cells,** the likelihood of creating tumors seems quite low. With embryonic **stem cells,** on the other hand, it's a much more real danger. And we've demonstrated, for example, that if one just takes a simpleton's approach--you know, take the undifferentiated cells, squirt them in and hope for the best--this doesn't work well at all; that you do, in fact, grow a specialized kind of tumor called a teratoma in the heart. And this was done in experimental animals. But the last think we would want to do to a patient, of course, who suffered a heart attack is give them a cardiac tumor to worry about. So we're going to have to have safeguards in place to make sure that these undifferentiated cells don't go into the heart and create tumors, that instead we have a very well-characterized population of cells that are further down the road in terms of t heir differentiation status.

PALCA: All right. We're talking with Dr. Chuck Murry at the University of Washington about the possibility of using **stem-cell**-based research to repair the heart.

I'm Joe Palca. And this is TALK OF THE NATION from NPR News.

And let's take another call now. Why don't we go to Will in St. Louis, Missouri? Will, welcome to SCIENCE FRIDAY.

WILL (Caller): Yes, thank you. I've had coronary bypass surgery. And I figure that if I'm still around by the time these implanted grafts wear out, maybe this technology will be available to replace them and keep me going. What I'm wondering about is the actual methodology for getting the **stem cells** into place to grow the new blood vessels that you discussed earlier. Can you--and will there be a possibility of doing that in an angioplasty-type method without actually making chest incisions an d doing open-heart surgery to implant them from outside the heart?

PALCA: OK, Will.

Dr. Murry, I gather there are a couple strategies for doing that right now.

Dr. MURRY: There are. And this is something that the medical device companies are working on very hard right now. I think it's a promising new area of research, because obviously nobody wants to have their chest opened if they can at all avoid it.

A couple of strategies that one might think about--the easiest one, of course, would be if we had cells that were smart enough to home to areas where this was needed. They could be injected simply through a vein, an intravenous injection; they could home to the areas of injury, and they could naturally result in the growth of new bypass vessels.

We know that this happens to some extent when you have an acute injury. In other words, if a patient has a heart attac k and maybe one or two or three days afterwards these kind of cells will home. In a patient such as yourself, well, it's less--you know, when a person's long out from having damage to the heart, it's unlikely that he area of injury is hot enough to make these cells home. So then I think we're talking about catheter-based approaches like you described. One possibility would be to have something with a needle where you could just, through a catheter, poke a needle directly into the wall of the heart and deliver the cells to the site where you want.

Other approaches that people are working on are to go in through the coronary arteries or the coronary veins themselves and either deliver downstream into the circulation or poke right through the wall of the vein or artery and deliver a population of cells right around an area of obstruction so that perhaps a natural bypass could be stimulated.

PALCA: OK. That's interesting. Well, I guess tha t day is not so far off. And some people think that California might be the place that these cures are going to come from because of that large **stem-cell** initiative voters there passed. What do you think about that?

Dr. MURRY: Well, Proposition 71, as it was called in California, is going to change the landscape of the way **stem-cell** research is done in the United States and maybe in the whole world. Just to give you a sense of scale, last year in the United States the federal government, who's of course the biggest supporter of research in the country, spent about $25 million on human embryonic **stem-cell** research. Next year, the state of California is going to spend $300 million on **stem-cell** research, most of it on human embryonic **stem cells.** So this is probably going to be the **stem-cell** equivalent of a gold rush that comes to California. And other place s, like the state of Washington where I happen to work, are concerned that there's going to be a brain drain and that many of the top scientists would end up leaving their universities and companies to set up shop in California.

PALCA: Are you thinking about doing that?

Dr. MURRY: I tell you, it's tempting because, you know, it's a constant struggle to find

research dollars to support my own laboratory. We're, of course, totally grant dependent. And to have access to funding like that--I mean, I'd be dishonest if I said it wasn't tempting.

PALCA: All right. Well, we'll have to leave it there. Thanks very much for talking with us this hour.

Dr. MURRY: You're very welcome.

PALCA: Chuck Murry is a pathologist and director of the Center for Cardiovascular Biology and Regenerative Medicine at the University of Washington in Seattle. And thanks to all my guests and ca llers this hour for making such an interesting show.

(Credits)

PALCA: If you'd like to write to us, please send your letters to SCIENCE FRIDAY, 55 West 45th Street, Fourth Floor, New York, New York 10036. For Internet mail, you can e-mail us. The address is scifri@npr.org. Check out sciencefriday.com for more information and links to today's program. You can listen to past editions of SCIENCE FRIDAY online or take them with you from the iTunes Music Store. And check out SCIENCE FRIDAY's Kids' Connection, free curricula material for teaching science using SCIENCE FRIDAY. Just click on the `teachers' link on sciencefriday.com.

For NPR News in New York, I'm Joe Palca.