

## BroadcastMed | Cardiac Cell Repair Therapy: A Clinical Perspective

BERNARD GERSH: I'm Bernard Gersh, consulting cardiovascular diseases at the Mayo Clinic, and Professor of Medicine at Mayo Clinic College of Medicine. And this interview is really based upon a review that I just published with some of my colleagues-- both in the clinical and the basic sciences-- on stem cell therapy, or cell repair therapy, a clinical perspective. And it's really a review of stem cell therapy from the cardiovascular standpoint.

Embryonic stem cells, of course, are, in a way, the prototype of a stem cell. An embryonic stem cell certainly can form a cardiac myocyte. But it can also become a tumor cell. An embryonic stem cell is a little bit like an undisciplined child. You don't know what quite direction it will go.

And so some of the work done at Mayo Clinic by Dr. Andre Terzic and his colleagues-- and he's one of the co-authors of this paper-- is to take these embryonic stem cells and guide them down a particular developmental route. So, as to take these cells, and basically treat them with a number of molecules so that they become cardiac cells, and not tumor cells. That's a very interesting group of cells.

I have a tremendous amount of interest in what are called mesenchymal stem cells, that are more primitive than the adult bone marrow cell-- not as primitive as an embryonic cell, but they are more primitive cells. And they've now been tested in clinical trials. The first clinical trial is now ongoing, on using what we call resident cardiac stem cells. And these are stem cells that appear to reside within the heart. We don't quite know what they do and why they are there, because they're obviously not enough to heal the heart after a myocardial infarction. But they did, and of course, that's of interest. Because if we can culture them-- which can be done-- and clone them and give them back, maybe they are certainly promising for repair.

It's interesting that fat cells-- adipose tissue-- is a rich source of perhaps mesenchymal stem cells, and also may be a rich source of a completely new technology, which is to take adult cells and reprogram them back to being stem cells. And it appears that just in the last week, that one group has been successful in taking adipose, or fat cells, and reinducing them-- or reprogramming them-- to be stem cells. And, of course, the attraction of adipose tissue is it's in no short supply in all of our society.

And then, this just incredible series of experiments that I've done in the last year, which is called the induction of pluripotent stem cells. Now, to understand what this-- this technique takes adult stem cells-- fibroblasts-- from the skin, or-- as I mentioned-- fat cells, adipose tissue. And then, by genetic reprogramming them, it takes this adult cell and turns it back into a stem cell.

Of course, this avoids all the huge social and ethical implications of embryonic stem cells, because that is a very legitimate debate. I mean, people have very polarized views about embryonic stem

cells. And it's not going to go away. It's a religion with debate. So this technique of induced pluripotent stem cells is fascinating. And what is so exciting about it is within-- I think-- weeks or a few months after the original experiments in Wisconsin, and-- I believe, in University of Wisconsin and Japan-- everybody else who tried this has been able to reproduce it, including our own laboratory.

So there are problems, because these stem cells-- again-- have the ability to go in different directions. But I think that's something one should really follow. It's very exciting.

Well, I think that all the animal in preclinical studies have been extremely promising, almost too good to be true. It doesn't matter what cell you use-- it appears-- what dose, where you give it, when you give it, how you give it-- just experiment after experiment, study after study shows an improvement in cardiac function, contractility. Some showed improvement in blood flow. It's like everything works.

And that's part of the puzzle, because we know that these cells do not survive. So really, what is going on? I mean, it's an overwhelming preclinical and animal evidence of benefit. And one of the explanations is that the cells don't work for the reasons we think they do. What we would like to do is put the cells in, have them replicate, generate new muscle cells, and that's the theory. That's the hypothesis.

But there's now another concept that's perhaps prevailing, the so-called Paracrine Hypothesis. And that is that it's not the cells that replicate that result in improvement in cardiac function, it's that these cells secrete proteins and molecules that, in themselves, may have a beneficial effect on contractility, on metabolism. The so-called prevailing-- the Paracrine Hypothesis.

It's quite fascinating, really. I mean, it's almost like you would milk these cells like you'd milk cows. You've milked the cell for whatever it is they produce, and then, that's what you'll give. Now, I don't know if it's going to work out that way, but certainly, at the moment, what we have to say is the degree of benefit appears to be out of proportion to the numbers of cells that we inject and their ability to survive. So other mechanisms prevail, and it's fascinating. It's part of the major interest in this whole field. And the same things happen in the clinical arena. There are modest benefits on function, but the cells don't survive.

Now, it may be that in 10 years' time, it's different. There are a lot of barriers set up that do not work in the cell's favor-- inflammation, scarring, just a whole host of barriers. And so it's not surprising, perhaps, the cells don't survive-- or at least, in the qualities we would like.

Now, ongoing research is attacking those barriers. And it may well be that new techniques offer and

enhance the survival of cells. And then, the mechanism of benefit will swing back again. Right now, it's the Paracrine Hypothesis, could be in 10 years. In fact, it may be cell survival again.

Having said that, I mean, the trend is always towards the positive, by and large. The worst I've seen is neutrality. But the majority of studies-- vast majority-- are positive. That's in the animal and pre-clinical.

Now, in the clinical studies, the benefits one has to say are modest at best, but always in the right direction. There are people that feel strongly that it is absolutely premature to be doing the clinical trials that we do, given the fact that we really do not understand how the cells work and the mechanisms of benefit. And that's a fair viewpoint.

The counterpoint to that is the many precedents of clinical trials providing answers or providing answers that generated new questions. And let me give you an example. Aspirin was around for 100 years before we knew its benefits on platelet function. The angiotensin-converting enzyme inhibitors, the ACE inhibitor drugs, they were blood pressure lowering drugs. We've now found out-- as a result of trials-- that some of the major effects are at cellular level on the basic pathophysiologic aspects of atherosclerosis. We wouldn't have found that out if we had not done the trials.

I can understand the apposition to trials. Equally, I would argue that every trial has either been neutral or positive, not harmful. And that, in a way, is a stimulus to do further trials. What I think is important is that if we run away with ourselves and we do a huge multi-million dollar trials and they are negative, we will kill this field. Because funding is like international capital funding, wants a return on its investment. And the funding agencies do not want to fund negative trials.

So I think what's really important is to be modest about the trials, is for clinicians to work with basic scientists, and to design trials that are really focused on specific mechanistic questions-- what cells? What dose? Where should we give them? When should we give them? How should we give them? What adjuvant therapies can we do? Just chip away at this bit by bit, chisel away.

To try and do a 50,000 patient trial based on mortality and heart failure would be premature. And I wouldn't want to see that. So I think we need to do small, focused, mechanistic trials. Now, one or two trials will be bigger. And there's one being set up in Germany that's looking at critical endpoints. And that's fine. I think that's fine. But the bulk of the studies in the United States and in Europe are going to be, I think, much more focused and mechanistic.

It's not as simple as we thought it was. This is not going to be a part of our clinical routine, clinical

armamentarium tomorrow. And we need a lot more answers. But I would fall on the side of people who say we should continue with trials, but be very specific about what each question is going to be asked.

About five years ago, a house of lords in the United Kingdom had a committee to look at science-- the House of Lords select committee. And there's some interesting statements that came out of it. And really, others have pointed this out too, that public's understanding of science is often inadequate. But as scientists, our understanding of the public perceptions is often inadequate.

And I think what came out of this committee was as we get into these areas of cloning and stem cell therapy-- pretty fundamental issues-- there is a real responsibility to engage the public. After all, this is done on taxpayer money. I mean, this is not just a simple experiment. I mean, we're out there very much in new territory. And I think it's really important that-- both from an ethical and other standpoint-- that the public be fully engaged.

I think the phrase that was used which I quite liked, was I think, involving the public in the decisions is something like the social equivalent of informed consent. I don't think I quoted it exactly right, but a nice term or phrase. So I think what is important, we read in the papers that stem cell therapy is here tomorrow. Why is the administration not funding it? We have a cure for Parkinson's disease. We have a cure for paraplegia. It's not there. It's down the line. And it may not happen, but it may.

But it's our job when that comes-- to be sure when we read those kinds of articles-- to be sure that there's responsible reporting. I think that there is now a massive worldwide effort to expand and understand this technology. It may bear fruit from a clinical standpoint in the future. And we simply don't know.

It is too early to accept that this is going to be a routine part of what we do clinically in a year or two-- far too early. It's down the line and in the future. What I'd say, though, to patients and to physicians who may not be interested in the field, don't ignore it. I don't think it's going to go away. I hope it doesn't. You don't have to become a stem cell biologist, but watch it, even if it's from a healthy distance. But I would just stay tuned.

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