

Brave Pioneers or Clinical Cowboys?

As some stem cell researchers move ahead with clinical trials of new therapies, they're facing criticism from others in the field who argue the transition is premature. Tensions between the two factions have been intensified by the spotlight of political controversy and media attention, triggering heated debates in the pages of journals and at meetings.

"People have very firm viewpoints on this," says Joshua Hare, a cardiologist and director of the Interdisciplinary Stem Cell Institute at the University of Miami's Miller School of Medicine. "There are different schools of thought because people perceive the stakes as so high."

Among researchers investigating potential cardiac therapies based on adult stem cells—currently one of the more contentious areas of research—"There's a huge spectrum of skepticism and concern, and enthusiasm," according to Richard Cannon, a cardiologist at the National Heart, Lung, and Blood Institute (NHLBI). "I don't think I'm overstating the tension there is between basic scientists and clinical investigators, at least in some quarters."

George Daley, a hematologist and director of the Stem Cell Transplantation Program at Children's Hospital Boston, attributes that largely to "a clash of cultures" between basic scientists and clinical investigators. Hare, who has begun clinical trials using bone marrow-derived stem cells to treat heart disease, agrees, saying, "Someone who sees patients and treats patients is going to be much more comfortable taking these therapies into trials, particularly in settings with major unmet needs."

The debate flared up at the NHLBI's third Symposium on Cardiovascular Regenerative Medicine late last year where clinical investigators were the targets of criticism during a panel discussion. Cannon, who is investigating the potential of bone marrow-derived stem cells to repair diseased and damaged blood vessels in patients with coronary artery disease, says, "We were pretty much taken to task for endorsing or performing clinical research without knowing everything there is to know about the mechanism of cell-based approaches to heart disease."

Clinical investigators, Daley says, "are much more tolerant of uncertainties in mechanism, whereas "arguably the greatest insight into mechanism comes from the stem cell scientific community," he adds. "I think that's where cultural wars will be fought."

Daley describes himself as "fairly conservative" on the matter of when it's appropriate to begin clinical trials of adult stem cell therapies. Understanding the mechanism of action isn't an absolute prerequisite, he says, but if it's not clear, "that does have to give one extra pause" if there's even a plausible risk to patients.

Nonetheless, Daley says he has "a healthy respect for the value of pure empiricism in medical innovation."

Many therapies that are commonly used today, Hare points out, were administered to patients for years before researchers understood their mechanism of action. When bone marrow transplants were first performed, for example, no one really knew how they worked. Plenty of other invaluable therapies, such as lithium, which has long been the standard treatment for bipolar disorder, remain largely a mystery in terms of their mechanism.

"If a patient had a problem," Hare says, "and there was a proven treatment, but we didn't know the mechanism, most treating physicians would use it."

Martin Friedlander, a cell biologist and ophthalmologist at Scripps Clinic and The Scripps Research Institute, says, "I'm not so hung up on the mechanism thing, I'm hung up on the safety thing." In particular, says Friedlander, who is investigating the use of adult stem cells to treat vision loss, but hasn't tested the approach in clinical trials, researchers should know exactly what kind of cells are being administered, and understand how they may behave, before testing them in humans.

"If there's evidence from large animal models that the cells do something beneficial, even if you don't know exactly how they accomplish that, and as long as there's no suspicion harm, I think it's reasonable to take those cells into trials in patients with potentially life-threatening heart disease," Cannon says.

"There's only so much you can learn about what cells can do and can't do," from animal studies, Cannon adds.

"The field is bound to move forward prior to us having a really good sense of the range of risks and rewards," Daley says. "This is something that is seen with any new medical technology. There's nothing new with stem cells other than them having attracted a lot of attention."

Unfortunately, Daley adds, the attention that's been paid to stem cells and their therapeutic potential—largely because of the political controversy over human embryonic stem cell research—has fueled medical profiteers.

There are advertisements all over the Internet from clinics around the world, touting stem cell treatments for everything from spinal cord injuries to autism to cancer. "It's unethical, and in the United States, it would be illegal," Friedlander says.

The therapies on offer at these rogue clinics may be pointless, or potentially dangerous, but there are plenty of people facing the prospect of losing their vision or living the rest of their life in a wheelchair, who are prepared to take that chance.

"There's so little being offered in the United States that people are leaving," says Hare, who sees that as all the more reason to proceed with clinical trials of potential stem cell therapies. He'd like to see a clinic set up in the United States to do "aggressive translational work, so that these poor people can get therapy ethically, rigorously, and with proper monitoring, and they can get the best therapy available. These programs need to be under FDA-approved research protocols so we can learn and optimize the approaches."

Daley worries that all the attention that's been paid to potential stem cell therapies has not only created an opportunity for medical profiteers, it's also generated tremendous optimism that can all too easily veer into wishful thinking. "There are some people out there who think they know more than they do," Daley says.

"It's like anything else. You're always going to have cowboys and cowgirls who are out there doing stuff before everyone else," Friedlander adds. "You've got

these predators who are looking to make a quick dollar, and then there are clinicians who are well-meaning but relatively uninformed about how to use these cells," Friedlander says.

"It's pretty easy for professionals in the [stem cell] community to look at some of these and recognize what's beyond the pale, but there's a huge gray area," of work that's well intentioned but misguided, Daley says. He regards cardiac stem cell therapies as a prime example of clinical studies that are advancing without an adequate understanding of mechanism, "There are a lot of stem cell biologists who believe they are an enormous waste of resources."

The criticism irks Hare, who is conducting Phase II trials using bone marrow stem cells, administered intravenously, to treat patients after heart attacks.

"We've done everything right. We should be beyond criticism," Hare says. "It's hard to understand why people stand up and say, 'You've gone too far.' The arguments against moving into the clinic go against conventional wisdom. We're following basic principles of therapeutic development," Hare adds. "No one would have questioned this if we were developing a drug."

Cannon says some of the discomfort over stem cell-based approaches to the treatment of heart disease may be because "we're talking about a very new approach." While hematologists have been using cell-based therapies for decades, for cardiologists, "this is a new paradigm," he says.

Friedlander worries that some researchers "may not have a clear understanding of how much damage you can do with an approach that hasn't been thoroughly vetted. If someone jumps the gun and there's a setback that's serious," he adds, "that puts the whole field back."

Gene therapy is a case in point. It was hailed as a potential medical revolution during the 1980s, but later clinical trials yielded disappointing, and in a few cases, tragic, results, although Hare says, "We learned something really important—that it had unanticipated toxicity."

Daley says those trials were premature and researchers had yet to learn how hard it would be to achieve gene transfer. That's a good lesson for the stem cell field, he says. "We've not yet faced the sobering reality of how difficult it's going to be."

It won't be easy, either, to achieve an armistice among stem cell researchers.

Those on the frontlines agree, though, that rather than letting the two sides huddle in their trenches, emerging only occasionally to face each other in battle, it's essential to get the warring factions engaged in productive discussions.

"We need to get basic scientists and clinical researchers in the room together so they can talk about their motivations and views and experiences," Cannon says, "so hopefully the field moves forward." The NHLBI aims to accomplish that via its Progenitor Cell Biology Consortium, established last fall.

It's also a goal of the ISSCR, says Daley, who was president of the society from 2007–2008 and led the ISSCR task-force that developed guidelines for human embryonic stem research. "We're trying to create opportunities to bring those two communities together."

"It should be a partnership," Cannon says. "Clinical trials should proceed along with basic research. It's not an either-or situation." After all, he adds, there's a good dose of mystery in medicine. "To wait to understand everything about these cells may delay the potential they have for therapeutic use. There's an unknown, and perhaps an unknowable."

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