Conversations With Researchers

Why We Need to Study Embryonic as Well as Adult Stem Cells

TERRY BURNS INTERVIEWS CATHERINE VERFAILLIE

Catherine Verfaillie, M.D., earned her medical degree from the Catholic University of Leuven, where she is now director of the Stem Cell Institute and one of the world's leading experts in adult stem cell research. Previously at the University of Minnesota, she founded the nation's first stem cell institute and was responsible for identifying multipotent adult progenitor cells (MAPCs), the first adult stem cell type shown to generate all major classes of tissues and cell types. Among her numerous honors, she was named by *U.S. News and World Report* as one of the Ten Innovators of 2001.

Burns: *As one renowned for your work with adult stem cells, have you had any personal experience in the political debate about adult and embryonic stem cells?*

Verfaillie: Yes, especially when I was in the United States, less so in Europe. I actually testified for the commission on stem cells put together by President George W. Bush during his first four years in office. It was a fairly conservative committee that wanted me to say essentially that I thought adult stem cells could do everything that embryonic stem cells could do, which I refused to say.

My research on adult stem cells has been misused a lot. People put words in my mouth using my research to support their arguments against embryonic stem cells. There are huge reasons why we have to study embryonic stem cells as well as adult stem cells.

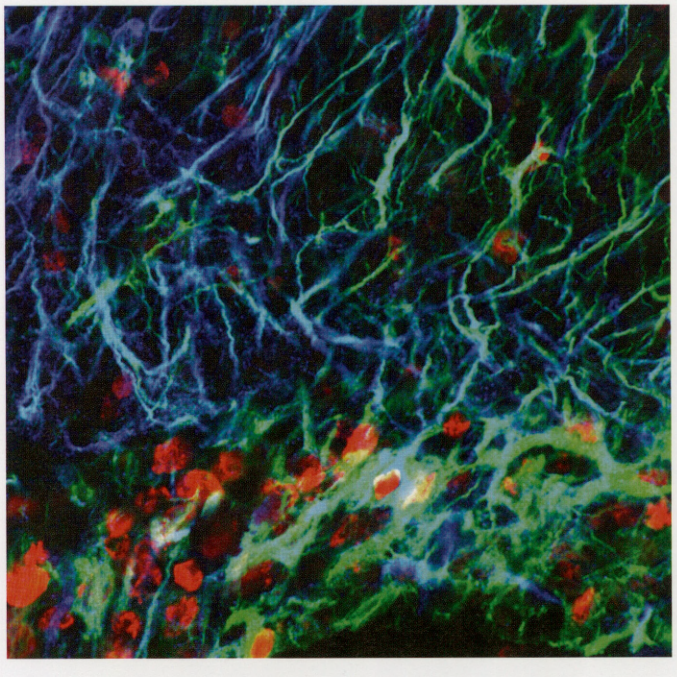
Burns: *What do you realistically think stem cells will or will not be able to accomplish for medicine in the future?*

Verfaillie: What is in the newspapers is not exactly what I think that stem cells might or might not be able to accomplish. The newspapers never talk about using stem cells to understand human development; the newspapers never talk about stem cells to develop medications; the newspapers don't talk about using stem cells to understand disease.

Stem cells allow us to assess the toxicity of medications on various types of human cells without using animals. If you were to make stem cells from embryos or individuals with genetic diseases, you would have human models to understand disease that are not currently available. I actually think these will be some of the biggest payoffs of stem cell research—not just taking the cells, culturing them, expanding them—making all sorts of things out of them and putting them back in.

In terms of specific diseases with which I think stem cell research may pay off within the next one to two decades, I think Type 1 diabetes is probably very high on the list—the advantage being that you don't have to integrate the cells in an organ. I know people talk about treating Alzheimer's and all kinds of diseases with stem cells, but brains are pretty complicated.

I'm aware of one recent study that came out suggesting that stem cells aided in Alzheimer's disease, but the researchers didn't actually



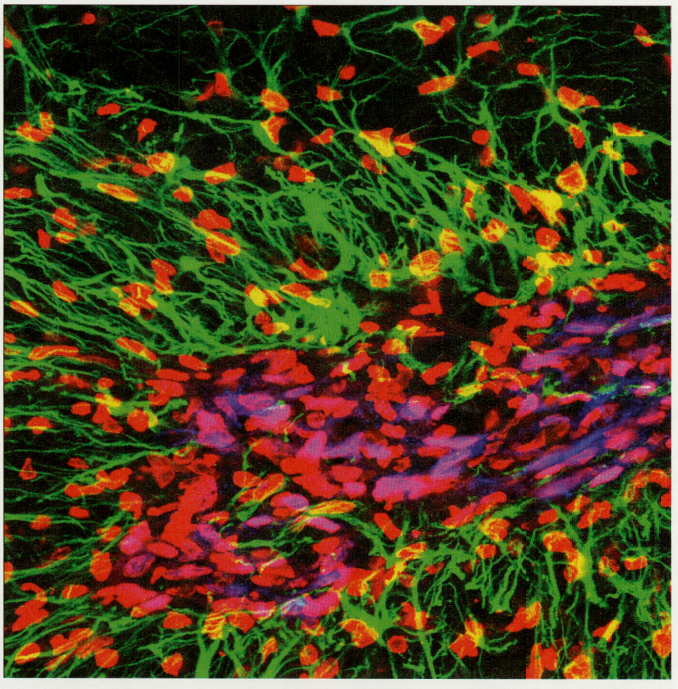
Some studies have argued that adult stem cells are almost as powerful as embryonic stem cells. However, many of these studies have suffered from methodological flaws. Verfaille's lab showed that BrdU (red), a marker used to track transplanted stem cells, can be released from transplanted cells that die. The label is then picked up by normal dividing brain cells, making them look like the transplanted cells.

STEM CELL PHOTOS THIS SPREAD: TERRY BURNS

replace anything. The approach in the study was actually a way of getting growth factors into a person, which is probably going to help a number of diseases, chiefly diseases associated with hypoxia, I think. I doubt whether we are going to be able to make new kidneys, new livers, new whatever.

Can we fix hearts? Through the mechanism of growth factors, probably Yes. By replacing the eight or nine square centimeters of heart tissue lost in an infarct. I think it is going to be a while. We can't even fix an infarct yet in a mouse heart, and it isn't even ten square centimeters in size. So I think it's going to take some time.

I think there are certain diseases that stem cells could successfully address. If you think about the brain, maybe Parkinson's, but it's not all that simple to get the cells to do what you want them to do and not do what you don't want them to do. That's why I think that one or two decades from now the understanding of development and disease, and using them to develop drugs, will pay off much faster than simple cell-based therapies.



One challenge of transplantation therapy is to ensure that cells survive after transplantation. This picture shows reactive astrocyte (green), responding to transplanted cells (blue).

Burns: *What are your thoughts about reports that certain ESCs may soon go to clinical trials?*

Verfaillie: I think we know little about how to program a cell, little about how to fit cells back into animals or humans, even in areas where there has been an enormous amount of work. If you look at what has been accomplished in mouse models of cardiac disease for instance, it's pretty close to zero. There are a couple of groups that can now make cells survive a little bit after transplantation, but they do not connect to the other cardiac cells.

In fact, the results of using ESCs or cardiomyocytes are no better than putting some totally unrelated cell type into the heart. You get a little bit of benefit, but it's not as though the cells are functionally integrating into the diseased heart, which is ultimately what you want.

I think we might not be too far from producing pancreatic beta cells, and that might allow movement forward for diabetes treatment. One could theoretically put the cells in an encapsulated type of system under the skin. So if a problem occurs, it could always be taken back out. The person won't die if you take the cells out because you can always put that person back on insulin.

So if you need to stratify risks, that seems be one of the areas that actually might be less risky to start trying to figure out how dangerous it is actually to take embryonic stem cell-derived cells back in vivo.

Burns: *The idea of "therapeutic cloning," and more recently iPS cells and adult stem cells, have all been suggested as ways to attain patient-specific stem cell lines that will not be rejected. What are your thoughts on these approaches?*

Verfaillie: There are two ethical problems with therapeutic cloning. Firstly, you make an embryo, the equivalent of a blastocyst, that could theoretically be used for procreation. But this is not going to happen tomorrow since its so hard to do in mice. Secondly, you also need a huge number of unfertilized eggs, and women are not completely happy to go through hormonal stimulation just to donate eggs.

So far, it's not totally clear if human iPS cells are equivalent to human embryonic stem cells, though I don't think it's going to take all that long to prove beyond any doubt that you can make something equivalent to ESCs. Also, there lots of different versions of adult stem cells with varying degrees of pluripotency.

From a practical standpoint, though, I ultimately don't think that stem-cell based therapies will use

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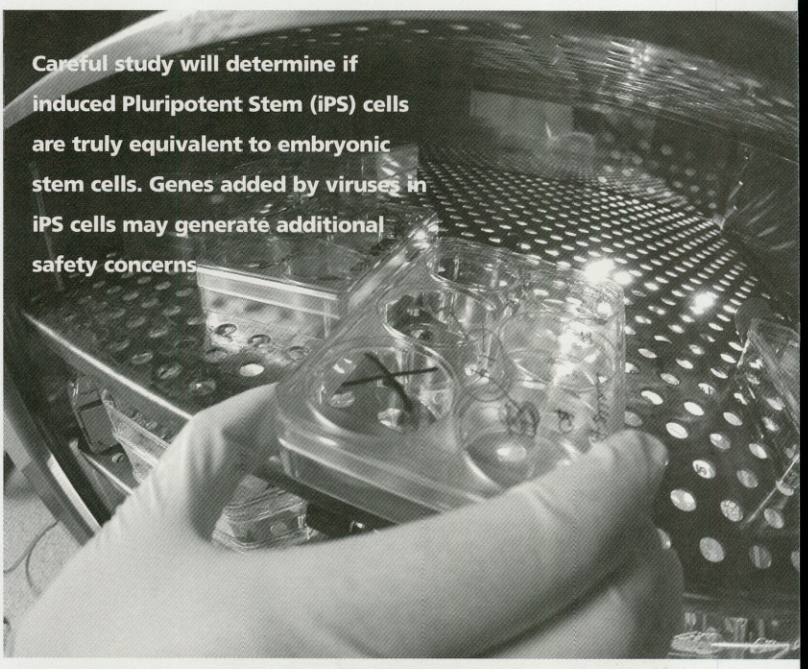
Kaufman: Well, there's a lot of confusion about what is permitted and what is not. The National Institutes of Health does fund human embryonic stem cells. George W. Bush supports human embryonic stem cells in the sense that he allows federal funding for such work with the caveat that we use only those lines derived before August 9, 2001. There's a lot we can do with these so-called "existing" federally approved cell lines.

There's a lot that we'd also like to do using newer cell lines that might be important for eventual therapeutic applications and developing disease models, but we are restricted. I guess I've done this long enough that I've become accustomed to the restrictions and understand that we just do what we can even though there's a lot that we can't.

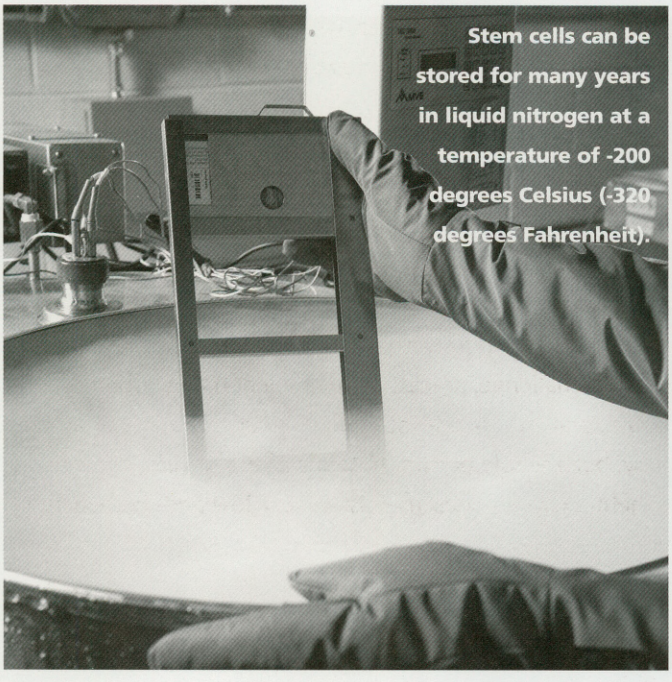
Hopefully things will change—one way or another; we'll either get private funding for more research or it will be approved at the federal level. This is an interesting area to be in—it's cutting edge stuff. If you're doing research, this is where you want to be

Burns: *How would you answer someone who likes the idea of embryonic stem cell research but is concerned about the idea of destroying an embryo.*

Kaufman: The important thing to recognize is that all of these embryos come from IVF / fertility clinics. I explain to people that these embryos were created for people who can't have children. This is a routine procedure. There are more than one million children who have been conceived through the process of IVF. It works and people don't complain about it, but during the process of IVF technicians always fertilize additional eggs and freeze them. If the couple wants more kids, they can go back to the freezer. But eventually, they have to figure out what to do with the extra embryos they haven't used.



Careful study will determine if induced Pluripotent Stem (iPS) cells are truly equivalent to embryonic stem cells. Genes added by viruses in iPS cells may generate additional safety concerns.

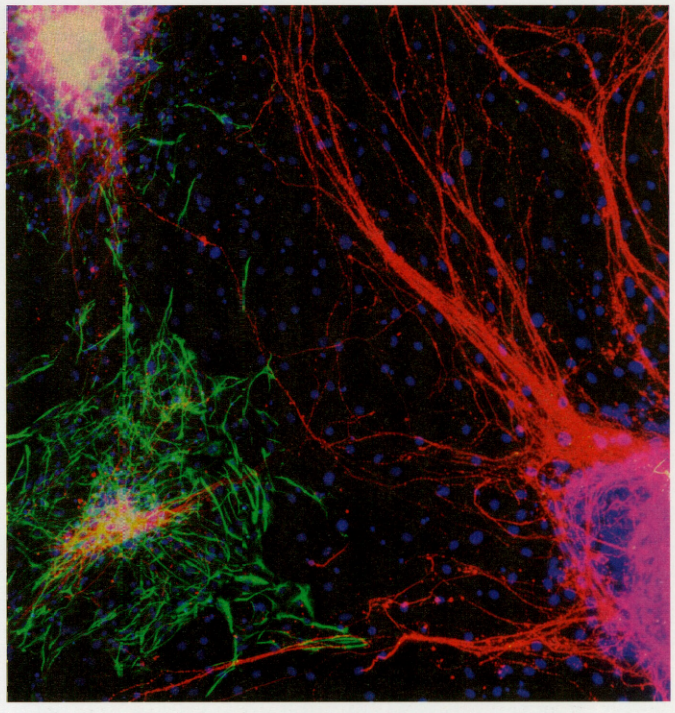


Stem cells can be stored for many years in liquid nitrogen at a temperature of -200 degrees Celsius (-320 degrees Fahrenheit).

Usually, they will be discarded. However, instead of discarding the embryos, they could be used for stem cell research—for studying blood cell, nerve cell, liver, and pancreas development. The important thing to recognize is that if none of this human embryonic stem cell research went on the number of human embryos saved would be zero. They would all be destroyed anyway. So if you're not going to save anything, why not go ahead and use the embryos to come up with potential therapies and understand developmental processes?

Burns: *Why do you think there is such opposition to embryonic stem cell research?*

Kaufman: It's politics. People want to stay in power, so they confuse others and use fear to retain their power. It is amazing how this happens. Most people who take the time to learn about embryonic stem cell research understand what is happening and are very supportive. If you look at the national surveys, more than 60 to 70



percent of the U.S. population supports stem cell research. I usually tell people that if you put them in a room with me for five minutes, that number goes up to about 95 percent.

Once I tell them what I just told you, people say "Oh, so what's the problem?" There really isn't a problem—it's just a matter of using confusion to gain votes. And it's not just stem cell research that's being used to do this. I just heard a discussion on National Public Radio this morning about global warming. Certain people are opposed to doing something about global warming because they think there's something wrong with the science. Well, the jury's not out; the scientists all agree. But for political reasons, some people want to make this a divisive issue.

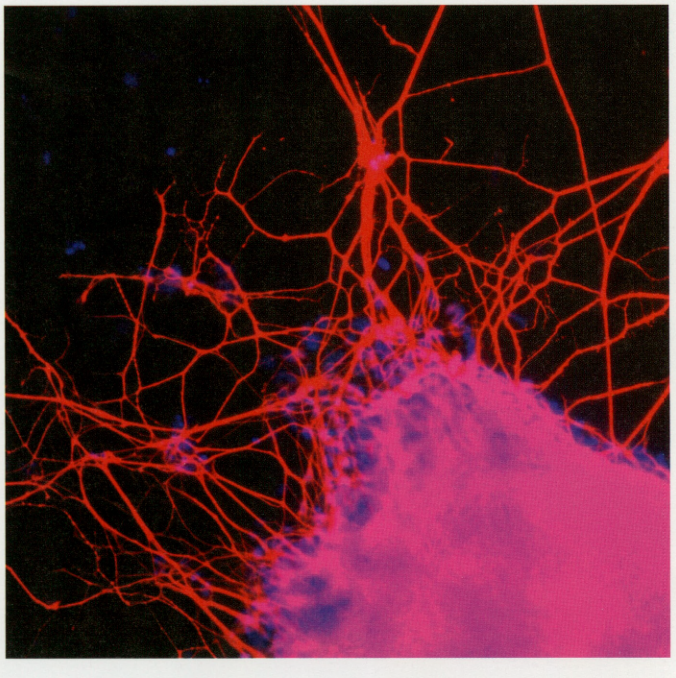
There's really no one scientifically opposed to human embryonic stem cell research—it's all politics. I think that even the ethical arguments are pretty weak, unless you want to shut down the IVF clinics. I find it entirely consistent if people want to shut down the IVF clinics and prohibit hESC research. That's fine. But IVF works, and you're not going to deny that to people. I think that once the hESC therapies start working and we don't run into problems this research will be a great boon.

Burns: *What are your thoughts on induced Pluripotent Stem (iPS) cells?*

Kaufman: This involves turning fibroblast cells into ESCs using only four genes. This was done with mice in 2006 and is possible now with human cells. This is very interesting and I think of potentially great importance. The key issue now is to compare these cells head to head with hESCs. Embryonic stem cells really remain the gold standard.

People have been studying mouse ESC cells now for almost thirty years. We have been studying and comparing human ES to mouse ESCs since 1998, so human ESCs are now very well-accepted. Hundreds of labs around the world use them. I think there will be a lot of refinements to iPS cells in the next year or two. This is very interesting.

A lot of the people who were opposed to hES cells now say that research with iPS cells is acceptable. But you need to realize that the people who did the work were actually using hESCs to develop iPS cells. So without the hESCs we could not have arrived where we are. ■



Left: Embryonic stem cells are very powerful, but can be difficult to control. Here identical embryonic stem cells generated completely different types of cells side-by-side in a dish. Below: Although embryonic stem cells can make functional neurons in a dish (red), it may take many more years before scientists will understand enough to help transplanted neurons recreate normal brain circuitry after stroke or other brain injury.

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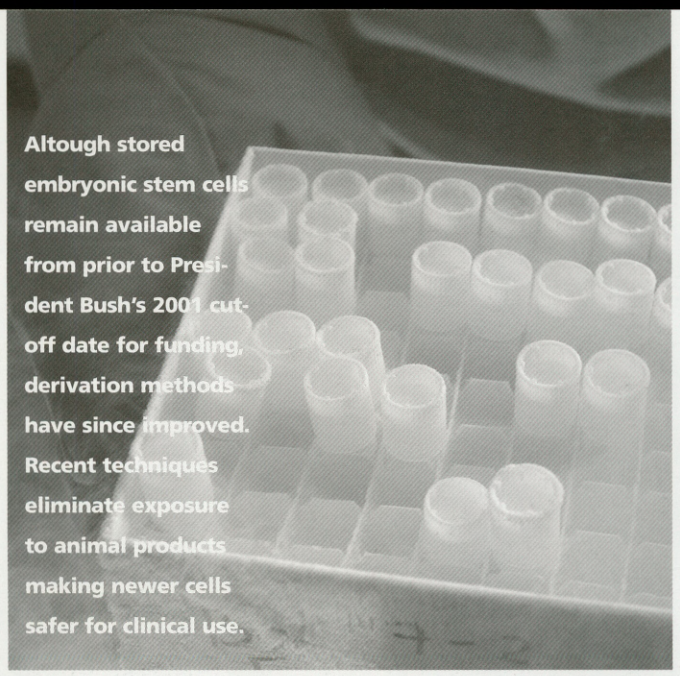

Altough stored embryonic stem cells remain available from prior to President Bush's 2001 cut-off date for funding, derivation methods have since improved. Recent techniques eliminate exposure to animal products making newer cells safer for clinical use.

Stem Cells: The Road Forward

BY TERRY BURNS

Stem cells have experienced a tumultuous debut into public life. They have been acclaimed as the future of medicine and the solution for incurable disease, but denigrated for the murder of embryos, and funded to the tune of multiple billions of dollars by individual states. Yet President George W. Bush has twice vetoed federal funding on their research. They have proven simultaneously to be the poster child and the black sheep of regenerative medicine.

Such popularity and scrutiny have provoked a proliferation of speculation regarding their future utility. Some people have promised that, if supported, stem cells will allow paraplegics to walk again. Others have shown the striking image of beating heart cells in a dish and forecast a cure for heart attacks. Beyond the media hype, the glossy publicity images, and polarized debates, however, is a fledgling technology: a potential but unproven future leader, as yet in its formative years.

What does the future hold for these celebrated, yet microscopic icons of hope? What challenges must be faced, what hurdles overcome before the fruits of labor and sacrifice can be realized?

First, the public face of stem cells will predictably undergo continual change. Already, we have seen embryonic stem cells make everything from blood in a dish to neurons in rodent spinal cords, yet their embryonic origins remain a point of contention. We have seen adult stem cells catapulted from humble capabilities to seemingly unlimited potential, only to be largely re-humbled again by exposure of flaws in experimental methodology. We have seen therapeutic cloning celebrated as a way to generate personalized stem cells, then crushed fraudulent claims unveiled in a setting of lingering ethical concerns.

Most recently, we have seen skin cells reprogrammed into the equivalent of embryonic stem cells (iPS cells). Perhaps tomorrow we will hear about the miraculous mobilization of innate, endogenous stem cells. After their brief moment of glory, each will most likely settle into the ever-expanding toolbox of scientists as they seek the most appropriate means to understand and treat a myriad of diseases.

Second, the fireworks of publicity will most likely decline to a sputtering fizzle. Maintaining sufficient interest to fund the maturing, yet less newsworthy technology may become the major challenge as stem cells from less ethically controversial sources are used more frequently and an increasingly educated and supportive public demand that even political opponents revise their agendas.

Third, after passing from the ethical spotlight, stem cells must maintain a good reputation. Pluripotent stem cells are defined by their capacity to form tumors called teratomas. As techniques evolve to make stem cells of all types more powerful, the risk of tumor formation will demand innovation, discipline, and rigor. Thus premature clinical trials without due precautions could have deadly consequences, both for patients and for the field.

Finally, stem cells will increasingly serve more functions than simple cell replacement. In addition to value as models to understand development, disease, and drug function, stem cells may carry therapeutic genes to regions of injury, secrete protective molecules, regulate endogenous regeneration, modulate the immunologic response, and provide targets for cancer.

Although the precise road ahead remains to be charted, stem cells will predictably represent a unique and exciting chapter in the history of medicine. ■

Terry Burns, Ph.D., is an M.D./Ph.D. student at the University of Minnesota. His research involves the study of stem cell behavior in animal models of stroke. Next year, he will begin a residency in neurosurgery.