



Brigid L.M. Hogan  
Photo: Robert Rathe

# ADVANCES IN STEM CELL RESEARCH

By **Brigid L.M. Hogan**

(Ed. note: Brigid Hogan has left HHMI and is currently Chair of the Department of Cell Biology at Duke University Medical Center.)

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**T**o produce a human being, a single fertilized egg must generate billions of cells and more than 250 different cell types. Fortunately, all is not over when the last cell is made and the last organ system assembled. Throughout life, most tissues continually generate new cells, either to replace those lost by wear and tear or to satisfy increased demand. For example, when athletes train at high altitudes the number of their circulating blood cells increases in response to increased need for oxygen delivery. This capacity for cell regeneration is particularly evident in adult tissues such as skin, hair, bone marrow and intestine, but it probably occurs to some extent in most organs—including the brain, where, until recently, conventional wisdom held that neurons were irreplaceable.

The ability of a tissue to renew and repair itself depends on small groups of cells known as stem cells. These stem cells exist throughout life in close proximity with specialized "nurse" cells located in tiny niches in the body. Nurse cells provide growth factors and other signals that help maintain the unique properties of the stem cells—their capacity to generate differentiated, or specialized, progeny with a limited life span while making more of themselves at the same time. Paradoxically, stem cells divide very little, while their descendants often multiply exuberantly en route to their final identity.

Stem cells, and the various strategies they use to maintain their numbers, have long fascinated biologists.<sup>1</sup> But that interest has now reached fever pitch with the unexpected discovery that stem cells from some adult tissues can be reprogrammed, albeit at extremely low efficiency, to give rise to differentiated cells of other tissues.<sup>2</sup> For example, it appears that under certain conditions a few blood stem cells can give rise to muscle, and neuronal stem cells to blood, in adult mice. These observations raise the possibility that we might someday be able to repair damaged organs starting with only a few residual stem cells taken from another tissue in the same body.

<sup>1</sup> Readers interested in references and further reading about stem cells and the ethical debates surrounding them should consult the many review articles in *Science*, 287, pp. 1417-1442 and *Cell* 100, pp. 143-168.

<sup>2</sup> *Science*, Vol. 287, Fig. 1, p. 1428, 25 February 2000, © AAAS.

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Photo: Robert Rathe

## Many Unanswered Questions

**T**wo other scientific advances have also captured the attention of the research community as well as the general public. Last year, two research teams announced that they had isolated pluripotential stem cells—stem cells that can give rise to many different cell types—from human embryos and fetal germ cells. This followed the well-publicized cloning of the sheep, Dolly, and of mice from mature adult cells.

The serendipitous overlap of these newsworthy discoveries precipitated an international ethical storm that still rumbles on. In the United States, for example, public opposition to research with stem cells derived from human embryos threatens to prevent NIH-funded scientists from using such cells. The debate has forced many researchers to realize that they must be able to communicate effectively with an anxious public and its legislators about fundamental questions such as "When does human life begin?" "What does it mean to be human?" and "What is an embryo and when does it become a human being?"

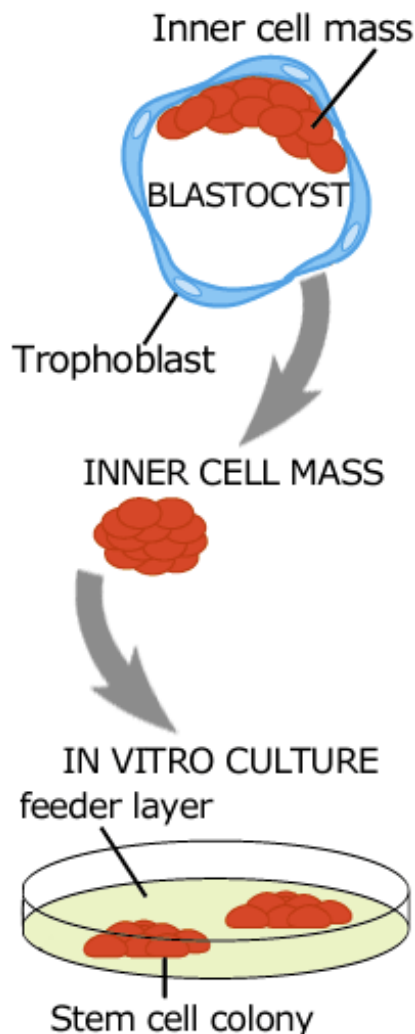
Whether science can answer these complex questions is open to debate, and is not something that I will discuss further here. I do, however, want to address the fact that we need far more information before we can answer another fundamental question: How might we use stem cells in medicine?

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### Which Approach to Take?



Human embryos in excess of clinical need and donated with informed consent are cultured to the blastocyst stage. The surrounding trophoblast layer is selectively removed by exposing cells successively to anti-human antibodies and complement, a component of the immune system. Illustration kindly provided courtesy of a collaboration between Monash University, the National University of Singapore, and the Hadassah Medical Center.

**A**t the most basic level, we still need to characterize the stem cells of all human tissues. To begin with, we need molecular markers that can separately identify the small pool of stem cells from the far larger number of their descendant cells. We also need more information about the interactions between stem cells and the niches in which they live, and how those niches respond to the body's needs. Such information, which we currently have only for the hematopoietic, or blood-producing, stem cells of the bone marrow, may suggest therapies to increase the number of residual stem cells in a damaged tissue. Already, such knowledge allows us to recreate a person's blood system from a few harvested hematopoietic stem cells.

What about a worst-case scenario, in which a chronically ill patient has lost most of the stem cells in a tissue and needs replacements to survive? Today, the most feasible option would be to supply stem cells from the same kind of tissue, but obtained from an unrelated donor. This approach involves the same serious risks of rejection associated with any organ transplant from an unrelated donor.

A better approach would be to supply so-called autologous stem cells, those that are genetically identical to the patient. This is not currently feasible, but we have ideas about how to accomplish the feat. One way would be to isolate and grow stem cells from a different tissue of the same patient, such as the bone marrow or skin, and reprogram them *in vitro*. To learn how to reprogram stem cells efficiently we need to study a whole range of experimental systems in which previously silent genes are reactivated and active ones switched off. Clues may come, for example, from studies on how the cells of an early embryo become restricted to different lineages. If we can understand the genetic circuits that control normal development, it may become easier to flip the switches in the laboratory.

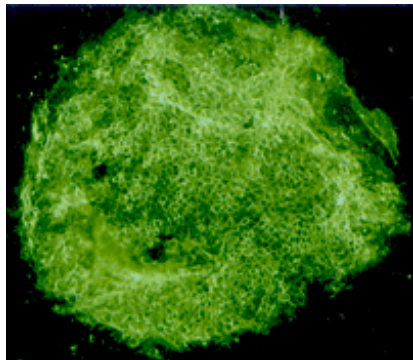
A second approach is to use pluripotent stem cell lines derived from embryos at the blastocyst stage, reached soon after fertilization of the egg and before implantation into the uterus. Blastocysts, which consist of about 100 cells, contain a few unspecialized stem cells that can be coaxed to multiply indefinitely in culture (see Figure at left). Under appropriate conditions these cells will give rise to many different cell types. The first human pluripotent stem cells were derived from blastocysts obtained from an *in vitro* fertilization clinic because they were in excess of clinical need. This milestone occurred in 1998 in James Thomson's lab at the University of Wisconsin, Madison. A group at Monash University in Australia has recently achieved similar results (see Figure on next page). Both groups are currently characterizing the cells and their differentiated descendants.

These studies will provide invaluable data about gene function during early human development. Woefully little is known about this topic at present, due in part to restrictions on federal funding for embryo research. Although developmental mechanisms have been highly conserved in evolution, enough differences in detail have been seen among vertebrate species to suggest that not all genes will function identically in mouse and man. Thus, research with animals only cannot reveal everything we need to know about how to manipulate human stem cells.

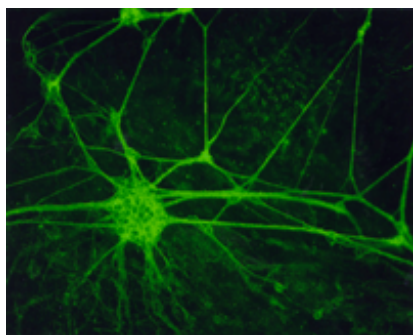
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## Stem Cells in the Public Eye



After several days, colonies of tightly packed, undifferentiated cells arise. Scale bar = 100 microns



If cultures become dense, differentiated cells appear after several weeks, including neurons. Scale bar = 200 microns

Photos kindly provided courtesy of a collaboration between Monash University, the National University of Singapore, and the Hadassah Medical Centre.

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**T**he use of human pluripotent stem cell lines is controversial because they are derived from fertilized human eggs, and for some people human life begins at fertilization. Theoretically, then, the use of somatic cell nuclear transfer to generate autologous pluripotent stem cells should be less controversial. This technique would involve injecting the nucleus from a patient's adult cell into an unfertilized egg from which the nucleus has been removed. In the laboratory, this egg would then grow into a blastocyst from which researchers could derive pluripotent stem cell lines. Apparently, the researchers from Monash University have recently achieved this technical tour de force with mouse cells. The scientists created one embryonic stem cell line after injecting almost a thousand eggs with nuclei from genetically marked cells. There seems to be no reason why this "therapeutic cloning" would not work with humans if it could be made more efficient.

This method for making stem cells might be ethically more acceptable to some people since the recipient eggs lack nuclei and are unfertilized. Thus the creation of a unique combination of genetic material from two people never occurs. Moreover, embryonic stem cells are not embryos, since by themselves they are unable to give rise to a complete fetus. Nevertheless, it is still theoretically possible to clone a human by implanting the blastocysts derived by somatic nuclear transfer into a woman's uterus, rather than using them to make stem cells. Any attempt to do this is contrary to all existing guidelines and violates some state laws. Moreover, such an action would require extensive collusion among many irresponsible people and would be ethically indefensible, given the likelihood that if a baby were to develop it would be malformed.

Nevertheless, these arguments are irrelevant to some detractors, who believe that nuclear transfer into an enucleated egg still brings into existence for research purposes only a human being who is subsequently killed. A great deal more public debate, based on mutual respect for strongly held beliefs, probably lies ahead before federal funds can be used to explore the potential of human pluripotent stem cells, both for therapeutic purposes and for basic knowledge.

It can be argued that this dialogue is, in itself, a good thing, since it stimulates public interest in biology and reproduction, subjects not always effectively taught in schools. (Cloning frogs does not capture the attention of high school students as vividly as does the possibility of cloning themselves, and the still farfetched idea of regenerating human limbs can lead to discussions about how embryonic limbs are patterned and which genes make arms different from legs.)

No matter what, the underlying assumption is that research on stem cells will indeed lead to substantial new therapies. Therefore scientists must be very careful not to overstate the case, and to avoid at all costs the kind of hype that surrounded gene therapy and led to a loss of public confidence. This mindfulness is of particular importance in relation to the use of human pluripotent stem cells. As we have seen, for some members of the public deriving these cells equates with destroying human life. The truth is that there are many hurdles to overcome before we know how useful stem cell therapies will be. We must be honest as we move forward to assess their potential.

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