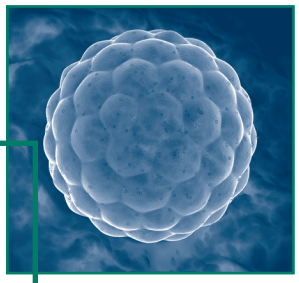

Stem cells and hope for patients

by Maureen Condic, Ph.D.

Most Americans know someone afflicted with an incurable medical condition. The possibility of stem cell "cures" has given hope to many who face such suffering and loss. Unfortunately, there is a tremendous amount of misinformation about stem-cell therapies. To make sound decisions about this rapidly advancing field of research, it is important to understand what stem cells are and what promise they actually offer patients and their families.

A stem cell is simply any cell that, when it divides, can make another cell like itself or make different kinds of cells with specialized functions. Because stem cells replace themselves at every cell division, they can continuously "restock" cells lost to age, injury or disease, without depleting the stem cell pool. For example, when skin cells are lost to the scuffs and scrapes of life, they are replaced from a pool of stem cells that generate new skin cells throughout life.

How might stem cells help human patients? Stem cells may be medically useful for replacing tissue damaged by injury or disease. Following a heart attack, for example, many cells of the heart die and are not replaced, leaving the heart weakened and less able to pump blood. If replacement heart muscle cells could be produced from stem cells, these muscle cells could be used to repair the heart and restore normal heart function.

Three sources of stem cells

Stem cells are present in human tissues, including many adult tissues, at all stages of life. Yet stem cells from different sources have different properties, and in some cases, involve grave ethical problems.

The earliest stem cells are found in the human embryo during the first few days of life. These embryonic stem cells (or ESCs) can reproduce themselves indefinitely and are very flexible: they normally give rise to all of the tissues of the mature body. To obtain such embryonic stem cells for research and for possible future therapies, however, the embryo must be destroyed. This raises the critical ethical question of whether the life of one human being (albeit at a very early stage) can be sacrificed in order to advance scientific research or benefit the health of an older human being.

In contrast to ESCs, there are many sources of stem cells that do not raise ethical problems. Stem cells can be obtained from a patient's own bone marrow or other tissues, as well as from a variety of birth-associated tissues, including placenta, amniotic fluid, umbilical cord and umbilical cord blood. All of these non-embryonic sources of stem cells are commonly (and somewhat confusingly) referred to as "adult" stem cells, to distinguish them from stem cells obtained by destroying human embryos.

Thirdly, recent work has shown that stem cells can be produced easily and without controversy by introducing a small number of factors into

ordinary adult skin cells. The added factors "reprogram" the mature cells into stem cells that have all the important properties of human embryonic stem cells. Like ESCs, such reprogrammed adult cells (termed "induced pluripotent stem cells" or iPSCs) are able to generate all the cells of the body. Unlike embryonic stem cells, however, iPSCs are genetically identical to patients and are generated without destroying human embryos and without using human or animal eggs.

In formulating a sound opinion about stem cell research, it is important to consider what kinds of stem cells are most likely to be useful for medical treatments and what kind of ethical boundaries we are willing to cross for the promise of medical cures.

The false promise of embryonic stem cells

Many people, including many scientists, claim that because ESCs can reproduce themselves indefinitely and, because they naturally generate all the cells of the mature body, stem cells from embryos will be the most useful for medical treatments. Are ESCs really the best option for human therapies?

Quite apart from the grave ethical problem of destroying human embryos for research, there are three significant, long-standing *scientific* problems with ESCs that must be overcome before they could be considered safe for use in human patients. First, when transplanted into mature tissues, embryonic stem cells make tumors containing multiple different cell types (hair, skin, bone, muscle, etc.). Indeed, formation of such tumors is the "gold standard" test of whether a stem cell is, in fact, an embryonic stem cell that is capable of producing multiple mature tissues. Making tumors is therefore not just an incidental problem with ESCs; it is a fundamental aspect of their biology.

Tumors produced by ESCs can be fatal if they form in vital organs, but they are generally "benign," i.e., the tumor cells are genetically normal, not cancerous. However, recent work has shown that ESCs are also genetically unstable, and tend to accumulate mutations that convert them to cancer cells. The tendency to convert into cancer cells is also linked to the intrinsic nature of embryonic stem cells: because these cells divide rapidly and maintain their genetic information in a relatively unprotected state, they are inherently prone to damage that results in cancer-causing mutations. Thus, the "advantages" of ESCs (their flexibility and rapid proliferation) also cause these cells to form tumors and convert to cancer. Until we find an effective way to control these adverse aspects of ESC biology, stem cells from embryos will not be safe for use in human patients.

A second serious hurdle that must be overcome before ESCs can be used for medical therapies is the problem of immune rejection. Embryonic stem cells, like any cell from another person, would be rejected by the immune system of the patient, unless a very close immune match is made. Yet unlike conventional organ transplant, because stem cells disperse throughout the body, they cannot be removed if the patient's body rejects them. The patient then risks developing a fatal immune rejection response.

Many millions of embryonic stem cell lines would be required to find a good immune match for most patients. The International Bone Marrow Registry, for example, includes more than ten million donors, and yet it is not uncommon for patients to die because doctors are unable to find a suitable immune match for bone marrow transplant. While it is often argued that "excess" embryos from assisted reproduction clinics would provide enough ESC lines for therapies, the most generous estimates suggest that only a few hundred stem cell lines could be obtained from "excess" embryos—nowhere near the enormous number of lines that would be required to make ESC-based therapies available to all Americans. Thus, stem cell therapies would almost certainly require the intentional production, and *destruction*, of many millions of embryos in the laboratory.

The final scientific and medical challenge facing development of ESC-based therapies is this: despite more than 25 years of research, no one has been able to coax embryonic cells to become mature, stable cell types that are useful in the clinic. Solving this problem is likely to be very

difficult. The signals that control the maturation of embryonic stem cells during normal human development are both complex and quite poorly understood. While it is relatively easy to make cells in the laboratory that have some of the properties of mature cell types, laboratory-produced cells generally do not survive when transplanted to mature animals. Alarmingly, cells that are not fully mature when transplanted often produce fatal tumors. Until science determines how to fully differentiate ESCs into stable adult cells, they will not be safe for use in human patients.

First practical conclusion: These three problems (tumor formation, immune rejection and stable differentiation) can all, in theory, be solved. Yet solving these problems is likely to take many decades of research and many billions of dollars before any benefit could be realized for patients. Importantly, money invested in research on embryonic stem cells (derived either from human embryo cloning or from "excess" fertility clinic embryos) is money that will not be spent on more promising medical approaches. As citizens and as Christians who truly care about patients and their families, we need to ask ourselves: Is research on ethically and scientifically problematic human embryonic stem cells the best use of limited medical research funds?

The real promise of "adult" stem cells

Stem cells can be derived from many of a patient's own tissues, including bone marrow, muscle tissue, nasal mucosa and even fat. While embryonic stem cells have been studied intensively for a quarter of a century, most types of stem cells from mature tissue have been discovered only recently. Consequently, we are just beginning to understand the properties of adult stem cells and to explore their current and future medical applications.

Many people, including many scientists, claim that adult stem cells will not be as useful for human medical therapies because these cells do not divide readily in the laboratory and they produce only a limited number of mature cell types. These claims have been discredited, however, by new data from the rapidly advancing area of adult stem cell research. Many of the more recently discovered adult stem cell populations divide as rapidly as embryonic stem cells. Recent studies also suggest that at least some kinds of adult stem cells are far more flexible than originally believed. Exactly how flexible adult stem cells will prove to be is not yet known, but it is already obvious that the old view of ESCs as the "only" fast growing and flexible type of stem cell is simply wrong.

In contrast to ESCs, stem cells from more mature tissues present significant advantages for use in medical therapies. First, stem cells from more mature tissues do not make tumors and are not genetically unstable. Because adult stem cells and their derivatives can be safely transplanted to patients, more than 1,500 clinical studies are currently underway, testing the medical usefulness of adult stem cells for diverse medical conditions, including (among others) diabetes, heart disease, amyotrophic lateral sclerosis (Lou Gehrig's disease), multiple sclerosis (MS), arthritis, sickle cell disorder and many types of cancer. In contrast, in the quarter century since their discovery, not a single clinical study has been approved for ESCs, due to the serious safety concerns discussed above.

Also in contrast to ESCs, stem cells from more mature tissues can be immune-matched to patients relatively easily. Stem cells taken from a patient's own tissues are a perfect match. When it is not possible to obtain stem cells from the patient directly, donor registries, similar to the bone marrow registry, could provide a wide range of immune matches. Finally, with over four million births in the United States every year, stem cells from birth-associated tissues (umbilical cord, umbilical cord blood, placenta and amniotic fluid) could provide immune matches for the great majority of American patients.

Lastly, while stem cells from mature tissue may be more limited in the kinds of mature cells they can produce, the flip-side of this "limitation" is that the cells produced are much more likely to be fully mature and therefore clinically safe and clinically useful.

Second practical conclusion: While "adult" stem cells have only recently been discovered, they have already proven themselves to be safe and clinically promising for a wide range of medical conditions. As citizens and as Christians who truly care about

patients and their families, we need to ask ourselves: Why should money be diverted from stem cell research that is currently helping patients in favor of ethically and scientifically problematic embryonic stem cell research?

Direct reprogramming: A win-win resolution

In the fall of 2007, three independent research groups stunned the world by showing that adult skin cells could be converted directly into stem cells having all the important properties of human embryonic stem cells. The ability to produce such "induced pluripotent stem cells" (or iPS cells) without ethical controversy, is one of the most important scientific advances of the last quarter century. By providing patient-matched stem cells, the iPS technique resolves one of the major practical difficulties of embryonic stem cells: the problem of immune rejection. Reprogrammed iPSCs are therefore superior to stem cells from embryos on both ethical and scientific grounds. While the problems of tumor formation and correct differentiation remain for iPSCs, just as they do for ESCs, reprogrammed iPSCs have already proven medically useful in an animal model of human sickle cell anemia.

Currently, iPSCs are produced using viruses that could pose additional risks for patients. The safety concerns raised by the use of viruses can almost certainly be addressed, however. Scientists already have found ways to eliminate the most risky virus used in iPSC production and have shown that small modifications of the procedure greatly improve iPSC safety. The availability of an ethically and scientifically uncompromised source of embryonic-like stem cells should be warmly embraced as a win-win resolution to the long-standing controversy over embryo-destructive research.

Third practical conclusion: Scientists have been able to convert ordinary skin cells directly into stem cells that have all of the important properties of embryonic stem cells. Thus, scientists who claimed that ESCs offered the "best" or the "only" hope for patients have been proven wrong by science itself. As citizens and as Christians who truly care about patients and their families, we need to ask ourselves: Why not embrace a method which proves that science and morality can point in the same direction?

What price are we willing to pay for medical cures?

Serious hurdles must be overcome before embryonic stem cells can be used for medical treatments, and surmounting these hurdles is likely to take many decades and huge sums of money. Out of compassion for patients, we are obligated to focus our research spending on approaches that are most likely to result in relief of human suffering. On purely practical grounds, embryonic stem cell research is not the most effective use of research money, and does *not* offer the greatest hope to patients.

On a more fundamental level, we must not be so blinded by our concern for patients and their families that we ignore the moral cost of scientific research. Science and medicine, like all human endeavors, cannot be justified by the "good outcomes" they might produce, independent of the means by which those outcomes are obtained. Medical stem cell research must operate within the constraints of ethical principles, with the first principle being "do no harm." Research on human embryonic stem cells involves the intentional destruction of human life at its earliest and most vulnerable stage. Regardless of any potential benefit this research may offer, as citizens and as Christians, we must ask ourselves: Can medical cures justify the price of destroying human life? As former embryos, we should all stand in solidarity with our brothers and sisters who are not yet capable of speaking for themselves on this question of vital importance to their future and our own.

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