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Creative Science Will Resolve Stem-Cell Issues

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The House of Representatives recently passed legislation to loosen President Bush's restrictions on federal funding of embryonic stem-cell research. The president has promised to veto the bill, however, and the legislation lacks the support of a veto-proof majority. So regardless of what happens in the Senate, it is clear that, at least until 2009, there will be no federal money for research involving stem cells derived from embryos destroyed after Aug. 9, 2001. Americans are divided as to whether this is good or bad, but it is the one thing about which there is now no debate.

President Bush's veto need not mean that new embryonic or embryonic-type stem-cell lines eligible for federal funding cannot be developed, however. The President's Council on Bioethics, in a recent White Paper, identified several possible methods for producing such lines that do not require the destruction or harming of living human embryos. There is good scientific reason to believe that this can be done using existing biotechnologies. These possibilities point the way towards a resolution of our nation's divisive debate over embryonic stem-cell harvesting -- one that can be embraced in good conscience by people on both sides of the ethical divide.

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What is fascinating about embryonic stem cells, and makes many people believe that someday they will have important therapeutic value (though they have not demonstrated such value as yet), is their "pluripotency" -- their capacity to form any and every type of human body cell. But a stem cell (even an embryonic stem cell) is not an embryo; it is not "totipotent" -- that is, capable of

developing to the next stage of maturity as a new individual of the species. Unlike an embryo, a stem cell is not a complete organism in the beginning stages of its natural development. It is merely part of the larger organism, like any other body cell.

The ethical problem arises because human pluripotent stem cells are obtained today by destroying living human embryos. The solution, if technically feasible, is to produce human pluripotent stem cells directly, that is, without first creating an embryo which must be destroyed or damaged in the process of harvesting stem cells.

One promising option is called oocyte assisted reprogramming (OAR). This is a variation of a broader concept known as altered nuclear transfer. It combines basic cloning technology with what is known as epigenetic reprogramming.

In cloning, the nucleus of a somatic cell (such as a skin cell) is transferred to an egg cell whose nucleus has been removed. An electrical stimulus is administered in a way that, if all goes as planned, triggers the development of a new and distinct organism, an embryo, that is virtually identical in its genetic constitution to the organism from which the somatic cell was taken. In OAR, however, the somatic cell nucleus or the egg cytoplasm or both would first be altered before the nucleus is transferred. The modifications would change the expression of certain "master genes" -- transcription factors that control expression of many other genes by switching them on or off.

These genetic alterations would permit the egg to reprogram the somatic cell nucleus directly to a pluripotent, but not a totipotent (i.e., embryonic) state. The altered expression of the powerful control gene would ensure that the characteristics of the newly produced cell are immediately different from, and incompatible with, those of an embryo. For optimal reprogramming, master genes known to control the pluripotency of embryonic stem cells would be used, for example the transcription factor known as "nanog." Thus, we would reasonably expect to obtain precisely the type of stem cells desired by advocates of embryonic stem-cell research, without ever creating or killing embryos.

This method of obtaining human pluripotent stem cells would not only be morally unimpeachable (assuming nothing unethical is done in obtaining somatic cells or oocytes used in the process), it would have other important advantages over using so-called spare embryos left over from in vitro fertilization efforts. Unlike stem cells from IVF embryos, scientists could control the genetic structure of OAR-produced stem cells. Their genetic constitution would be virtually > identical to that of the donor, thus helping to overcome the problem of immune rejection.

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Our proposal is not the only possible way for pluripotent stem-cell science to work around the ethical impasse. Progress has recently been reported on another strategy similar to OAR, but using embryonic stem cells, rather than eggs, for reprogramming adult cells to the pluripotent state. Like OAR, further research is needed to confirm that this "cell fusion" strategy will work. If it does, the required embryonic cells could be taken from lines created prior to Aug. 9, 2001, making this research eligible for federal funding.

When he announced his intention of vetoing the embryonic stem-cell bill, President Bush noted that researchers are exploring "different ethical ways of getting the same kind of cells now taken from embryos without violating human life or dignity." He added: "With the right policies and the right techniques, we can pursue scientific progress while still fulfilling our moral duties." The country will likely remain divided about the ethics of research using human embryos. But we believe that creative science can help us find a way forward and thus put pluripotent stem-cell research on a footing that all citizens can enthusiastically support. That would be a great day for science, for morality, and for our nation.

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