

Altered Nuclear Transfer
As a Morally Acceptable Means
To Procure Human Pluripotent Stem Cells

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Introduction.

The present conflict over the moral status of the human embryo reflects deep differences in our basic convictions and is unlikely to be resolved through deliberation or debate. Many Americans oppose embryo destruction for the procurement of stem cells, believing that there is an implicit dignity and inviolability in the individual continuity of a human life from fertilization to natural death. Many others, however, believe that the benefits of advances in biomedical science outweigh these moral concerns.

A purely political solution will leave our country bitterly divided, eroding the social support and sense of noble purpose that is essential for the public funding of biomedical science. While there are currently no federally legislated constraints on the use of private funds for this research, there is a consensus opinion in the scientific community that without NIH support for newly created embryonic stem cell lines, progress in this important realm of research will be severely constrained.

Notwithstanding this seemingly irresolvable impasse, we believe there may be morally acceptable ways to obtain embryonic stem cells or their equivalents, such as those ways discussed in the recent publication by the President's Council on Bioethics, entitled, "Alternative Sources of Human Pluripotent Stem Cells." As one of those alternative sources, the techniques of Altered Nuclear Transfer may allow us to generate pluripotent stem cells (the functional equivalent of embryonic stem cells) even apart from the embryonic context in which they are normally produced.

1) What Altered Nuclear Transfer (ANT) proposes to accomplish:

A) produce pluripotent stem cells (which, like embryonic stem cells, are able to form all the different types of cells in the body) without the creation and destruction of human embryos.

B) provide a technological means to bypass the current ethical and legislative impasse over federal funding of new human stem cell lines derived from disaggregation of embryos 'left over' from *in vitro fertilization* (IVF) or specifically created by cloning (SCNT).

2) How ANT works:

A) Standard nuclear transfer (NT) is the technology popularly known as cloning, but in scientific terms is called 'Somatic Cell Nuclear Transfer' (SCNT).

The nucleus (which contains the DNA) is removed from an adult body (somatic) cell and implanted (transferred) into an egg cell that first has its own nucleus removed. The egg then has a full set of DNA and, after it is electrically stimulated, starts to divide like a naturally fertilized egg and forms an embryo. This is how Dolly the sheep was produced.

B) Altered Nuclear Transfer uses the technology of NT but with a preemptive alteration that assures that no embryo is created.

The somatic cell nucleus or the enucleated egg contents (cytoplasm) or both are first altered before the somatic cell nucleus is transferred into the egg. The alterations cause the somatic cell DNA to function in such a way that no embryo is generated, but pluripotent stem cells (PSCs) are produced.

3) ANT is a broad concept with many possible means of implementation, including:

A) alteration to silence or delete genes essential for the integrated and coordinated organization that characterizes a living being. The partial and unorganized trajectory of organic growth would still create an inner cell mass from which PSCs could be harvested. Proof of principle for this approach has been established in mice by MIT stem cell biologist Rudolf Jaenisch.

B) alteration to promote forced expression (jump-starting) of genes characteristic of a later and more specialized cell type that is unable to generate an organism but capable of producing PSCs. A recently proposed version of this type of alteration is called 'oocyte assisted reprogramming' (OAR) because the egg cell (oocyte) cytoplasm assists the transferred somatic cell nuclear DNA to become reprogrammed so the cell behaves directly like a pluripotent cell and not like an embryo.

4) Why the cell produced by ANT is not an embryo and cannot produce an embryo:

Because the alterations are made before the somatic cell nucleus is transferred into the egg, the result of the ANT procedure is a cell whose DNA and pattern of gene expression are not only altered, but altered from the very start. Therefore from the very start it does not have the capacity for the integrated organization and coordinated development that characterize a human embryo. This is clearest in the case of ANT-OAR where the cell directly behaves like a pluripotent cell.

5) Advantages of ANT over current methods of obtaining embryonic stem cells:

A) In the process of obtaining PSCs no embryos are created or destroyed.

B) Unlike the use of embryos from IVF clinics, ANT would produce an unlimited range of genetic types for the study of disease, drug testing, and possibly generation of therapeutically useful cells. Furthermore, the genetic material of the somatic cell used in ANT would have a proven capacity for normal development, unlike that of an IVF embryo which has never fully formed an organism and may carry unrecognized mutations or potentially pathogenic gene combinations. PSC lines produced by ANT will be genetically similar to the donor of the somatic cell nucleus and therefore might serve as a customized source of immune-compatible cells for tissue transplantation.

C) As a direct laboratory technique, ANT would unburden embryonic stem cell research from the additional ethical concerns of the 'left over' IVF embryos, including the attendant clinical and legal complexities in this realm of great personal and social sensitivity.

D) By allowing controlled and reproducible experiments, ANT would provide a uniquely flexible research tool for a wide range of useful studies of early gene expression, imprinting, and intercellular communication. The basic research essential to establishing this technique would advance our understanding of developmental biology and might serve as a bridge to transcendent technologies such as direct reprogramming of adult cells.

E) In technologically bypassing the ethical impasse over the instrumental use of human embryos, ANT allows PSC research to proceed with broad public consensus and the support of federal funding essential for coordinated research collaboration and unified ethical oversight on a national and international level.

F) In the opinion of leading stem cell biologists, ANT is technically feasible, could be rapidly developed (12-24 months or maybe sooner), and would not burden stem cell research with excessive cost or inconvenience. Furthermore, preliminary animal studies necessary to establish and optimize the technical procedures for ANT could be confidently extended to the use of human cells

Although the full range of possible approaches using ANT are currently being discussed and explored, the general concept of ANT has already received broad endorsement by leading scientists, moral philosophers and religious authorities.

Conclusion.

As we enter an era of rapid advance in biotechnology, ANT sets a positive precedent for maintaining constructive ethical dialogue and creatively using science. In recognizing the important values being defended by both sides of our difficult national debate over embryonic stem cell research, ANT opens positive prospects for scientific advance while preserving our most fundamental moral principles. Such a solution is in keeping with the American spirit and would be a triumph for our nation as a whole.