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Latest Developments in Stem Cell Research

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During the past few weeks, significant developments have occurred that may strongly affect the progress of human stem cell research. Advances in both Somatic Cell Nuclear Transfer (SCNT) and in the so-called Yamanaka technique to produce patient-specific human pluripotent stem cells hold great promise not only for understanding disease development and progression, but for organ and tissue replacement. Unfortunately, progress has been delayed due to legal constraints that have restricted public access and wide-spread experimentation in many states of the nation. Although SCNT has worked effectively in experimental animals including mammals, it has not yet been used to produce patient-specific stem cells in humans. Last week, a research team led by Dr. Shoukhrat Mitalipov at the Oregon Health & Science University reported success using SCNT with rhesus macaque monkeys, the first report of success in using SCNT in primates. It offers considerable promise and renewed hope that the procedural modification will work in other higher primates, including humans. The successful breakthrough was praised as "highly encouraging" by stem cell researchers far and wide, including Dr. Paul Simmons, Professor of Molecular Medicine at the University of Texas in Houston's Texas Medical Center. Even the British creator of Dolly the cloned sheep, Prof. Ian Wilmut (Edinburgh University), praised the work of the Oregon team as a significant step forward toward human application. However, in a separate report, Prof. Wilmut personally vowed to abandon the SCNT technique for cloning human cells in favor of an emerging new procedure that utilizes somatic cells (i.e., skin cells), rather than human blastocysts, the Yamanaka technique.

Dr. Wilmut was referring to a new stem cell technology created by a Japanese investigator that enables scientists to create pluripotent human stem cells from human somatic cells (i.e., skin fibroblasts) using a process known as reprogramming or dedifferentiation. The procedure, developed by Dr. Shinya Yamanaka, utilizes a molecular biological approach in which cells are reprogrammed by exposing them to specific signaling agents (transcription factors) that reprogram the genetic expression pattern of a cell. This prompts the cells to switch from becoming skin cells to becoming more stem cell-like. Although this approach is still in early stages, several seminal papers have just appeared in journals this week that give great credence to this alternative approach. Such developments should be seriously considered by the stem cell research community, as they offer yet another rational approach to making patient-specific, pluripotent stem cells. What is the Yamanaka technique and why is it considered such a breakthrough? To understand, let's first review some basic stem cell biology.

A stem cell is one that can replicate itself indefinitely while maintaining the ability to transform into other cell types. Stem cells presently come in two flavors: so-called adult and embryonic. Adult stem cells are found resident in most body organs while embryonic stem cells are present in a developing embryo for just a few days. Adult stem cells are said to be multipotent while embryonic stem cells are said to be pluripotent. The degree of potency conforms to the plasticity and degree of differentiation of the developing cell. At the time of the union of egg and sperm, the unified cell is said to be totipotent, meaning the cell can develop into any of the three types of tissue known as endoderm, mesoderm, or ectoderm as well as the placental tissues needed for the embryo to implant. As the cell progresses to two cells, then four, eight, and so forth, it reaches a stage where it is called a morula (berry in latin). About day four, the solid ball of cells begins to transform from a compressed morula into a hollowed out ball called a blastocyst. About the size of the period at the end of this sentence, this blastocyst contains a thin ridge of cells.

These are the embryonic stem cells. They were first isolated from and cultured in humans by James Thomson in 1998. These embryonic stem cells are said to be pluripotent. They can develop into any of the 210 or so cell lines of a human. As the blastocyst continues to develop the cells become more differentiated, more specialized. If the cell mass were divided before about day 14, it would create two viable identical cell masses. By day 14, the cells have differentiated to the point that if one were to try to divide them, the cell mass would arrest. By day 14, the cells have become so specialized, or differentiated, that they are no longer pluripotent, but are multipotent.

Adult stem cells have been used for over 40 years in such therapies as bone marrow transplantation. Embryonic stem cells have only been available for research and study for less than a decade. Adult stem cell research, whether the cells come from bone marrow, cord blood, peripheral blood, or aborted mesenchymal tissue, has not met with the controversy that has surrounded embryonic stem cell research. This is for one simple reason: the derivation of human embryonic stem cells. Their derivation requires the destruction of human embryos. For this reason, George Bush issued a presidential proclamation in August, 2001 in which he proclaimed that the only federal funding for human embryonic stem cells would be for those embryonic stem cell lines already in existence. These became known as the presidential cell lines. His proclamation, combined with the Dickey amendment, effectively blocked any federal funding for human embryonic stem cell research.

The Dickey Amendment is the name of a piece of federal legislation passed by the United States Congress in 1995 which prohibits the Department of Health and Human Services (HHS) from using appropriated funds for the creation of human embryos for research purposes or for research in which human embryos are destroyed. HHS funding includes the funding for National Institutes of Health (NIH) funding. Technically the Dickey Amendment is a "rider" to other legislation, which amends the original legislation. The rider receives its name from the name of the Congressman that originally introduced the amendment, Representative Jay Dickey. The Dickey amendment language has been added to each of the Labor, HHS, and Education appropriations acts for FY1997 through FY2006. The original rider can be found in Section 128 of P.L. 104-99. The wording of the rider is generally the same year after year. For FY2007, the wording prohibits HHS from using FY2007 appropriated funds for:

- (1) the creation of a human embryo or embryos for research purposes; or
- (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.208(a)(2) and Section 498(b) of the Public Health Service Act [1](42 U.S.C. 289g(b)) (Title 42, Section 289g(b), United States Code). For purposes of this section, the term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 (the Human Subject Protection regulations) . . . that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes (sperm or egg) or human diploid cells (cells that have two sets of chromosomes, such as somatic cells).

As a result of the federal embargo on funding human embryonic stem cell research, many of the 50 states have enacted various laws, propositions, and executive decrees that have created a patch quilt of legal and financial discord. This has impeded collaborative research. As well, key U.S. researchers have left the U.S. or have been recruited by foreign countries. The political fallout is part and parcel of the ethical debate, one fueled by the means used to produce embryonic stem cells -- the destruction of an embryo. To date, the only way to produce a human embryonic stem cell line is by extracting the little ridge of cells from the blastocyst.

SCNT, also called therapeutic cloning, has been used in mammals to create an embryonic stem cell line which is animal specific. Such a nuclear transfer was used to clone Dolly the sheep by Prof. Wilmut in 1995. It was the appeal of such a technique as SCNT that could generate patient-specific embryonic stem cells that allowed the Korean scientist Woo-Suk Hwang to captivate the world in 2006 with the promise of readily available, patient-specific human embryonic stem cells...until his work was shown to be fraudulent.

Last summer, at the annual ISSCR (International Society of Stem Cell Research) conference held in Australia, Dr. Shoukhrat Mitalipov and colleagues at the Oregon Health and Science University in Beaverton announced that they cloned the first nonhuman primate, a fact just recently appreciated by the general public with the pending publication of the scientific article. In all, Mitalipov used 304 eggs from 14 rhesus monkeys to make two lines of embryonic stem cells, one of which was chromosomally abnormal. Mitalipov admits the efficiency is low and, though his work is a proof of principle and the efficiency of his methods has improved, he admits it is not yet a cost-effective medical option. SCNT has been advanced by the advocates supporting human embryonic stem cell research as a means for producing a stem cell line without the destruction of a classically defined embryo.

In August, 2006 at the Stem Cell Conference in Keystone, Shinya Yamanaka, Professor of Stem Cell Biology at the Institute for Frontier Medical Sciences at Kyoto University in Japan, electrified the attending scientists by proving that it was possible to deprogram mouse somatic cells (specifically, fibroblasts) into embryonic-like stem cells by expressing four genes: c-myc, oct3/4, sox2, and klf4. According to Yamanaka, the proteins encoded by these genes, identified from a pool of 24 candidates, each serves a specific role. The Yamanaka technique offers a way to create human stem cells without destroying human embryos.

The significance of the work being published this week by two independent researchers is that for the first time the Yamanaka technique has been demonstrated as proof of concept in human beings. This process converts routine body cells, or somatic cells, into pluripotent stem cells by adding various transcription factors which cause reprogramming or dedifferentiation of the somatic cells. These reprogrammed somatic cells are called induced pluripotent stem cells or iPS cells. These are just as plastic as embryonic stem cells. The one drawback to them is that they are created using virus vectors to introduce the genes. This is a major problem that must be solved before these cells can be used in humans. IPS cells have all the same characteristics of the pluripotent embryonic stem cells. They hold the same promise for use in regenerative medicine for cell replacement therapy.

Having been informed of these Richter-scale developments in creating pluripotent stem cells...the easy way, Prof Ian Wilmut, the father of modern therapeutic cloning is said to have "shunned" cloning. "I decided a few weeks ago (when he first heard about the studies) not to pursue nuclear transfer." He went on to say that the Yamanaka approach represents the future for stem cell research. Dr. Paul Simmons, immediate past president of the ISSCR, agrees with Prof Wilmut but suggests that "SCNT may still have a pulse, and is worth continued study." He goes on to point out that the long term comparisons of the iPS cells and embryonic stem cells still need to stand the test of time. "Embryonic stem cells derived from excess IVF embryos are still the gold standard for pluripotent stem cells. IPS cells are the new kids on the block. They need further study with comparisons made over time." Thomas Zwaka, MD, PhD, assistant Professor of cell and molecular biology at the Baylor College of Medicine in Houston is more forceful in his opinion. As a long time collaborator of Yamanaka's and having spent four years as a post-doc fellow in James Thomson's lab, Zwaka -- who attends to five presidential stem cell lines of his own -- is well positioned to offer an overview. In his opinion, SCNT merits continued attention, while supporting active research utilizing the Yamanaka technique. "There is no excuse now for not funding this research," he said in an interview, "this is the beginning of a whole new frontier of medicine, a medicine of cures, not just treatments. Regenerative medicine will thrive using the cells derived from the Yamanaka technique." However, he echoes Paul Simmons in saying that other forms of stem cell derivation should be kept on reserve until all the kinks are worked out of the Yamanaka technique. He warns that "now is not the time to restrict any experimental approach, but to expand on all fronts until the right approach is confirmed."

Has the Yamanaka technique killed stem cell research as a political wedge issue in the upcoming elections? "No, probably not," says Bernard Siegel, executive director of the prestigious Genetics Policy Institute, a stem cell think tank based in Wellington, Florida whose advisory board reads like a who's who in stem cells. "Remember that the primary bone of contention has always been the use of embryos to derive the cell lines. "The pro-life movement is still on the march, but with the Yamanaka technique, there's a different tune that appeals to all parties involved, Democrats and Republicans, right and left wings. The perennial argument over embryo use is muted, but still important. Now is the time to band together to get the cell replacement cures for spinal cord injury, Parkinson's, diabetes, and so many more disorders in place." Mr. Siegel, a successful attorney who has been a major leader in the advocacy movement for stem cell research, went on to point out that the Yamanaka procedure will offer both parties a compromise without the heated debate about the ethics and morality of using excess IVF embryos. "Stem cell research remains a potential wedge issue."

The following passage was written by Bill Brinkley, Ph.D., Professor of Cell and Molecular Biology, and Dean of the Graduate School of Houston's Baylor College of Medicine. "Although we are excited by these new discoveries, and remain even more optimistic about future developments of techniques that may utilize human stem cells for regenerative medicine, we believe that to disregard any procedure that currently holds promise is short-sighted and scientifically risky. A clear example is the Oregon team's development of the procedure that has worked effectively to produce a wide array of embryonic cells in non-human primates. To choose to focus on only one avenue of research or type of cell source, would -- at this stage of regenerative medical research -- be irresponsible, unreasonable, and premature. Promising and successful research exploring human stem cells should be supplemented with--not supplanted by -- new and potentially exciting approaches, with all forms of research moving forward along multiple independent paths. Scientific research -- whether it be in cancer, diabetes, tissue regeneration or other areas -- should proceed freely and openly along all viable lines of investigation until sufficient progress has been made to be successfully applied to the treatment and alleviation of diseases and human suffering. In fact, these various lines of research will probably produce new findings that will complement each

other and expand our depth and breadth of knowledge. Exciting new discoveries will be made in the field of stem cell research, and no one knows what important discoveries would be missed if we were to abandon SCNT to focus on only one approach, especially if that decision were largely driven by emotional and political expediency."

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