

# Stem Cells without Embryos

## Solving Dilemmas for Human Rights?

By Julie A. Burger

**R**ecent stem cell research results have raised hope that the heady promise of stem cell technology will soon be realized. Two independent teams of researchers in November 2007 separately announced they had successfully modified human skin cells into cells that behave essentially the same as embryonic stem cells. Reaction to the research has been favorable, uniting proponents and opponents of embryonic stem cell research in the hopes that this is an advance that can move us beyond the political and ethical problems with research on embryos. A seldom discussed consideration, however, is where the tissue came from for these studies, and whether the people from whom it was taken knew, or agreed, that their tissue could be used in this way. Solving the debate over the use of embryos is just the first of the human rights issues that must be addressed.

Researchers at Kyoto University in Japan and the University of Wisconsin induced adult facial skin cells and infant foreskin cells to behave like embryonic stem cells by using retroviruses to introduce regulator genes—genes that function by turning other genes on or off—into the skin cells. They discovered that the resulting cells, called human-induced pluripotent stem cells, develop characteristics similar to those of embryonic stem cells, including the ability to differentiate into many tissue types.

The new method, if successful, will enable scientists to sidestep many of the moral, religious, and political objections and practical problems surrounding the other main way of acquiring such universal human cells: the harvesting of embryonic stem cells from a human embryo soon after fertilization, a process that destroys the embryo. Couples who have used the

services of fertility clinics and have embryos left over might choose to donate their embryos to this research, although this is not a popular option. In theory, the embryos also might derive from cloning, where the genetic material of a body cell (such as a skin cell) is transferred into a human egg that has had its nucleus (where its DNA is located) removed. The egg, which now has the same number of chromosomes as if it had been fertilized by a sperm, is jump-started to begin division into an embryo. Embryonic stem cells could be harvested from the resulting embryo. The embryo and the embryonic stem cells would have the same genetic makeup as the person from whom the body cell originally came.

Cloning, however, has not been proven to be successful in humans and comes with ethical concerns, such as the possibility of reproductive cloning, as well as the practical problem of securing human eggs. Researchers have had difficulty acquiring enough donated eggs because women have not stepped forward to undergo the painful and risky egg donation process. Furthermore, the long-term health effects of the egg donation process are not fully known.

The reprogramming of regular body cells to behave like stem cells is being hailed as a way to avoid these dilemmas. As Cardinal Justin Rigali, chairman of the Committee for Pro-Life Activities at the United States Conference of Catholic Bishops, explains: “This technology avoids the many ethical land mines associated with embryonic stem cell research: It does not clone or destroy human embryos, [and] does not harm or exploit women for their eggs . . .” William Hathaway, *Stem Cell Coup Acclaimed*, HARTFORD COURANT, Nov. 21, 2007. Ian Wilmut,

the researcher who led a team of scientists in 1997 to clone Dolly the sheep, welcomed the accomplishment, announcing that his laboratory plans to abandon embryonic cloning in favor of the reprogramming process because the “technique of changing cells directly from a patient into stem cells, without the step of making a clone, has better potential.” Colin Nickerson, *Breakthrough on Stem Cells: Reprogramming of Human Skin May Circumvent Ethics Controversy*, BOSTON GLOBE, Nov. 21, 2007, at A1.

Better potential? Maybe. More ethical? Potentially. But the question still remains: Where do stem cells come from? Or, rather, where do the precursors to these new human-induced pluripotent stem cells come from? As part of their research, both teams of researchers used adult and neonatal cells that are readily available from biotech companies or nonprofits, such as ATCC, which provides cell lines, bacteria, and viruses to researchers. Cell lines are established cell cultures that, given the appropriate conditions, can proliferate indefinitely. The cells that began the culture could originally have been the by-products of a medical procedure (such as a circumcision), left over from a diagnostic test or routine blood draw (such as a cholesterol check), or the remnants of samples provided by people who participated in research studies (such as a study investigating the genetic causes of breast cancer). In many instances, the cells are taken without the knowledge or consent of the patient under the mantra of “finders-keepers.”

Yet the people from whom the material came might not want their or their children’s tissue and genetic information immortalized and used worldwide in research. People might

not want to participate in certain types of research, or they might prefer to choose which types of research their tissue is used in, just as they might prefer to provide money to one charity over another. Removing the “embryonic” part of embryonic stem cell research does not remove all ethical considerations from research that is conducted on human tissue.

### The Principles Governing Research

The paramount ethical principle governing any research on human beings is that participation in research must be voluntary. People have the right to not be researched upon without their informed consent, and this includes research on tissue that has been removed from their bodies. Potential participants in research have the right to be told that they are participating in research and to be told any material information about the research that would affect their initial willingness to participate and to continue participation. Material information is, of course, the information required for a participant to make a reasoned and informed decision whether to incur certain risks by becoming involved in the research. Once they decide to participate, research subjects also have the right to withdraw from further participation without penalty. These principles are codified at Title 45, Part 46, of the Code of Federal Regulations, known as the “Common Rule,” which provides minimum standards of protection for participants in federally funded research, with some states providing additional protections.

In the past, these principles were frequently described as being based on the familiar concepts of bodily integrity and the right to be free from unwanted touching. But when the research is performed on blood or other body tissue that has been removed from the body, the principles are more appropriately described as autonomy and the right to self-determination. People should have the right to choose what will or will not happen to them, even when the “them” is their own tissue.

### Public Opinion Regarding Use of Tissue

People do care about what happens to their tissue (blood, tumors, urine, biopsy samples, etc.) even after it is removed from their bodies. Rather than waste, these materials are potentially the next big—and lucrative—medical breakthrough. Not only do people have the right to choose whether they will allow their tissue to be used in research, but evidence from surveys and other studies demonstrates that people do want to exercise this right. Factors influencing people’s decisions about whether to participate in research include

- the type of research,
- the potential sharing of tissue with other researchers beyond the confines of the particular study or its storage after the current project is over,
- the previous experiences of racial or ethnic groups,
- the level of trust in the researcher or institution, and
- religious beliefs.

A recent survey of people who had not already provided their tissue for use in research examined whether they would be willing to donate their own or their children’s tissue and, if so, whether the specific type of research was important to them. Eighteen percent said they were unwilling to provide their own tissue for any type of research, and half indicated they would not be willing to provide their children’s tissue. The researchers found that 82 percent of respondents would be willing to donate tissue samples for cancer research, 65 percent for research on genetic disorders, 59 percent for research providing general knowledge of tissue, and only 26 percent for genetic cloning research. Michael L. Goodson & B.G. Vernon, *A Study of Public Opinion on the Use of Tissue Samples from Living Subjects for Clinical Research*, 57 J. CLINICAL PATHOLOGY 135, 136 (2004).

People who agree to participate in research studies by providing their tissue for use by researchers have strong

feelings about whether and how their tissue is used beyond the confines of the specific research protocol they agreed to participate in. Consent forms given to research participants frequently offer different options for the uses of their tissue, for example, whether the institution can share the tissue with other institutions, whether it can use the tissue in future research without additional consent, or whether the person wants to be recontacted for permission. In a study analyzing the responses on different variations of National Institutes of Health consent forms between 2000 and 2002, almost a fifth of participants given the option between recontact before their tissue was used in the future or authorizing all future research chose recontact. When participants were given the option between refusing all future research, authorizing all future research, or recontact before future use, 26 percent chose recontact. Donna T. Chen et al., *Research with Stored Biological Samples: What Do Research Participants Want?* 165 ARCHIVES INTERNAL MED. 652, 654 (2007). These numbers were even higher for people who had not already agreed to participate in research on tissue but were being asked about their potential participation. Thirty-nine percent of respondents expressed a desire to be consulted if future research was to be undertaken on stored tissue samples. Goodson & Vernon, *supra* at 136. This indicates even people who are willing to participate in future research still want to retain control and the ability to make a contemporaneous choice.

Perhaps because of past research abuses, race and ethnicity also affect people’s willingness to participate in research. People of color have expressed concern about being used as “guinea pigs” in medical research. In 1999 and 2000, investigators with the National Health and Nutrition Examination Survey asked participants if they could collect and store blood samples for future, unspecified genetic research. Overall, approximately 85 percent of the participants agreed, but non-Hispanic blacks were significantly less likely to

consent to the storage of their tissue for future genetic research. Geraldine M. McQuillan et al., *Consent for Genetic Research in a General Population: The NHANES Experience*, 5 GENETICS IN MED. 35, 38 (2003). In an analysis of consent forms for a study examining the genetic causes of heart disease in African Americans, 29 percent of the participants indicated they did not want their tissue shared beyond the confines of the specific research protocol they consented to. NATIONAL HEART, LUNG, & BLOOD INSTITUTE, EXECUTIVE SUMMARY: REQUEST FOR INFORMATION MODIFICATIONS TO THE NHLBI POLICY FOR DISTRIBUTION OF DATA FROM CLINICAL TRIALS AND EPIDEMIOLOGY STUDIES (Aug. 2006).

Distrust of researchers is a commonly expressed reason for not participating in research, especially among minorities. In focus groups exploring these issues, some people indicated for them to trust the researcher, they would need to see that white people were also included in the study. Others linked their distrust of researchers to prior research scandals, such as the Tuskegee syphilis study, saying that participants should expect dishonesty and nondisclosure from investigators. Minorities are not alone. In 2007, the Institute of Medicine commissioned a poll to determine how, among other things, the public views privacy in medical research. Of people who have been asked to have their personal medical information used in research and decided *not* to participate, 30 percent were concerned that their personal medical information would not be kept private or confidential, while 22 percent did not have trust in the people or organization conducting the research. Harris Interactive Polls, *IOM Privacy and Research Studies for Dr. Alan F. Westin* (Sept. 11–18, 2007) at 2. It is not hard to see the negative impact that human rights violations, research abuses, and breaches of trust could have on biomedical research.

### **Litigation to Enforce Participants' Rights**

Disputes over tissue that is used in

research are being played out in the courts. One of the more infamous cases of late, leaving research participants feeling as if their rights are not being upheld, is *Washington University v. Catalona*, 490 F.3d 667 (8th Cir. 2007). For decades, men sought treatment for their prostate cancer from Dr. William Catalona, an internationally renowned surgeon and researcher. Over the

overlooked the university's failure to provide the potential participants with material information: it never informed the men it intended to own their tissue. Instead, the informed consent documents continually reiterated the patient's rights to his tissue: "your genes," "your blood samples," and "your pathological specimen." Disregarding promises in the informed consent documents that

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years, thousands of men and their families provided tissue for Catalona to use in his research. But as time passed, Catalona's employer, Washington University, began to realize the financial value of the tissue the research participants had provided. As his relationship with Washington University deteriorated, Catalona decided to move his research and practice to Northwestern University. Six thousand of his patients sent letters directing Washington University to send their samples to Catalona in Chicago.

Washington University filed suit against Catalona in federal court, asking the court to declare it to be the owner of the tissue. It claimed the tissue had been a gift from the participants and was now worth over \$1,000,000. The judge joined eight research participants as necessary parties who testified that when they agreed to participate in research, they intended to allow Catalona to use their tissue for his prostate cancer research and did not intend to give their tissue to the university.

Despite this, Judge Stephen Limbaugh found that the university was the sole owner of the tissue. Ignoring the cornerstone ethical and legal principles governing research studies on human subjects, the court disregarded informed consent documents, dubbing them "inconsequential." The court also

if the men changed their mind about participating they could withdraw from the research, the court held that if a participant decided to withdraw from research, the university could simply remove his name and continue to use his tissue. But allowing the university to continue research *after* a person says "no more" violates the letter and the spirit of voluntary and informed consent, as well as a person's right to withdraw completely from research.

On appeal, the Eighth Circuit held that under Missouri state law and the facts of the case the participants transferred ownership of their tissue to the university as a gift. But it also held that the research participants had the right to stop the university from using their biological materials for future research. While returning some measure of the rights these participants should have, this decision unfortunately leaves the participants with what many might consider to be unacceptable alternatives. Either they can allow the university to keep the tissue and use it in its "sole discretion"—including sell it or use it for objectionable or stigmatizing research—or they must order the university to destroy it, thus making it unavailable for research that could be beneficial to themselves and their families.

The *Catalona* case is not the only litigation in which research participants

feel that their rights have been trampled on by researchers or research institutions. In another case, members of the Havasupai Tribe, a Native American group which lives in a remote part of the Grand Canyon, sued a researcher who told the tribal elders she would undertake diabetes research on the samples she wanted to collect from the tribe. *Havasupai Tribe v. Ariz. State Univ.*, No. CV2005-013190 (Maricopa County, Ariz.). But the researcher had already filed grant applications for schizophrenia research when she allegedly made this representation. The samples were shared with researchers at other universities and were used not only for potentially stigmatizing schizophrenia research but also for origins and migration studies that conflicted with the tribe's religious beliefs. If true, the allegations point to alarming violations of human rights. Other Native American groups have indicated their support for the Havasupai people, and one tribe has withdrawn from a federally funded study because of the Havasupai situation. It could take decades to reestablish relationships with groups such as this, if it is even possible.

### **Tissue Can Never Be Made Anonymous**

An argument cropping up in discussions about research on tissue is that if a participant withdraws from research, the institution can take the name off a sample that was collected and continue to use it. Or institutions argue that if names or other "identifying information" are removed from samples, they can be shared beyond the study in which the people agreed to participate because the samples are anonymous and

not linked to a person. Even the Office for the Protection of Human Rights, the federal agency charged with enforcing the Common Rule and protecting participants in federally funded research, has taken the position that some research on people's tissue, even tissue that is linked to a person's name, is not human subject research if the particular researcher does not have the key to unlink it.

However, tissue contains DNA, the ultimate identifier. As technology continues to improve, it is becoming easier to more accurately identify individuals using less genetic material. The possibility of a person being identified through his or her tissue is a growing concern, especially as data and samples are increasingly shared and the federal government even mandates online posting of research data and results. Sound unlikely? A few years ago, a child was able to track down his biological father, an "anonymous" sperm donor, by using his own DNA and online genetic genealogy resources. Clearly people's DNA cannot be made anonymous.

The World Medical Association provides the Declaration of Helsinki to guide physicians and others conducting medical research. A recently released draft of revisions to the Declaration calls for informed consent before tissue is used in research, and re-consent before tissue is used for another purpose, with no apparent exception for anonymous tissue. Perhaps it is time that research institutions in this country follow suit. And this is true not just for tissue used in research but the leftovers of routine clinical procedures as well. A study published in 2001 examined how Jewish persons in the United States felt about their tissue being used

for future genetic research. The majority indicated that their consent should be required before their DNA was used, regardless of whether the sample was collected in a research or a clinical setting. People should be told what might happen to their tissue (e.g., stored for future use or sold to a biotech company) and should be asked permission before it happens.

When the rights of people who participate in research are not upheld, the negative effects on institutions and on biomedical research are obvious: litigation, distrust of researchers, people's refusal to participate in research, bad publicity, and loss of funding. Evidence demonstrates that people do care about what is done with their tissue, and they will not put up with bait and switch tactics by researchers and institutions that promise one thing to induce participation but then turn and do something else.

The new stem cell technologies are being hailed as a breakthrough from the White House to research labs. With greater potential payoff comes greater motive and opportunity to abuse the trust and the rights of research participants who are so very necessary for medical science. For research to move forward, researchers claim they need a steady supply of human tissue for their experiments. But people will not agree to this, and should not agree, if they cannot rely on legal protections and the researchers' promises.

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