FROM BIRTH TO DEATH AND BENCH TO CLINIC

THE HASTINGS CENTER BIOETHICS BRIEFING BOOK

for Journalists, Policymakers, and Campaigns

CHAPTER 6

Cloning

Christopher Thomas Scott and Irving L. Weissman, "Cloning," in *From Birth to Death and Bench to Clinic: The Hastings Center Bioethics Briefing Book for Journalists, Policymakers, and Campaigns*, ed. Mary Crowley (Garrison, NY: The Hastings Center, 2008), 25-30.

cloning

by Christopher Thomas Scott and Irving L. Weissman

Framing the Issue

Most cloning—the process of making an exact genetic replica of a cell, a tissue, or an organism—happens naturally. When the fertilized egg first divides, occasionally each daughter cell goes on to form separate embryos. The result: identical twins, each one a clone of the other. Organisms that reproduce asexually, such as aphids, brine shrimp, yeast, and bacteria, are clones. Horticulture uses the term clone for a form of propagation that involves cutting up one plant into pieces that are used to grow hundreds or thousands of identical seedlings.

Scientific cloning takes up where nature leaves off. Genetic, or molecular, cloning makes copies of genes or segments of DNA. They can be used to create colonies of genetically modified bacteria or viruses, which can produce drugs and vaccines. Laboratory culture methods can clone a single cell into a population of cells, comprising a limitless number of identical progeny. Various techniques to make copies of whole animals are called reproductive cloning. Finally, there is reprogramming, in which the genes from adult cells are reset to an embryonic state. The hope is that these cells can help scientists understand genetic disease mechanisms and create stem cell-based therapies for diseases and injuries that are genetically matched to individual patients. As of this writing, no such therapies exist.

Cloning technologies are essential tools; without them modern biology would still be the stuff of science fiction. Cloning has led to scores of important drugs and newly developed therapies, such as human insulin, interferon to fight viral infections, and blood growth factors such as erythropoietin to generate new red blood cells.

The ethical debates surrounding cloning pivot on several issues. One controversial method of cloning—somatic cell nuclear transfer (SCNT)—involves the production of a two-to-four day-old blastocyst (a preimplantation embryo), whose cells are then removed to make a line of embryonic stem cells—a process that destroys the embryo. Another concern is over what might be done with these embryos prior to deriving a stem cell line. Because the technique employs some of the same culture methods used by in vitro fertilization clinics, some fear a cloned human embryo could be transferred to a woman, possibly resulting in a baby. And experience with animal reproductive cloning suggests more ethically troubling issues—early implantation of these clones always results in their death and often causes mater-

Christopher Thomas Scott *is a senior research scholar at the Center for Biomedical Ethics at Stanford University and* ***Irving L. Weissman, MD,*** *is a professor at Stanford University.*

HIGHLIGHTS

- Cloning technologies are essential tools of modern biology.
- Cloning has lead to important drugs and new therapies, such as human insulin and interferon to fight viral infections.
- Cloning also holds the promise of helping scientists understand the genetic basis of human development and disease.
- Cloning could produce a lifetime supply of therapeutic stem cells that are genetically matched to a patient and pose little risk of rejection.
- Cloning raises many ethical controversies. One of the greatest concerns the production and destruction of a two-to-four-day-old embryo to make a line of embryonic stem cells.
- Another concern is assuring that women donating eggs for research give proper informed consent.
- Some fear that a cloned embryo could be implanted into a woman, possibly resulting in a baby.
- Every major ethical scientific body around the world condemns human cloning.
- The United States is the only nation conducting human embryonic stem cell research that does not have a law prohibiting human reproductive cloning.

EXPERTS TO CONTACT

Christopher Thomas Scott, *Senior Research Scholar, Center for Biomedical Ethics, Stanford University* • cscott@stanford.edu, 650-725-6103

Irving L. Weissman, MD, *Professor, Stanford University* • irv@stanford.edu, 650-723-6520

Gregory E. Kaebnick, PhD, *Research Scholar, The Hastings Center* • kaebnickg@thehastingscenter.org, 845-424-4040, x227

nal death or morbidity. With cloning that involves human embryos, still another concern is assuring that the process for obtaining human eggs for research involves proper informed consent from the donors.

Historical and Scientific Overview

How does the embryo control development by gene expression, the process by which genes turn on and off? Could a developmentally older or differentiated cell have its genes reset to an earlier version of itself by being put into an embryo?

Researchers first addressed these questions in the 1950s (see box, "Cloning and Stem Cell Milestones: A Timeline"). A nucleus from an unfertilized frog egg cell was removed by sucking it out with a very fine, hollow needle called a micropipette. In the same fashion, a nucleus was removed from a cell inside a developing frog embryo. Injecting it into the empty egg began the process of embryogenesis. This process rarely resulted in tadpoles, a few of which grew into frogs. This was the earliest version of nuclear transfer, the cloning technique in which a nucleus without a cell is inserted into a cell without a nucleus. The evidence of the egg's power to reprogram genes was an important result, and the research moved to mammals.

Until the appearance of Dolly, a cloned sheep, most animal clones resulted from nuclei taken directly from embryos. Ian Wilmut, a Scottish researcher, inserted a somatic cell taken from the udder of a six-year-old sheep into an unfertilized sheep egg whose chromosomes had been removed. After the procedure, the proteins in the egg's cytoplasm reprogrammed the developmental instructions contained in the DNA. The genes switched from their fully differentiated "mammary cell program" to a program that produced a baby sheep. This is an enormously inefficient method for producing offspring, presumably because there is not enough time for the egg's cytoplasm to correctly reprogram all the genes from the udder cell to a pluripotent state. Over 99% of such clones die after implantation. Also, animals made in this fashion are not true genetic clones. The egg contains genetic material outside the chromosomes in organelles called mitochondria. The resulting organism or cell line is a clone at the chromosomal level, but has a mixture of mitochondrial genes.

The same method used to produce an animal clone—SCNT—could theoretically be used to make a cloned line of human cells with a near genetic match to any person who needed them. The nucleus from a donor cell would be inserted into an egg stripped of its nucleus. Then, just as in animal cloning, the egg would divide, and an embryo might be cultured to the blastocyst stage and have its stem cell line harvested.

Another hope is that reprogrammed cell lines made by SCNT could be powerful tools for studying the genetic basis of human development and disease, as well as for drug discovery. In the most optimistic scenario, cloning could produce a lifetime supply of therapeutic stem cells genetically matched to a patient and, therefore, posing minimal risk of immune rejection. Unfortunately, the mitochondrial mismatches usually lead to immune rejection, albeit at a slower rate than when the chromosomal genes are also unmatched. As in other dimensions of stem cell research, the promise of therapeutic stem cells has proven difficult to realize due to moral and technical obstacles.

Cloning Glossary

Blastocyst – In humans, a two-to-four-day-old embryo, roughly the diameter of a human hair.

Embryo – An early stage of human development. Medical texts describe embryonic development as a gradual process, beginning when the blastocyst attaches to the uterus and ending eight weeks later, as the organs begin to form.

Differentiation – The process by which stem cells make other kinds of cells and tissue in the body.

Stem cell – A cell that has the capacity to make new copies of itself and differentiate.

Somatic cell – A differentiated cell of the body, such as a skin or intestinal cell.

Induced pluripotent stem (iPS) cells – Stem cells derived from somatic cells following transfer of reprogramming genes taken from embryonic stem cells. The cells exhibit pluripotence, or the ability to copy themselves and change into different types of cells.

Reprogramming – The molecular and chemical mechanisms at work in SCNT and iPS cell experiments that reset genes in differentiated cells (such as skin cells) to an embryonic state.

Somatic cell nuclear transfer (SCNT) – Also called nuclear transfer. A technical step in which a somatic cell nucleus (containing the genetic material) is removed and transferred to an egg with no nucleus.

Therapeutic cloning – A popular term for the anticipated application of SCNT to make genetically-matched embryonic stem cell lines for therapies.

These difficulties came into sharp focus with the South Korean stem cell scandal. A research team announced in 2004 and 2005 that, using somatic cell nuclear transfer, they had established the first patient-specific human embryonic stem cell lines. Moreover, the researchers claimed to have accomplished the cloning with astounding efficiencies, easing worries that hundreds or thousands of human eggs would be needed. It was later revealed that thousands of eggs were indeed used, and some were obtained under questionable circumstances from women working in the laboratories. The lines themselves were not made by SCNT; they were derived from parthenotes—eggs treated in a way that causes them to divide without being fertilized—or possibly directly from IVF embryos.

This fraud fueled efforts to find uncontroversial substitutes for cloned human cells. First, experiments in which somatic and embryonic stem cells were fused successfully reprogrammed the genes in the somatic cell nucleus. This meant that genes expressed in embryonic cells keep them pluripotent, or able to make any cell or tissue in the body. More recently, researchers have reprogrammed skin cells with subsets of these embryonic genes by introducing them with mouse leukemia virus vectors. These experiments make cell lines with embryonic qualities (see chapter 34, "Stem Cells"). These lines—called induced pluripotent stem cells (iPS)—express markers and genes indicative of embryonic stem cells; they also possess the ability to redifferentiate into adult cell types. If they are found to be equivalent to embryonic cells, then they could—in principle—replace nuclear transfer as a means of generating pluripotent lines that genetically match a patient. Since both the chromosomes and the mitochondria come from the induced cell, iPS cells are a better match than stem cells from SCNT. Though several labs have now made human iPS lines, experiments with mouse iPS cells show that the genes and the vectors that carry them cause cancer. Elimination of these oncogenes is a goal of many reprogramming labs.

Cloning and Stem Cell Milestones: A Timeline

1950

1950s: In the United States, Robert Briggs and Thomas King clone frogs using nuclei from embryonic cells.

1960

1962: British scientist John Gurdon clones frogs using nuclei from adult intestinal cells.

1980

1984: Steen Willadsen, a Danish researcher, reports cloning a sheep using the nucleus from an embryonic cell.

1990

1996: In Scotland, Ian Wilmut clones Dolly, a sheep made from an udder cell.

2000

2001: Konrad Hochedlinger and Rudolph Jaenisch clone mice from white blood cells. All the cells in the mouse's progeny have the cells' signature genes.

2002: George Daley and Rudolph Jaenisch use nuclear transfer to make an embryonic cell line from a mouse with an immune disorder. Replacing the defective gene with a healthy one, they make blood-forming cells from the embryonic line. When transplanted, the healthy cells partially restore the mouse's faulty immune system.

2003: Death of Dolly

2005: South Korean Hwang Woo Suk's report of patient-specific embryonic stem cell lines made using nuclear transfer uncovered as a fraud.

2006: Shinya Yamanaka reports induced pluripotent stem (iPS) cells using mice.

2007–08

2007–08: Several labs report making human lines of iPS cells.

Bioethical Considerations

Nuclear transfer is a crude disruption of a delicate and barely understood biological process. Most cloned animals die during gestation and, because of abnormal placentas or abnormally large fetuses, can kill the surrogate mother. Of the few reproductive clones that survive, many are unhealthy, most likely due to failures of reprogramming. Skeletal abnormalities and arthritis are common, as are malformed organs, circulatory disorders, respiratory problems, and immune system dysfunction. Cloned animals often suffer from either abnormally high or low birth weight. For these reasons alone, attempting to clone a human being would be clearly unethical. As a result, every major national and international ethical and scientific body condemns human cloning.

However, even if cloning humans could be done as safely as IVF, opinions on whether it should be allowed are divided. Would we deny an infertile

couple a chance to have a cloned child? Are there other personal and private reasons for humans to clone a lost loved one, and should we deny them that possibility? Critics maintain that research cloning may lead to a slippery slope—condoning the process for research purposes could eventually result in condoning it for reproductive purposes. Cloning babies also creates life without sexual reproduction, which some believe undermines a vital dimension of humanness.

These arguments are based on an imagined world without societal checks or balances invoked by a moral consensus against the practice of cloning humans—the same pressures that condemn unethical treatment of human subjects in clinical research or payment for organs used in transplant procedures. Once it was clear that a stem cell line could make all tissues, we would certainly have a moral responsibility to use the line of cells to understand disease. These cells could also eventually provide therapies and cures. The moral justifications rest on the positive principle of beneficence: the research may reduce human suffering due to aging, injury, and disease, especially for those who may have a very short window of opportunity for treatment.

Resource constraints join funding restrictions as major hurdles to producing human stem cell lines by somatic cell nuclear reprogramming. Current technology requires the use of thousands of surplus or donated human eggs. The egg retrieval procedure is invasive and not without risk to women, raising concerns about obtaining proper informed consent. Whether women should be paid for removal of their eggs is hotly debated among ethics and policy scholars; national and state guidelines prohibit paying women for eggs over and above reasonable expenses related to the clinical procedure. Others point out inconsistencies in social policy that permit women to sell their eggs for reproductive purposes. Nevertheless, research using human and primate eggs may dramatically improve the efficiency of reprogramming, and, unlike the creation of iPS cells, nuclear transfer does not involve introduction of cancer genes.

Legal and Policy Issues

The United States is the only nation conducting human embryonic stem cell research that does not have a federal law prohibiting human reproductive cloning. This incongruous fact springs from legislative wrangling in Congress since 2001. Opponents of human embryonic stem cell research introduced measures that would criminalize both human reproductive cloning and production of such lines

RESOURCES

Web sites

- www.genome.gov – the National Human Genome Research Institute at the National Institutes of Health. Includes an illustrated fact sheet on the science of cloning.
- http://learn.genetics.utah.edu – the University of Utah's Genetic Leaning Center. Includes "Cloning in Focus," an interactive learning module that explores the reasons for cloning, its history, its risks, myths concerning it, and ethical issues surrounding it. Also includes additional resources.

Recent news

- Andrew Pollack, "Cloning Said to Yield Human Embryos," *New York Times*, January 18, 2008.
- Richard Hayes, "Beyond the Embryo Fight," *Los Angeles Times*, November 22, 2007.
- Gina Kolata, "Scientists Bypass Need for Embryo to Get Stem Cells," *New York Times*, November 21, 2007.
- Rick Weiss, "Monkey Embryos Cloned for Stem Cells," *Washington Post*, November 15, 2007.
- Nicholas Wade, "Biologists Make Skin Cells Work Like Stem Cells," *New York Times*, June 7, 2007.
- Arthur Caplan, "Cloning: Hype Begat Hype," *Philadelphia Inquirer*, March 1, 2007.

Further reading

- Gabor Vatja, "Somatic Cell Nuclear Transfer in its First and Second Decades: Successes, Setbacks, Paradoxes and Perspectives," *Reproductive Biomedicine*, November 2007.
- Christopher Thomas Scott, *Stem Cell Now: An Introduction to the Coming Medical Revolution*, Plume, 2006.
- Rudolf Jaenisch, "Human Cloning: The Science and Ethics of Nuclear Transplantation," *New England Journal of Medicine*, December 30, 2004.
- President's Council on Bioethics, *Human Cloning and Human Dignity: An Ethical Inquiry,* July 2002. Report available at http://bioethics.gov.
- Irving L. Weissman, "Stem Cells--Scientific, Medical, and Political Issues," *New England Journal of Medicine,* May 16, 2002.

See legislation appendix.

See online-only campaign appendix at www.thehastingscenter.org/briefingbook

by nuclear transfer. The tightly bound issues prevented a majority rule against reproductive cloning that would have carried easily in other countries. The vacuum in federal policy has led to a welter of state laws, some of which are permissive and others restrictive. It also leads to border dilemmas (by restricting the movement of eggs and cloned lines from permissive to restrictive states and vice versa) and, in South Dakota and Michigan, the threat of jail and other penalties for researchers. The regulatory environment is uncertain in the majority of states that are either silent on cloning or have laws that consider donated IVF embryos separately from embryos made for research purposes, including embryos made by nuclear transfer.

What is lost in the discussion about human embryonic stem cell funding restrictions is a long-standing federal prohibition on funding of embryo research generally, a legislative action that swept essential questions about infertility, reproductive medicine, and prenatal diagnosis beyond the reach of many American clinicians and scientists. Just as political controversies surrounding abortion and assisted reproductive technologies are used as proxies for restrictions on embryonic stem cell research, lines made by nuclear transfer are presumably bound by the same prohibitions as frozen embryos, despite national ethics committees and advisory groups such as the National Academy of Sciences recommending that the research proceed.

What Lies Ahead?

The future of cloning research faces at least four major scientific and policy questions.

- What are the genetic differences among standard embryonic cell lines, cloned cell lines, and directly reprogrammed cell lines? Understanding these differences will help us understand the cause and progression of disease, developmental disorders, and reproductive failures.
- Will induced pluripotent stem cell lines free of cancer risk eclipse nuclear transfer as a method to generate disease-specific (and eventually patient-specific) lines?
- Will political change in Washington lift funding restrictions for embryonic stem cell and cloning research, and will it impact long-standing restrictions on embryo research?
- Technologies are disseminated across a flat landscape caused by globalization. Differences in law, policy, and normative ethical frameworks cause gradients in access to research materials, discovery, and treatments. In the future, where will the United States stand among nations that seek to realize the full research and therapeutic potential of cloning?