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Five Ethical Questions for SCNT Stem Cell Research

Ronald M. Green

In August 2000, I received a phone call from Michael West, President and Chief Scientific Officer of Advanced Cell Technology (ACT), a small Massachusetts biotech company. West told me that ACT was about to embark on a program of research involving the use of somatic cell nuclear transfer (SCNT), also called therapeutic or research cloning, for the purpose of creating immunologically compatible embryonic stem cell lines. He wanted to know whether I was interested in serving as Chair of an Ethics Advisory Board (EAB) that ACT was setting up to provide guidance for its research.

Thus began an adventure that continues to occupy my time seven years later. Like all adventures, it has had its emotional highs and lows: moments of exhilarating accomplishment and others of seeming failure. Among them: the year-long collaborative effort of setting up the world’s first SCNT research egg donor program and watching the first eggs arrive for cloning experiments;¹ the November 2001 announcement of the creation of the world’s first cloned human embryo;² and then days later, a bitter controversy over whether the announcement was premature in terms of its

From 2002 to 2004, the Bush Administration threatened to ban SCNT research. The Republican-dominated Congress eliminated the trickle of venture capital funding that kept ACT afloat. These hostilities forced the termination of the expensive therapeutic cloning program and impaired ACT’s ability to meet its payroll expenses, leading some key researchers to seek positions elsewhere. In February 2004, there was combined disappointment and excitement when Korea’s Woo Suk Hwang announced that he had been able to derive lines of stem cells using the SCNT procedure. The disappointment derived from the awareness that the Koreans had accomplished what was just beyond ACT’s reach, given its cash-starved and politically harassed circumstances. The excitement came in the “I told you so” moment when Hwang’s work appeared to vindicate ACT’s commitment to therapeutic cloning research. Working beyond the reach of the Bush Administration, the Koreans had done it.

Then, more disappointment and excitement came a year later when Hwang’s systematic fraud was revealed and his findings were discredited. This episode tarnished all stem cell research and heartened its critics. But the goal still beckoned, and the experience ACT and its EAB had developed was once again of value. Investors returned and the race was on.

As I review the highs and lows of this adventure, I am struck by how many additional small achievements and setbacks there are to recount. In meeting after meeting, the EAB has been confronted by the many novel ethical questions this research involves. It has had to answer these questions in the context of an ongoing research program, in some cases with the safety of research participants at issue. This article details five of the most challenging questions that the EAB has had to address: (1) what the correct name is for ACT’s

research; (2) whether SCNT research is ethically appropriate; (3) what the entity produced by SCNT is called and its moral status; (4) whether it is ethical to financially compensate women who provide eggs; and (5) whether there are alternatives that reduce or eliminate the morally questionable aspects of SCNT research.

1. WHAT IS THE APPROPRIATE NAME FOR ACT’S RESEARCH?

It is a measure of how controversial this whole area is that the seemingly trivial question of what to call ACT’s research occasions dispute. From the start, ACT’s EAB identified its program as “therapeutic cloning” research. This term was already used to distinguish cloning aimed at the use of SCNT technology to create immunologically compatible stem cells from reproductive cloning, the use of SCNT to create a child. Nevertheless, voices were immediately raised criticizing this name. In its July 2002 report, *Human Cloning and Human Dignity*, the Bush-appointed President’s Council on Bioethics (PCBE) replaced “therapeutic cloning” with the term “cloning for biomedical research.”7 It did so for two reasons. First, the term was changed because Council members believed that the distinction between reproductive and therapeutic cloning was inaccurate, since all cloning involved the creation or reproduction of a human being.8 Second, because, in the words of the report, while “[t]he act of cloning embryos may be undertaken with healing motives . . . it is not in itself an act of healing or therapy. The beneficiaries of any such acts of cloning are, at the moment, hypothetical and in the future.”9 Both of these objections are questionable. The claim that “all cloning is reproductive”10 reflects a strong position on the nature and moral status of entities produced by SCNT cloning. The elimination of the use of the term “therapy” is tendentious because it is quite obvious that the therapeutic benefits of this research lay in the future. Nevertheless, these objections are not surprising from a Council that would ultimately take the unprecedented

8. Id. at 44.
9. Id.
10. Id.
step of proposing to criminalize this whole area of scientific research by recommending a four-year moratorium on it.\textsuperscript{11}

2. IS THIS RESEARCH ETHICALLY APPROPRIATE?

That the members of ACT’s EAB chose to provide ethical guidance for the conduct of this research illustrates that all of those who signed on to the project believed, in principle, that therapeutic cloning research can be ethically conducted. That judgment rested on three main convictions.

First, the EAB believed that therapeutic cloning research has lifesaving potential and could dramatically address urgent medical needs. Many of the disease conditions that remain without adequate therapies or cures are disorders caused by cell death or degeneration. This includes both juvenile and late-onset diabetes, Parkinson’s disease, osteoporosis, skin and bone injuries, heart disease, and a host of neurological and neuronal disorders and injuries.\textsuperscript{12} Stem cell research offers new approaches to treating these conditions. But what many regard as the most promising line of development, human embryonic stem cell research, still does not resolve the problem of tissue rejection. This rejection is because stem cells from an embryo are perceived by the recipient’s body as foreign tissue.\textsuperscript{13} Medications could be used to prevent rejection, but they carry a steep price: increasing susceptibility to infections and cancers.\textsuperscript{14} Therapeutic cloning promises all of the benefits of embryonic stem cell research plus a solution to the problem of rejection.\textsuperscript{15} By creating cells or tissues for which the recipient provides the somatic cell nucleus for the cloning procedure, it is possible to generate immunologically compatible tissue or organs.\textsuperscript{16}

The viability of this approach was demonstrated by a proof-of-principle experiment conducted by ACT scientists

\begin{itemize}
\item \textsuperscript{11} Id. at 205.
\item \textsuperscript{12} Robert P. Lanza et al., \textit{The Ethical Validity of Using Nuclear Transfer in Human Transplantation}, 284 JAMA 3175, 3175 (2000) [hereinafter Lanza, \textit{Ethical Validity}].
\item \textsuperscript{13} Id.
\item \textsuperscript{14} Jennifer Couzin, \textit{Gently Soothing a Savage Immune System}, 296 SCIENCE 456, 456–57 (2002).
\item \textsuperscript{15} Lanza, \textit{Ethical Validity}, supra note 12, at 3175.
\item \textsuperscript{16} Id.
\end{itemize}
working with researchers from Harvard, the Mayo Clinic, and the University of Miami. In this experiment, bovine renal tissue was created through a cloning procedure that began with the body cells of one cow and the enucleated egg of a second cow. Samples of the resulting cloned tissue were then attached to microtubules and plastic bladders. Some of these renal constructs were inserted under the skin of the original cell donor cow while others were inserted under the skin of control cows that had donated neither the original somatic cell nor the egg. When subsequently removed from the animals’ bodies for examination, the constructs inserted into control cows evidenced rejection and necrosis. The tissue of the constructs removed from the original cell donor cow was pink and perfused. Amazingly, these cells also produced urine that collected in the plastic bladder. Here were miniature, immunologically compatible kidneys. This experiment graphically illustrates the scientific promise of therapeutic cloning research.

A second factor supporting EAB’s judgment about the moral acceptability of this research was its agreement that the moral status of the entity created by the SCNT procedure was, at most, identical to a fertilized human egg (or early embryo). The EAB did not have a moral problem with the creation of SCNT embryos because it was of the opinion that sexually produced embryos could be used in potentially lifesaving research, whether the embryo was left over from infertility procedures or deliberately created for the purpose. The EAB believed that if it was permissible to create supernumerary embryos in in vitro fertilization (IVF) for reproductive purposes, it was also permissible to create embryos for lifesaving research. Some EAB members further believed that the SCNT embryo has even less moral status.

18. Id. at 694.
19. Id.
20. Id.
21. Id. at 690.
22. Id. at 692.
23. Id.
24. Although this experiment is illustrative, “[b]ecause the cloned cells were derived from early-staged fetuses, this approach is not an example of therapeutic cloning and would not be undertaken in humans.” Id. at 689.
than the early, sexually produced embryo.

Third, and finally, while all the members of the EAB shared the widely held view that for safety reasons alone it would be unethical to produce a child by means of cloning, no member believed this research would significantly hasten the advent of reproductive cloning or that refraining from this research would prevent reproductive cloning. Members understood that breakthroughs in therapeutic cloning techniques might contribute to the work of those seeking to accomplish reproductive cloning, but they believed that anyone bent on the latter would eventually be able to accomplish it with or without the help of therapeutic cloning researchers. To explain through an analogy: abstaining from therapeutic cloning research in order to prevent reproductive cloning research would amount to avoiding giving a baby a bath because of the remote possibility of harming the baby.

3. WHAT SHOULD WE CALL THE ENTITY PRODUCED BY SCNT (I.E., CLONING) AND WHAT IS ITS MORAL STATUS?

Is the immediate result of human SCNT (i.e., cloning) a human embryo? Is it a product of human reproduction, as the PCBE maintained? If so, does it have the same moral status (whatever that status might be) as the embryo produced when a human sperm fertilizes a human egg? Here again we have a terminological question that conceals powerful moral disagreements.

To some people, it is obvious that the SCNT unit is morally equivalent to a human embryo. It has a full complement of chromosomes as well as the potential to develop into an adult being.25 For these people, it is irrelevant that this potential requires intensive technological intervention and that it may have developmental potential significantly inferior to that of a sexually fertilized egg.26 Embryos acquired from IVF also require intensive technological intervention, and scientific advances are likely to significantly reduce the current high mortality of SCNT

25. THE PRESIDENT’s COUNCIL ON BIOETHICS, supra note 7, at 153.
26. Id. at 156.
units.\textsuperscript{27} The mere chance that an entity could become a child, the critics maintain, should lead one to place it on a par with the product of fertilization.\textsuperscript{28}

Not everyone agrees. During the EAB's initial debates, one of its scientist members surprised the other members by launching into what can only be called an “ode to fertilization.” She said that while working in reproductive medicine for many years, she never lost her sense of awe at watching a sperm fertilize an egg. But she insisted that for her, the SCNT process had none of this sanctity. It was an entirely artificial process and it could be arrested for research purposes as readily as it had been begun. In a subsequent letter to a scientific journal, this colleague proposed a new name for the product of SCNT.\textsuperscript{29} She would call it an “ovasome,” or egg-body.\textsuperscript{30} This term, she believed, better described the very limited moral importance of what SCNT researchers were doing.\textsuperscript{31}

Whatever this entity is called, and however its moral status is assessed in relation to the sexually produced embryo, in no case would it rank higher. Hence, individuals willing to use or create embryos for research purposes should be willing to support therapeutic cloning research. For a more extensive treatment of this issue and defense of using human embryos in lifesaving research or research of outstanding biomedical value, one might look at the 1994 Report of the National Institute of Health Human Embryo Research Panel.\textsuperscript{32}

4. IS IT ETHICAL TO PAY WOMEN TO PROVIDE EGGS FOR THIS RESEARCH?

Therapeutic cloning research requires an abundant supply of eggs. In the case of Dolly the sheep, it took 277 nuclear transfers to produce one viable embryo.\textsuperscript{33} While

\begin{itemize}
  \item \textsuperscript{27} Id. at 137.
  \item \textsuperscript{28} Id. at 152–57.
  \item \textsuperscript{30} Id.
  \item \textsuperscript{31} Id.
technical advances may reduce this ratio, a viable therapeutic cloning research program still requires over a dozen egg donors to have even a chance at producing a stem cell line.34

Egg donation requires the use of powerful drugs that stimulate a woman’s ovaries to produce multiple mature follicles instead of the single fertilizable egg of a normal cycle.35 Although some studies have suggested that these medications do not create significant risks for healthy women, the safety of their repeated use has not been confirmed.36 The non-aqueous drugs are painful to administer (requiring repeated injection directly into the buttocks) and they can cause the intense emotional reactions usually associated with hormonal irregularities.37 There is also a very small (and largely preventable) risk of ovarian hyperstimulation, a life threatening overreaction to the drugs.38 In view of all these risks and burdens, why should women volunteer to provide eggs for research unless they are adequately compensated? The experience with reproductive egg donation is instructive. In the United States, reproductive egg donors are paid varying but substantial sums of money and there is an adequate supply of donors.39 Great Britain, in contrast, prohibits payment for reproductive and research donors and has suffered a virtual standstill in supply.40 In an effort to address this problem, the Human Fertilisation and Embryology Authority (HFEA), the agency that provides oversight for all infertility medicine and embryo research in

36. Id.
38. Ronald M. Green, The Ethical Considerations, SCI. AM., Jan. 2002, at 48, 49 [hereinafter Green, Ethical Considerations].
39. Id.; see also Gruen, supra note 6, at 296. But see id. at 285 (reporting a shortage of eggs in California following the 2004 ballot initiative prohibiting sale of oocytes for research purposes).
that country, has permitted egg-sharing programs, whereby women undergoing IVF can receive discounted services for offering some of their eggs to other women who need them for reproductive purposes.\(^{41}\) Last year, the HFEA expanded this permission to include research egg donation.\(^{42}\)

In 2005, an influential report by a committee of the National Academy of Sciences recommended against payment (beyond out-of-pocket expenses) for research egg donation.\(^{43}\) In the wake of this, several states, including California and Massachusetts, passed laws prohibiting payment for eggs for research.\(^{44}\) Because both states have significant public or private commitments to therapeutic cloning research, these bans have had the effect of preventing this research from starting. Since the passage of the Massachusetts law, despite expressions of interest from over one hundred women in response to advertising, ACT has been able to secure only one voluntary donor.\(^{45}\) This compares to over eighty women who donated eggs under the previous paid research donor program.

Why, if payment is so clearly needed to facilitate research, do so many authorities oppose it? Some of the answers given to this question do not withstand close scrutiny and may even proceed from sexist premises. The view that women can be paid for eggs for reproductive but not research purposes may reflect the belief that maternally related sacrifices are somehow proper to women, whereas a commitment to science research is not. Some fear that poor women and women of color will be disproportionately attracted to research egg donation since the mother’s genetics and accomplishments do not matter in this sphere as they do in the reproductive one.\(^{46}\) The concern is that such payments may constitute an “undue influence,” compromising women’s ability to provide free and informed consent and risking their

\(^{41}\) Id.
\(^{42}\) Id.
\(^{44}\) Green, It’s Right to Pay Women, supra note 37.
\(^{46}\) Gruen, supra note 6, at 303.
health. But it can also be asked why women should be protected from their own decision-making and whether such attitudes reflect unjustified paternalism—or patriarchalism. In a world where normal research volunteers are often paid for their participation in risky research, why should women be denied similar opportunities?

An unpublished review of reports from the ACT research egg donors indicates that the more than eighty women who served in this capacity tended to express two equally significant reasons for doing so: (1) a desire to contribute to stem cell research and (2) a desire for the money. Many of these women reported having family members who suffered from diseases like diabetes that stem cell therapies might address. In view of this, the prohibition on payment becomes even more problematic. Why should women who wish to contribute to research, but who need a financial incentive to overcome their natural reluctance to submit to a demanding drug regimen, be held to a purely altruistic standard?

Seven years ago, ACT’s EAB asked all these questions regarding compensation for egg donors. The EAB discussed—and rejected—egg sharing on the grounds that it unwisely mixes the sensitive issue of infertility treatment with research donation. If a women’s reproductive quest fails, will she come to regret and resent her decision to donate eggs for research purposes? Will she harbor the view that researchers took the best of her eggs? The EAB also carefully developed guidelines to protect women from harm. These guidelines covered everything from age limits, psychological testing, and reproductive history to safe estradiol levels. In the end, the EAB concluded that a well-developed program was ethically and scientifically appropriate. It is distressing that seven years down the line, as programs around the country renew their attention to therapeutic cloning, these lessons need to be learned all over again.

48. Green, Ethical Considerations, supra note 38, at 49.
FIVE ETHICAL QUESTIONS FOR SCNT

5. CAN THE SCNT PROCEDURE BE ALTERED TO REDUCE OR ELIMINATE ITS MORALLY QUESTIONABLE ASPECTS?

Several technical ideas have been advanced to address some of the ethical questions raised by SCNT technology. For example, it has been proposed to use animal oocytes to replace the use of human eggs in the cloning procedure.\(^{50}\) There have been reports of success with this approach, although they have not been replicated.\(^{51}\) Unfortunately, although the use of animal oocytes eliminates the problems associated with human egg donors, it raises additional problems associated with the production of animal-human chimeras or what have been termed “cybrids.”\(^{52}\) These include concerns ranging from the possibility that the resulting stem cells may be unsuitable for transplant and could introduce animal DNA or pathogens into the human population to the nightmarish possibility that chimeric embryos might be diverted for reproductive purposes.\(^{53}\) Ethically, this approach raises more questions than it answers.

A more radical change in the SCNT procedure has recently been proposed as a way of eliminating the moral discomfort with human embryonic stem cell research experienced by those who regard the early embryo as a human being. This proposal, known as Altered Nuclear Transfer (ANT) was made by William Hurlbut, a member of the PCBE.\(^{54}\) It involves using the standard SCNT cloning procedure for the purpose of stem cell derivation—with one notable difference. In ANT, the somatic cell used for cloning is first genetically altered so as to impair the resulting SCNT unit’s developmental capability.\(^{55}\) Hurlbut states that

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51. Id.
52. Id.; see also Constance Holden, Report Backs Interspecies Lines, 316 SCIENCE 1683 (2007).
53. Schirber, supra note 50, at 317.
55. Alexander Meissner & Rudolf Jaenisch, Generation of Pluripotent NT-ES Cells from Cloned Cdx2 Deficient Blastocysts, 439 NATURE 212, 212 (2006). This was done experimentally by impairing the Cdx2 gene that is responsible for placental development. Id. Lacking a functioning copy of
because this modification is undertaken before the clonal embryo is even created, the resulting entity would have “no inherent principle of unity, no coherent drive in the direction of the mature human form, and no claim on the moral status due to a developing human life.” He prefers the term “clonal” or “biological artifacts” for these entities.57

Unfortunately, it is by no means clear that many of the people who morally equate the early human embryo with a full human being will be satisfied with this strategy for producing immunologically compatible stem cells. ANT embryos develop normally until Cdx2 function is required, at which point they die.58 This suggests that people with a high estimate of the status of early nascent human life might reasonably interpret this procedure as involving the deliberate creation of an impaired human being in order to justify destroying it. In effect, they would see it as doing two wrongs in order to do a right.

A simple example supports this objection. If the early embryo is fully a human being, as the opponents of embryo destruction believe, how does ANT differ morally from the deliberate creation of an anencephalic infant as an organ donor? Lacking a cerebrum, this child can also be said to have “no inherent principle of unity, no coherent drive in the direction of the mature human form, and no claim on the moral status due to a developing human life.” If we find such a proposal morally repugnant, it is not clear why an analogous impairment imposed on a “human being” at a much earlier stage is acceptable.

CONCLUSION

Despite the serious reverses represented by the Korean scandal, therapeutic cloning remains one of the most promising biomedical technologies before us. As my tenure as Chair of ACT’s EAB indicates, I believe that none of the
ethical concerns resident in these five questions constitutes a reason for refusing to go forward with this research. Whether we call the entity created by SCNT an embryo or an SCNT unit, that creation need not be given more—and probably should be given somewhat less—moral weight to it than is given to the early human embryo, which can responsibly be used to derive stem cell lines. Payment for research oocytes seems to be fully justified and does not raise problematic, long-term issues. Some people fear that the successful development of therapeutic cloning will create a vast market in human eggs that will lead to the exploitation of poor women. However, several promising technologies are on the horizon, including *in vitro* egg maturation and the development of oocytes from stem cells themselves that will obviate the need to call on large populations of egg donors. Furthermore, therapeutic cloning is a “transitional” form of research. Once scientists better understand which components of egg cytoplasm remodel a cell’s nuclear DNA in the cloning context, they can use these purified cytoplasmic factors for direct cellular dedifferentiation and reprogramming.

All of this suggests that research should be furthered. States like California and Massachusetts, where therapeutic cloning research is permissible, should repeal the bans on adequate compensation for research egg donors. Congress should also abandon its previous efforts to criminalize this research.

Seven years ago, when I accepted the leadership of ACT’s EAB, I nourished the hope that we would see clonally


63. This does not preclude the need for more intensive animal research to increase the efficiency of the cloning procedure before we expose women to risk by seeking eggs from human donors.

produced stem cells within a few years. We almost did. If it had not been for continual political meddling, that hope might have been realized. It is now time for good science and good research ethics, not politics, to shape the future.