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Perspective

Somatic Cell Nuclear Transfer: A Call to Reevaluate Stem Cell Research Policies

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Abstract

Somatic Cell Nuclear Transfer (SCNT), also known as "therapeutic cloning" is a scientific technology in the field of stem cell research. Used in science for decades using animal models, this technique was recently achieved in human cells and has spawned a number of subsequent breakthroughs in the stem cell field. However, due to ethical concerns both in research practice and the outcomes of science, SCNT is prohibited in many legislative contexts in the United States. The recent breakthroughs precipitate the need to reevaluate stem cell research policies in the United States so that this science can continue to advance.

Keywords: Stem cell research; Research ethics; Justice; Law

Perspective

Over the course of the past two years, New York was home to a series of advancements in the field of stem cell research, each of which, in some noteworthy degree, has shaken the foundations of the stem cell field. Stem cell research, particularly embryonic stem cell research, has, for over a decade, sat at the precipice of the most cutting-edge and potentially groundbreaking frontiers of science, yet has been impeded by policy and legislative obstacles that have prevented the research from gaining its stride. The recent breakthroughs achieved have demonstrated how a favorable scientific and regulatory environment can have an impact on significant advances in this burgeoning field. These breakthroughs similarly raise the question of what adjustments need to be made to stem cell policy at the state and federal levels, in order to achieve the scientific milestones that the stem cell and regenerative medicine disciplines might present.

SCNT, also known as "therapeutic cloning", has been used in biological research since the mid-1970s. First achieved by Gurdon using amphibians, the process involves the removal of the nucleus of a somatic cell, which is then implanted in an enucleated egg [1]. With the assistance of external stimulation and factors found within the egg, the nucleated egg begins to divide and proceed down a course of development. This technology creates embryos that are genetically matched (clones) to the donor somatic cell. While SCNT has been used to clone animals, its use in embryonic stem cell research has been with the goal of deriving embryonic stem cells that are patient-specific, thereby circumventing potential immune responses to stem cell-based treatments and allowing scientists the opportunity to watch, *in vivo*, the progression of disease as it attacks cells.

The implications that this technology has for regenerative medicine are considerable, however the creation of embryos through SCNT using human cells has, for quite some time, been elusive. However, the dubious success of this technology using human cells was eroded following a series of recent studies.The first of these studies took place in 2011, by Noggle and colleagues. These researchers achieved what had never before been accomplished using human cells: the generation of pluripotent stem cells from an unfertilized oocyte (egg). A form of SCNT, this breakthrough allowed researchers to reprogram human somatic cells into a pluripotent state by transferring its genome into an oocyte [2]. As previous attempts at cellular reprogramming using oocytes resulted in developmental arrest, this breakthrough was made using the novel approach of keeping the haploid oocyte genome in place rather than removing it, as has been done in other mammalian species. The product of this experiment was the derivation of triploid human stem cells that could be used to study disease development. Tellingly, the authors concluded, "with a reliable source of human oocytes, it should be possible to overcome the requirement of the oocyte genome for somatic cell reprogramming, allowing the generation of diploid pluripotent stem cells." [2]. Fortunately, New York's stem cell policy efforts allow for such a reliable source of human oocytes.

The second breakthrough, made in 2013 by Egli and colleagues [3], developed directly out of the first, and highlighted the practical and translational nature of SCNT in practice. The investigators found that it was possible to transfer the nucleus from one human oocyte to another and leave behind the mitochondrial DNA. Through this procedure, the investigators demonstrated that it would be possible to prevent the inheritance of mitochondrial disease in children [4]. The technique of oocyte nuclear transfer results in an egg containing the genome of a donor but the mitochondrial DNA of another egg cell, thereby, circumventing the possibility of passing on mitochondrial disorders from mother to child. These landmark scientific achievements have been lauded by such publications as *Time Magazine* and *Genetic Engineering and Biotechnology News* as the 2011 Scientific Breakthrough of the Year and one of 2012's "10 Predictions That Will Transform Healthcare". The prerequisite of these medical breakthroughs was the availability of eggs on which to conduct research.

The two preceding experiments established the groundwork for one of the most transformative and ground-shifting advances to take place in stem cell science when, in April 2014, scientists announced that they had derived a colony of patient-specific embryonic stem cells from embryos created through somatic cell nuclear transfer.

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What was revolutionary about this advance was that this stem cell line was derived from the cells of an adult with type I diabetes, and were induced into becoming insulin-producing beta cells, the very type of cells that are lost or dysfunctional in type I diabetes [5]. This breakthrough, the first of its kind, is a significant step in the potential of creating healthy stem cells, and then genetically matched replacement therapies, to treat long-untreatable conditions in which stem cells are diseased or damaged.

The most recent milestone in SCNT was built upon years worth of painstaking work needed to unlock the mysteries of cellular reprogramming, and then additional work to induce the stem cells to differentiate in a specified manner. However, this is a scientific technology that, just several years ago, was believed to be all but antiquated or unfeasible, for a multitude of reasons. With the rise of induced pluripotent stem (iPS) cells, which allowed for adult cells to be reprogrammed into an embryonic-like state quickly and more efficiently, it was believed that the patient-specific and genetically-matched benefits that SCNT provided would no longer be necessary. Recent research, however, has indicated that there are numerous and important irregularities in iPS cells that call their therapeutic potential into serious question [6-8]. Pluripotent stem cells derived from SCNT appear to present none of these therapeutic challenges and closely mirror the characteristics of embryonic stem cells. Additionally, as several researchers have pointed out, iPS cells are still not adequately understood and may house potentially harmful abnormalities [9-11].

The practical considerations that slowed the progress of SCNT were, at minimum, paralleled by several regulatory and policy challenges that have nearly brought this technology to a halt.Now that SCNT has been achieved using human cells, and the mechanics of the science are becoming more fully understood, the scientific barriers may begin to present much less insurmountable a challenge than the legislative barriers. While New York State presents a regulatory environment in which SCNT can be pursued without political consequence, changes ought to be considered in other contexts so that interstate collaborations can take place and SCNT can progress with greater ease.

How public policy has affected the evolution of SCNT, and therefore the types of breakthroughs that are only now taking place, can be traced back 20 years, when, in 1994, the federally-assembled Human Embryo Research Panel (HERP) was convened to develop guidelines for how embryonic research could take place in the United States [12]. The experts on the Panel recommended that, under certain conditions and oversight, federal funding could be directed to research using embryos that had been created explicitly for research purposes. Despite this recommendation, however, President Clinton encouraged the NIH to focus its funding for research using embryos to only those embryos that had been surplus due to *in vitro* fertilization procedures. This decision excluded embryos created exclusively for scientific research [13], of which SCNT embryos were a part. Though not a legislative measure, the encouragement by President Clinton to direct attention primarily, or even solely, to supernumerary IVF embryos set up an implicit tension between research experts and the federal government on how to regulate research using embryos created for research purposes.

The dictate given to the NIH by President Clinton was codified in 1996 when two Congressmen, Jay Dickey and Roger Wicker, expressed their concern on how embryos might be used in scientific research. Given their conservative, pro-life ideology, these two Congressmen introduced a legislative amendment to the Balanced Budget Down Payment Act of 1996, which stated that no federal monies could be spent on research involving the creation or destruction of a human embryo. This amendment, which came to be known as the Dickey-Wicker Amendment, was voted on and implemented by Congress in 1996 and has been upheld every year since then. Though this amendment was passed several years before the first human embryonic stem cell line was derived in 1998, its functional and continuing implications on human embryonic stem cell research are enormous [14]. What this legislative decision meant, and continues to mean, for embryonic stem cell research is that the process of deriving embryonic stem cells, which necessarily results in the embryo's "destruction", would not be supported by the federal government. This amendment also establishes a prohibition on the utilization of technologies like SCNT, which involves the creation of an "embryo".

The Dickey-Wicker Amendment, having been approved every year since 1996, in addition to the limitations implemented under the Bush administration, have had a strong impact on embryonic stem cell research in the United States. On March 9, 2009, President Obama gave an address from the White House and signed a much-anticipated executive order, Executive Order 13505, to relax some of the Bush administration's stem cell research restrictions. The President delivered his address in front of an audience of scientists, advocates, legislators, and ethicists who had been involved in the stem cell issue over the years. Using language that reflected how embryonic stem cell research had been contextualized in the United States since its inception [15], President Obama attempted to erase the distinction between morality and scientific progress. For instance, the President stated, "in recent years, when it comes to stem cell research, rather than furthering discovery, our government has forced what I believe is a false choice between sound science and moral values. In this case, I believe the two are not inconsistent. " He continued by arguing, "After much discussion, debate and reflection, the proper course has become clear. The majority of Americans – from across the political spectrum, and of all backgrounds and beliefs – have come to a consensus that we should pursue this research. That the potential it offers is great, and with proper guidelines and strict oversight, the perils can be avoided."

In Executive Order 13505, President Obama gave the NIH the charge of drafting guidelines for federal funding for embryonic stem cell research, which were to be drafted within 120 days of the executive order. While, in principle, the objectives behind Obama's change in stem cell policy were widely applauded by many researchers and advocates, the draft guidelines established by the NIH Workgroup fell below what many of these researchers and advocates had hoped. Specifically, the NIH guidelines called for five specific items or criteria: 1) that embryos from which stem cells were derived were created for reproductive purposes and no longer needed; 2) embryos were donated by individuals who gave voluntary written consent for the embryo's usage; 3) stem cell lines not meeting the drafted criteria could be submitted to the NIH for a case-by-case review for funding; 4) the NIH would not fund the actual derivation of stem cell lines,

pursuant to the Dickey-Wicker Amendment; and 5) such scientific pursuits as somatic cell nuclear transfer and parthenogenesis will not be funded.

Were it not for SCNT and the creation of embryos for research purposes, both of which are expressly prohibited under the current NIH guidelines, the breakthroughs that are taking place today might not have come to pass. This would have been a loss, not only to science, itself, but also to humanity. While there may have been a time when complex and controversial technologies like SCNT and the provisions necessary for its conduct needed to be approached with caution, recent advances in the stem cell field have allowed them to demonstrate their worthiness. With this in mind, it is time to reevaluate the policies that have impeded this work, both at the state and federal levels.

While basic research is the vehicle by which scientific advancement reaches its potential destination, a policy framework serves as the roadmap, wrought with detours and stop signs, that sets the parameters of how far science can go. Science is increasingly becoming the product of public policy, and when it comes to public policy there is perhaps no scientific field that has been more influenced than embryonic stem cell research. What is more, within the context of stem cell research, one of the facets of the research that has generated the most controversy, and therefore the greatest public deliberation, has been how to regulate therapeutic cloning. The use of the term "cloning", irrespective of the context, incites a host of fears about the perils of scientific research and where it is headed. As a result, how different regulatory agencies and policy makers, both within the United States and around the world, have legislated in response to SCNT has not only focused on the permissibility of the technology, itself, but also on the permissibility of the procedural steps, like egg (or oocyte) donation, that must be taken in order for SCNT to be conducted at all.

As a result of the Dickey-Wicker amendment, and what was stipulated subsequently in the 2009 NIH stem cell guidelines, the federal government prohibits funding used for SCNT and its resulting stem cell lines. When these guidelines were drafted and adopted, the prohibition on SCNT and the creation of embryos for research purposes was considered by many stem cell researchers to be a shortcoming. Among those who supported such a prohibition, the claim was made that there was insufficient evidence that SCNT was even a valuable or efficient technology, especially with the patient-specific and disease-specific stem cell lines that could be generated more quickly through iPS. However, three of the recent breakthroughs in stem cell research, which stand to fundamentally change not only the state of the field but also the quest for medical cures, have come from work using SCNT and embryos created for research purposes. From this perspective, stem cell research policies and guidelines as they are currently stipulated might very well be prohibiting an avenue of research that has the potential to yield revolutionary advances for the field.

As Hyun [16] has noted, stem cell governing agencies in other countries, including Australia, Singapore, and the UK, have permitted the creation of embryos for research purposes, including SCNT, under governmental oversight and regulation. Looking to strategies that have been implemented in these other countries might provide a basis upon which to establish similar frameworks in the United States. Under these international agencies, clear regulations and oversight have taken the place of the United States' strategy of immediate prohibition. The latter course of action not only generates unnecessary social anxieties regarding therapeutic cloning and embryonic stem cell research but also diminishes opportunities for scientific advancement. In countries like Australia, Singapore, and the UK, a different, more scientifically friendly approach has been pursued, in which specific experiments that require the creation of embryos are subject to approval and licensing after a review process. This regulatory mechanism allows for important research, research that is currently beyond the scope of US federal permissibility, to take place under regulatory oversight and, as a result, with the confidence of the public [17].

In other countries, the concern over unethical research practices or the improper use of scientific knowledge has been met with oversight rather than outright prohibition, and oversight that is conducted by agencies that operate quite analogously to ethical oversight committees already in existence in the United States. We can ensure adherence to the highest ethical standards through the reliance on local and institution-based Stem Cell Research Oversight (SCRO) committees, which operate in a manner similar to Institutional Review Boards (IRBs), yet with specific expertise and attention on stem cell science [17]. When it comes to stem cell research protocols that utilize SCNT, SCRO committees can ask the very same questions as are asked by regulatory authorities established in other countries. Just as President Obama stated in 2009, "with proper guidelines and strict oversight, the perils can be avoided". There is no one who cares about the future of stem cell research who would want otherwise.

Given the contentious political climate that pervades the halls of Congress, it seems unlikely that the Dickey-Wicker Amendment will be removed anytime soon, and equally as unlikely that the 2009 NIH guidelines will be liberalized, despite the fact that there is need for both of these. Fortunately, it is not simply the federal government in the United States that has dedicated public funds to stem cell research, but initiatives have also taken place at the state level and through private philanthropic endeavors. In these local or private contexts, the Dickey-Wicker amendment does not apply and, as a result, the creation of embryos for research purposes is not expressly prohibited due to this legislative measure.However, state legislatures and private institutions need to find the political and the scientific wherewithal to meet the challenge of facilitating this research in a manner that compromises neither important science nor the ethics of scientific practice.

When it comes to the ethics and legalities of SCNT, many state legislatures and nonprofit research organizations are bound by regulatory impasses, but not those that are as prohibitive or politically sensitive as the Dickey-Wicker Amendment at the federal level. What has complicated some of these state-based initiatives, for instance that of California, relates to the logistics of the egg donation process that necessarily accompanies SCNT and the creation of embryos. Specifically, the debate has centered on what, if any, responsibility there is to provide remuneration to women who have made the significant contribution to scientific advancement in the form of the donation of an oocyte: whether such compensation should not take

place at all, whether it should be strictly limited to reimbursement for out of pocket expenses, or whether it should be some amount above and beyond that to compensate for time and burden, in accordance with similar guidelines established by the American Society for Reproductive Medicine (ASRM) in egg donation for reproductive purposes.

The forerunner among state-based stem cell research agencies, the California Institute for Regenerative Medicine (CIRM), established in 2004, legislated to permit the reimbursement to women for out-of-pocket expenses immediately associated with the egg donation procedure, but not compensation for time, effort, or contribution to science. This has significantly impeded California's ability to advance in this area. New York's Empire State Stem Cell Board, however, took an unprecedented position, not only by legislating in favor of SCNT and the creation of embryos for research purposes, but also by allowing for compensation to women who donate eggs for research purposes, an amount comparable to that provided for donation for reproductive purposes [18]. It was the hope of the Board that creating a more permissive research environment might facilitate the spread of scientific knowledge and breakthroughs that might otherwise not take place. The hopes of the Empire State Stem Cell Board proved to be founded, as the change in policy has yielded significant scientific returns. It is perhaps no coincidence that the breakthroughs that are currently being made using SCNT are being made in New York.What has become clear in the past two years is that the scientific culture created by New York's regulatory environment has provided the latitude for strides to be made that could not readily be made in other places.

Policy differences, such as those involving oocyte donation and the permissibility of SCNT or embryo creation for research purposes, have had tangible effects on stem cell science. Positions taken by such institutions as the NIH and CIRM have placed a tacit moratorium on advances using these technologies, and even on the ability of researchers to share this knowledge from one context to another. As Hyun asks, "with neither CIRM nor NIH funds available for studying human SCNT stem cells, how are researchers supposed to extend the contributions of SCNT research to the entire stem cell field?" [9]. This is an important question to be asked, and one that speaks to the exceptionalism that has been directed to stem cell science over many others. The differing policy frameworks and regulations that have dictated embryonic stem cell research since its inception have significantly slowed the progress of this field and have undermined the critical collaborations on which science relies.

As an increasing number of research institutions, states, and countries around the world address stem cell research policy, they ought to bear this question in mind. The creation and dissemination of scientific knowledge depends as much on its context as it does on the science, itself. A favorable scientific environment, complete with necessary ethical boundaries, yields favorable scientific strides.What has taken place in New York: developments that could not take place anywhere else in the United States, is a testament to this idea. It is also a testament to the idea that research embryo creation and SCNT can be done in a way that does not compromise ethical, safety, or scientific concerns. With proper regulations, this research and these technologies can move forward in a manner that is both scientifically and ethically sound.

The United States has long been a global leader in the realm of science, and remains so in the discipline of stem cell research. Indeed, there is no country around the world that commits as much funding or as many resources to this work as does the United States, and it is home to many of the most equipped research institutions to be found. In order to maintain this status, it is important to likewise maintain regulatory initiatives that properly combine ethical oversight with an eye toward scientific progress. The current US policy that governs this research may not have successfully struck this balance. Policies grounded in the Dickey-Wicker Amendment and the 2009 NIH guidelines are bound by concerns that not only impede scientific work like SCNT but also are of a time unrelated to current scientific realities. In this instance, scientific need can facilitate political change, whether taken at the state, institutional, or, at some point, federal level. For therapeutic advances to be accelerated to laboratories throughout the country, policy adjustments as they relate to embryonic stem cell research and SCNT ought to be made to accommodate this quickly evolving field. Policies like Executive Order 13505, which have their origins in sensibilities held 20 years ago – a veritable eternity in science – are no longer feasible or practical for this field. As the science evolves, so, too, must public policy. The pursuit of stem cell based therapies and treatments might very well be hampered for failure of it.

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