Somatic Cell Nuclear Transfer: the Promise and the Perils

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Abstract The scientific goal of deriving human pluripotent stem cell lines via somatic cell nuclear transfer (SCNT) has become a reality in the past few years. In the early days of this research, however, the degree of hype and promise surrounding human SCNT was matched by equally ardent warnings of its ethical perils. This commentary compares the predicted promises and perils of human SCNT to the current scientific and ethical realities, taking note of underappreciated issues that have emerged in the interim.

Keywords SCNT · iPS cells · hES cells · Bioethics · Egg donation · Scientific justification

Introduction: the Predicted Promises and Perils

Scientific interest in human somatic cell nuclear transfer (SCNT) began in earnest soon after the arrival of Dolly the sheep in 1996 and the announcement of the derivation of the first human embryonic stem (hES) cell line in 1998 [1, 2]. These breakthroughs were received with great expectations because of their anticipated clinical applications. Onlookers speculated that human SCNT research could yield a multitude

of biomedical advances that would give researchers opportunities to study new therapies and disease mechanisms by creating patient- and disease-specific stem cell lines. Many also predicted that human SCNT research would usher in the advent of regenerative medicine, whereby medical professionals could use healthy patient-matched stem cells derived via nuclear transfer (NT-hES cells) to replace damaged tissues. Moving forward, the prospect of human SCNT research appeared rich with promise.

Still, the brightest lights cast the darkest shadows. Other people received the news of mammalian SCNT with apprehension, arguing that the harms of pursuing this line of research with human somatic cells and oocytes far outweighed the potential benefits. They proffered dystopian visions of corrupt social institutions exploiting the fertility and reproductive labor of oocyte donors—usually portrayed as indigent women pressured into commodification by their lack of financial resources. Critics also warned that human SCNT research would open the door to reproductive cloning. After all, if scientists could clone a sheep, what would prevent them from cloning humans? What would stop individuals from cloning themselves? Sliding down the slippery slope of human SCNT research, they thought, would force society to confront a host of contentious bioethical issues.

In the early days of hES cell research, the warning bells around human SCNT research matched the hype surrounding its perceived promises. The aim of this commentary is to re-examine these aforementioned speculations. We seek to explain which visions of human SCNT research have stood the test of time and which have not. We shall compare the predicted promises and perils of human SCNT to the current scientific and ethical realities, taking note of unforeseen issues that have emerged. For many people, the Hwang cloning fabrication scandal may have underscored the dangers around oocyte procurement and the hype around SCNT for patient

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therapies [3]. While this is certainly true, an overlooked lesson in the Hwang scandal is the issue of research oversight—a theme we return to in part three.

The Current Realities

The first confirmation of successful human SCNT occurred nearly a decade after the scandal in Hwang Woo Suk's lab in Korea in 2004. Why did it take so long? One reason was the need to overcome unforeseen technical barriers. For instance, Mitalipov et al. discovered that donor cell fusion, cytoplasm activation, and spindle removal dramatically improves blastocyst development and cellular reprogramming [4•]. Egli et al. demonstrated that changes to the oocyte activation protocol—e.g., utilization of kinase and histone inhibitors at key transitions—significantly improve the quality of the NT-hES cells [5]. Uncovering these technical tweaks was a painstaking process, which is one reason why it took so long to derive hES cells via SCNT.

In addition to these necessary technical advancements, perhaps the single most impactful reason was that, historically, prohibitions against egg donor compensation for research acted as a critical bottleneck, preventing scientists from gaining access to these important starting biomaterials. Human SCNT research requires, of course, human eggs, which are not easy to obtain. The processes of hormonal induction and egg retrieval are labor intensive, time consuming, and physically taxing for donors. Despite these acknowledged burdens, research egg donors were prohibited from being paid for their efforts by national stem cell research guidelines and state laws in California and Massachusetts. Women who were recruited to undergo hormonal induction and egg retrieval were permitted only reimbursements for their out-of-pocket expenses, not compensation for their substantial time, effort, and inconvenience. Regulators who drafted these policies worried that providing financial payments beyond reimbursements would lead to exploitation and undue inducement [6]. As a result of these policies, essentially no women in the USA chose to provide their eggs, leaving SCNT researchers empty handed and unable to carry out their experiments [7].

The dearth of available eggs forced many supporters of stem cell research to reconsider this restrictive policy. The two aforementioned research teams were able to compensate women for their time, effort, discomfort, and inconvenience, since they operated in states where compensation for research egg donation was allowed. Moving forward, reasonable compensation practices will be necessary to give SCNT researchers access to more eggs, which will enable them to continue their studies [8].

It bears mentioning that during the early years of proposed human SCNT research in the USA, predictions abounded that compensation would lead to widespread exploitation.

However, when examining the current state of SCNT research, donor exploitation does not appear to be a problem. And there is no evidence to suggest that it will become one anytime soon. Thus, this particular dire prediction appears to have missed the mark. Furthermore, many people expected a huge public outcry in response to any reports of human SCNT research being conducted in the USA. Yet, the public reacted with general silence upon the publication of the American SCNT studies, which was surprising, given the emotional intensity around stem cell research during the Bush Administration.

Perhaps one major reason for this current lack of controversy was the advent of human induced pluripotent stem (iPS) cells, which arrived on the scene well before the published human SCNT work. Shinya Yamanaka was awarded the Nobel Prize in 2012 for successfully reprogramming differentiated cells to a pluripotent state, generating cells known thereafter as iPS cells. He and his team did this by identifying and introducing four transcription factors to fibroblasts—Oct3/4, Sox2, c-Myc, and Klf4—that, in turn, triggered the morphology and growth properties of ES cells [9, 10]. The derivation of iPS cells is considered a crowning achievement in the history of science, partially because of the ease by which they can be extracted from patients. Fibroblasts (skin cells) and other types of differentiated cells are not difficult or risky to procure. As a result, more scientists are able to conduct iPS cell research. Moreover, it is often believed that iPS cells are politically significant because they avoid the ethical pitfalls of hES cells (a notion which some experts have questioned, including Yamanaka himself) [11, 12].

Recognizing the ease and simplicity of iPS cell technology highlights the difficulties of engaging in other types of stem cell research. Human SCNT requires donor eggs, which, as previously mentioned, are challenging to obtain. Thus, the only researchers who can participate in SCNT research are those who are fortunate enough to have access to research eggs due to permissive local policies. Moreover, human SCNT continues to be associated with the risk of sliding toward human reproductive cloning (SCNT techniques employed for the purpose of creating a cloned baby). What about the predicted perils of reproductive cloning? Were these perils real or imagined?

In retrospect, it is now clear that the FDA would forbid reproductive uses of SCNT without an investigational new drug (IND) application by investigators and all the documented preclinical work necessary to secure an IND. In other words, no one can simply “attempt” to clone a human baby. We know this because the FDA has recently asserted their authority to govern over similarly manipulative reproductive procedures, like mitochondrial replacement therapies, cytoplasm transfer between oocytes, and germline genome editing [13].

Moreover, human reproductive cloning has already been made illegal preemptively in more than 30 countries and in

13 US states. In short, the regulatory reality today blocks the legal possibility of renegade scientists trying their hand at reproductive human cloning. But even without these existing safeguards, SCNT-based reproductive cloning will probably never work to produce healthy babies for scientific reasons [14].

The lack of public reaction to research egg donor compensation, combined with the recent flexing of FDA muscle, indicates that the predicted perils of donor exploitation and reproductive cloning were overstated. That being said, the discovery of iPS cells may serve to detract from the perceived clinical applications of human SCNT.

How do NT-hES cells compare to their iPS cell counterparts? According to one recent study, it appears that human NT-hES cells and iPS cells share similar biological capacities, characteristics, and clinical applications.

Egli and Mitalipov et al. found that, of the NT-hES and iPS cells they derived from the same somatic cell cultures, both of these reprogrammed stem cell types maintain similar gene expressions and DNA methylation profiles, as well as comparable levels of genomic aberrations such as *de novo* mutations [15]. Does this mean then that all NT-hES cells are equivalent to all iPS cells? The researchers argue that such a conclusion would be premature. Due to differences in various research teams' techniques used to generate iPS cells (transient RNA transfections vs. retroviral vectors vs. Sendai virus, etc.), it is too early to claim that this one study proves that all human NT-hES cells are equivalent to all human iPS cells. Further research comparing different iPS cell derivation methodologies against a larger number of NT-hES cell lines is necessary to settle the question about the equivalence of these reprogrammed stem cell types. In short, this study concludes with a rationale for more human SCNT research, not less.

Still, many observers may be left wondering whether human SCNT research ought to move forward if its promise seems to be losing much of its initial luster and allure. Is further research into human SCNT scientifically justified?

Conclusion: Issues Beneath the Radar—Research Embryo Creation and Oversight

The answer to this question hinges on the meaning of “scientific justification,” which can be understood in one of two ways—the potential for clinical application and benefit, or the promotion of basic scientific understanding. With regard to the former, the pursuit of science is rationalized by means of the potential medical utility and curative benefits that may come about because of this pursuit. Proponents of human SCNT, for example, contend that medicines and therapies that may be discovered because of SCNT research justify the use of valuable resources, such as human eggs. With regard to the latter, the pursuit of science is justified by the intrinsic value of

the knowledge obtained. For example, other proponents argue that human SCNT should move forward because discovering generalizable knowledge about the basic mechanisms of developmental biology is good in its own right. These two understandings are grounded in different types of reasons and justificatory conditions. Which of these two understandings should be employed to answer the question of whether human SCNT research ought to proceed further?

Normally, questions about the proper balance of scientific justification and potential harms are addressed by research oversight committees. For decades, institutions have deployed their own oversight committees to ensure that the necessary scientific considerations and ethical safeguards are in place. However, in the USA and many other countries (besides the UK and Australia), no such specialized oversight system currently exists for protocols involving the creation and use of human embryos for research. Thus, there is presently no review committee in the USA and many other research locales that would wrestle with the question “Is the creation of SCNT human embryos scientifically justified?” This is true regardless of which interpretation of “scientific justification” one advocates for analyzing the appropriateness of more SCNT research.

This is a quirk about the US regulatory system that needs to be addressed soon. This issue had been flying under the radar well before the start of hES cell research. Although an NIH embryo research task force in 1994 identified the need for such a review committee, people soon lost track of this important issue during the stem cell wars of the Bush Administration. It is resurfacing today, in light of other types of embryo research looming in the horizon. Advances in mitochondrial replacement therapy research and the possibility of germ line editing are evoking similar reactions to the cloning of Dolly the sheep. Review committees must be formed to evaluate scientific proposals concerning the creation and use of research embryos for these types of laboratory procedures as well [16].

Embryo research committees—however they are formed and wherever they are located institutionally or regionally—will have to deal with the scientific justification question for human SCNT. It is unclear how that would be determined and which threshold for scientific justification should be used (humanitarian importance and clinical application or expansion of knowledge and basic discovery). Perhaps this is an artificial distinction (application versus basic discovery) but the promise and perils of SCNT need to be reassessed in light of the current realities.

Compliance with Ethics Guidelines

Conflict of Interest Scott Ijaz and Insoo Hyun declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance

1. Wilmut I, Schnieke AE, McWhir J, et al. Viable offspring derived from fetal and adult mammalian cells. *Nature*. 1997;385:810–3.
2. Thomson JA, Itskovitz-Eldor J, Shapiro SS, et al. Embryonic stem cell lines derived from human blastocysts. *Science*. 1998;28:1145–7.
3. Cyranoski D. Verdict: Hwang's human stem cells were all fakes. *Nature*. 2006;439:122–3.
4. • Masahito T, Amato P, Sparman M, et al. Human embryonic stem cells derived by somatic cell nuclear transfer. *Cell*. 2013;153:1228–38. **This study describes optimized SCNT approaches to circumvent past limitations, allowing for the derivation of human NT-ESCs.**
5. Yamada M, Johannesson B, Sagi I, et al. Human oocytes reprogram adult somatic nuclei of a type 1 diabetic to diploid pluripotent stem cells. *Nature*. 2014;510:533–6.
6. Hyun I. Fair payment or undue inducement? *Nature*. 2006;442: 629–30.
7. Egli D, Chen AE, Saphier G, et al. Impracticality of egg donor recruitment in the absence of compensation. *Cell Stem Cell*. 2011;9:293–4.
8. Hyun I. Moving human SCNT research forward ethically. *Cell Stem Cell*. 2011;9:295–7.
9. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126:663–76.
10. Kazutoshi T, Tanabe K, Ohnuki M, et al. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell*. 2007;131:861–72.
11. Hyun I, Hochedlinger K, Jaenisch R. New advances in iPS cell research do not obviate the need for human embryonic stem cells. *Cell Stem Cell*. 2007;1:367–8.
12. Hyun I. The bioethics of iPS cell-based drug discovery. *Clin Pharmacol Ther*. 2011;38(5):646–7.
13. Cohen IG, Savulescu J, Adashi EY. Transatlantic lessons in regulation of mitochondrial replacement therapy. *Science*. 2015;348:178–80.
14. Jaenisch R. Human cloning—the science and ethics of nuclear transplantation. *N Engl J Med*. 2004;351:2787–91.
15. • Egli D, Johannesson B, Sagi I, et al. Comparable frequencies of coding mutations and loss of imprinting in human pluripotent cells derived by nuclear transfer and defined factors. *Cell Stem Cell*. 2014;15:634–42. **This study compares key developmental characteristics of NT- hES cells and iPS cells.**
16. Hyun I. Regulate embryos made for research. *Nature*. 2014;509: 27–8.