The importance of valid disclosures in the human embryonic stem cell research debate

J. L. Sherley

Programs in Regenerative Biology and Cancer, Boston Biomedical Research Institute, Watertown, MA, USA

Received 1 December 2006; revision accepted 25 February 2007

Abstract. Misinformation erodes the legitimacy of any public debate. Since the start of human embryonic stem cell research deliberations in the USA, misinformation concerning the nature of human embryos, their availability for research, and the potential for using them to develop new medical therapies have been widespread and persistent. Basic facts, well understood by physicians and biologists, have been so misstated and misrepresented in the news media and political speeches that the general public has been put in a state of constant uncertainty. The solution to the present troubling condition is better education in the form of diligent, honest, and complete scientific disclosure by responsible scientists and physicians; and more care given to accurate reporting by news media. Several key aspects of newly emerging embryonic and non-embryonic stem cell technologies are defined and discussed as they relate to the debate over the use of human embryos for medical research. An important topic for consideration is how to disclose with clarity the scientific basis for human embryonic life. Thereafter, failings in proposed technologies for developing new therapies with human embryonic stem cells, that have been grossly under-reported, are examined. Finally, properties of adult stem cells are presented in contradistinction to embryonic stem cells, both in terms of adult stem cells as a scientifically better alternative to embryonic stem cells and in terms of the technological challenges that must be overcome to realize the potential of adult stem cells for new medical therapies.

INTRODUCTION

As seekers of scientific knowledge and truth (as it can be known to us) and as engineers of technologies for improving the quality of human life, we are tested by how we go about the act of disclosing our knowledge and predictions to the public, who depend on us for faithful information that is crucial to resolving difficult questions about the impact of science on society. Our disclosure is complicated by an inherent conflict of interest. The public's views can impact significantly on our freedom to conduct research and apply knowledge derived from it. This

Correspondence: J. L. Sherley, Boston Biomedical Research Institute, 64 Grove Street, Watertown, MA 02472, USA. Tel.: 617 658 7892; Fax: 617 972 1761; E-mail: sherleyj@bbri.org

The author declares no conflicts of interest.

science–society balance is appropriate, especially when the studies and application development is supported by public funds. Moreover, natural laws demand morally and ethically responsible conduct whether funding is provided by public or so-called private sources. Thus, steps must be taken to insure that our excitement and zeal for discovery and the novel possibilities it creates do not paralyse our integrity when scientific progress is disclosed and extolled to the public. Such safeguards are especially called for when human life and well-being are factors in the equation.

In the history of science, stem cells and stem cell biotechnologies may be unrivaled for capturing the interest and imagination of contemporary society. But it is not the scientific content that is responsible. Instead, the lens of record is the question of the nature of embryonic human life and an even greater issue, its moral status. The worthiness of the resolution that the public will reach regarding the issue of whether human embryos will be accorded the same rights and protections as children and adults will depend heavily on what the public is told and what the public believes from scientists and physicians. Full and honest disclosure is the mark to be met. History will not be kind to anything less.

Herein, I present recent and current failings on the part of some scientists to meet this charge, leading to misinformation propagated by physicians, scientists, and non-scientists, such as journalists and politicians. Undoing this misinformed prejudice in the public discussion on the future of stem cells and stem cell biotechnologies requires constant education and vigilance. If the public will make informed decisions, they must have valid information about stem cells and their technological potential. Our responsibility, as experts in this endeavour, is not only to seek the truth, but also to disclose it fully and with integrity.

INVALID DISCLOSURE 1

Scientists are not able to determine when human life begins.

It is scientists and physicians who are the most able members of society for making this determination. And they can do so definitively. Living forms on earth are defined by their ability to take up energy and transform it into the work of self-replication. Therefore, human embryos are certainly alive.

The suggestion that human embryos are not human beings is an untenable assertion. Of course they are human beings. What else could they be? The question of how the initial single-cell human embryo, called the zygote, is different than a human somatic cell, which is not a whole human being, is answered straightforwardly based on scientific knowledge. The human egg endows the human genome with a special molecular program that sets the plan for complete development of a human being. The egg confers this information on a complete human genome, whether it is produced by natural fertilization, *in vitro* fertilization (IVF), or the transfer of a somatic cell nucleus into an enucleated egg (so-called somatic cell nuclear transplantation, which is the basis for human embryo cloning).

INVALID DISCLOSURE 2

In the USA, there are ~400 000 IVF human embryos, designated for discarding, which could be used instead for development of human embryonic stem cell lines.

This statement is a now common gross misrepresentation of a study by Hoffman *et al.* published in 2003. In fact, these investigators estimated that, at most, only 11 000 IVF embryos were potentially available for donation for human embryo research. It is also important to emphasize that while 11 000 is not an insignificant number, the authors' estimate was for embryos 'awaiting donation to research', not embryos already designated for research projects, which is likely to be a much smaller number in the current climate of the debate. Whether or not these embryos will become a source of cells for research will depend on the public's opinion of their moral status as living human beings.

INVALID DISCLOSURE 3

Extraction of single cells from early stage embryos is an acceptable alternative to destroying later stage embryos for development of human embryonic stem cells.

This technique is misleadingly referred to as pre-implantation genetic diagnosis (PGD), after the clinically accepted procedure for removing single cells from early stage IVF embryos to evaluate their genotype before implantation. As such, the technique would be better named 'early cleavage-stage cell extraction.' Scientists at Advanced Cell Technologies, a human embryonic stem cell development company in the USA, recently reported the ability to derive human embryonic stem cell lines with cells from early stage embryos (Klimanskaya *et al.* 2006). Although these authors presented this concept as a source of human embryonic stem cells that would not require destruction of embryos, the embryos in the study were in fact destroyed. Moreover, they did not report the successful establishment of embryonic stem cell lines from a single diagnostic cell as suggested. Therefore, demonstration of the feasibility of the PGD concept is still lacking. The authors of the report failed to disclose that an emerging clinical view is that removal of cells from later stage embryos for PGD will reduce the risk of harm to evaluated embryos (McArthur *et al.* 2005).

Development of embryonic stem cell lines from such late stage diagnostic cells has not been demonstrated, and is likely not to be feasible. Beyond this incomplete scientific disclosure, scientists promoting the derivation of human embryonic stem cell lines from cells extracted from early stage embryos ignore a fundamental ethical objection that the public must address. Will we accord embryos the right to self, the right not to have their parts removed without their consent and for the gain of others? Certainly, society's resolution of this ethical question will depend on its understanding of the increase in risk to the embryo that is associated with derivation of human embryonic stem cell lines during PGD by extraction of early cleavage stage cells. The authors also assert that none of the cells extracted from early stage embryos are themselves cloned embryos (Klimanskaya *et al.* 2006). Based on their published report, so far, this possibility is indeterminate.

INVALID DISCLOSURE 4

Pluripotency is required for development of therapeutic applications.

This misinformation is the basis for assigning greater therapeutic potential to embryonic stem cells over adult stem cells. Pluripotency is the property of embryonic stem cells to yield all the

different cell types found in the adult body. Although a marvellous property, for sure, pluripotency is not obligatory for developing therapies for diseased, injured or aged mature tissues. In general, disease and injuries do not affect all of the cells in the body at once. Therefore, in many, if not all, cases where embryonic stem cells have been highlighted for potential for new therapies (e.g. in liver disease, diabetes and neurodegenerative disorders), adult stem cells with potency restricted to the targeted tissue have a greater likelihood for success, as I will now describe.

INVALID DISCLOSURE 5

Human embryonic stem cells can be used to treat diseases and injuries in the mature tissues of children and adults.

This pervasive misinformation is due to careless, superficial statements by scientists, politicians and journalists who have sought to promote human embryonic stem cell research. Ill-informed pronouncements by non-specialists are only partly responsible. Stem cell experts merit the greater share of responsibility for incomplete and inaccurate disclosures, whether due to lack of integrity or lack of in-depth knowledge of stem cell and tissue biology. It is amazing that this invalid disclosure continues to fuel the rhetoric of promoters of human embryo research. However, when presented in the context of acknowledged uncertainties concerning future outcomes, misinformation is particularly difficult to discern and correct.

In the early days of excitement about the promises of new therapies based on embryonic stem cell biotechnologies, it was well appreciated that all the available experimental evidence indicated that when transplanted into mature tissues, embryonic stem cells form tumours. This serious shortcoming is a direct manifestation of their pluripotency. Hence, this earlier invalid disclosure, presented as a desirable advantage of embryonic stem cells over adult stem cells, is in fact one of embryonic stem cells' two (not one, but two) Achilles' heels in terms of their application for new medical therapies.

The second Achilles' heel undoes the proffered solution for the pluripotency-tumour formation problem. The tumour formation issue was largely tabled in the ongoing discussion from the suggestion that it can be evaded by using embryonic stem cells to make non-tumourigenic mature cells to develop tissue therapies. However, mature cells lack an essential property that is required to sustain mature tissues. This property, called asymmetric self-renewal, is a unique property of adult stem cells (Loeffler & Potten 1997) (Fig. 1).

Tissues are sustained by the asymmetric self-renewal of adult stem cells. These cells divide asymmetrically, to maintain their own number, while at the same time producing non-stem cells that then differentiate and mature to constitute tissue architecture and function. Eventually, these mature cells expire and are lost from the tissue. Therefore, for normal tissue structure and function, they must be continuously replaced by the asymmetric self-renewal of adult stem cells. This type of adult stem cell-based cellular renewal has the potential to operate in nearly all human tissues. Rates of cell production and lifetimes of mature cells differ from tissue to tissue, but the basic cell kinetics format is universal in vertebrate tissues (Potten & Morris 1988). Based on their own tumourigenic properties and the inadequacy of mature cells to sustain normal human tissues, it can be validly disclosed that embryonic stem cells would be ineffective for developing cellular therapies for adult tissues.

Figure 1. Schematic of the general form of the adult stem cell-powered cell kinetics of postnatal tissues. In many postnatal tissues (especially epithelia, Potten & Morris 1988), adult stem cells (black squares) undergo continuous asymmetric self-renewal divisions to replenish expiring mature differentiated tissue cells. Asymmetric self-renewal allows adult stem cells to retain the tissue construction program while at the same time producing relatively short-lived functional cells of the tissue (Sherley 2006). Limited symmetric divisions by differentiation-committed cells provide the expanded number of transient cells required to populate the tissue.

INVALID DISCLOSURE 6

Adult stem cells are not a viable alternative to embryonic stem cells for developing new cell-based therapies.

As identified above, adult stem cells are the ideal cell type for developing cell replacement therapies for diseased and/or injured tissues (Sherley 2004). However, their potential utility has been questioned because of significant challenges in identifying them and producing them in numbers sufficient for research and eventually clinical development.

Let me first suggest that, even if no new adult stem cell therapy is ever developed, adult stem cells are still a superior scientific choice compared to embryonic stem cells for such enterprises. In existing adult stem cell-based therapies, transplantation tumour formation is not a problem, and lifelong tissue replacement can be obtained. It is important to remember that current therapies are possible with small numbers of impure adult stem cells that cannot be unambiguously identified, as is the case of bone marrow reconstitution by transplantation of cell populations containing haematopoietic stem cells. The success rate for current adult stem cell-based cellular treatments is far below the ideal of 100%. However, continued research to increase the efficacy of existing adult stem cell-based techniques will also inform efforts to reduce barriers to the development of new therapies using such cells.

In addition to potential for applications in cellular medicine, adult stem cell biotechnologies have great potential to enable novel advances in traditional branches of medicine. Besides tissue therapy, there are several major potential applications for mature human cells. These include demand for such human cells for drug toxicity testing in the pharmaceutical industry (e.g.

Figure 2. The suppression of asymmetric cell kinetics (SACK) concept for expansion of adult stem cells *ex vivo* for production of mature functional tissue cells that have low proliferation potential. Explanted adult stem cells (black ovals) retain asymmetric cell kinetics due to a p53- and inosine-monophosphate dehydrogenase-dependent biochemical pathway. Medium supplementation with guanine ribonucleotide precursors like xanthosine (+Xs) promotes a shift of adult stem cells from asymmetric cell kinetics to symmetric cell kinetics (SACK) that promotes their exponential expansion. Removal of the SACK agent (-Xs) permits adult stem cells to reversibly regain asymmetric cell kinetics and to produce mature functional cells that undergo a terminal division arrest.

hepatocytes, renal tubule cells, and haematopoietic cells); demand for cells for developing drug metabolism profiles (mainly hepatocytes); and demand for production of therapeutic human biomolecules that cannot be produced in active form using recombinant systems in microbes (because of failure to perform important modifications like glycosylation, for example). Human cells with these highly desirable properties are also highly refractory to long-term propagation in culture, which is essential for mass production on the scale required for industrial development. The basis for this universal problem is that in culture, mature cells retain their programming for a finite and short lifespan.

The solution to this problem is to expand adult stem cells in culture by inducing them to adopt a state of symmetric self-renewal instead of asymmetric self-renewal (Sherley 2002). Symmetric self-renewal is similar to the cell division of embryonic stem cells in culture. During symmetric self-renewal, cell divisions produce two identical stem cells, promoting their exponential expansion in number. However, because this is a conditional state for adult stem cells, after production of large numbers of them, individuals can be reversed back to asymmetric self-renewal that yields large numbers of new non-stem cells that can differentiate to express mature cell functions. Regulated changes in self-renewal pattern are postulated to occur during adult tissue maturation (Sherley 2002). *In vivo*, symmetric self-renewal is necessary to increase the number of stem cells required for production of new tissue units during body growth; *in vitro*, it promotes long-term culture propagation and production of industrial scale numbers of human cells (Lee *et al.* 2003).

An example of how this stem cell expansion technology can be utilized is as follows. Our team has identified a pathway that regulates conversion of adult stem cells between asymmetric self-renewal and symmetric self-renewal (Merok & Sherley 2001; Rambhatla *et al.* 2001, 2005; Sherley 2002; Lee *et al.* 2003). The pathway is responsible for production of cellular guanine ribonucleotides, and it also has a direct functional link to the p53 tumour suppressor protein, that regulates inosine-monophosphate dehydrogenase activity (the rate-limiting enzyme in the pathway). By addition of exogenous purine compounds like xanthosine, thus, we can bypass regulation of the p53 protein and induce adult stem cells to switch from asymmetric self-renewal to symmetric self-renewal, reversibly (Lee *et al.* 2003).

Figure 3. Requirements for efficacious tension between stem cell science and society. Stem cell research investigators and practitioners produce new knowledge and raise expectations for advances in beneficial stem cell-based applications. Society processes this information to form views on how stem cell science can improve the quality of life and/or create detrimental costs and problems. The output of this assessment can lead to public opinion for regulation of stem cell science in a manner that is viewed to be too restrictive by originators of initiating new scientific ideas. For society on the whole, this tension is beneficial. However, it suffers when disclosure of new scientific knowledge occurs without vigilant education of both scientists and non-scientists; this essential balance is lost altogether when scientific disclosures are invalid.

We consider that this approach to expanding adult stem cells, called SACK, for suppression of asymmetric cell kinetics (Lee *et al.* 2003) (Fig. 2), will have universal application to adult stem cells in diverse mammalian tissues, including those of humans, as asymmetric self-renewal is predicted to be a universal, unique property of adult stem cells (Loeffler & Potten 1997; Sherley 2002). Thus far, we have reported success in expanding hepatocyte stem cells and biliary epithelial stem cells from the adult rat (Lee *et al.* 2003, 2005; Semino *et al.* 2003). In addition, more recent work in the laboratory demonstrates preliminary success with adult stem cells from mouse pancreas, mouse hair follicle, and human liver (J-F Paré, J King, K Panchalingam, JL Sherley unpublished data).

CONCLUSIONS

In conclusion, the current public debate on whether human embryos should be destroyed or could be manipulated for biomedical research is undermined by misleading misinformation due to invalid disclosures by some scientists who wish to conduct human embryo research. This misinformation has been propagated by some journalists, politicized by elected and would-be-elected politicians, and exploited by scientists and entrepreneurs who seek perceived benefits from the research. This misinformation has allowed promoters of human embryo research to sculpt the public discussion as a religion versus science debate, when in fact there are highly significant scientific arguments against human embryo research as a means to developing beneficial therapies for children and adults. By validating stem cell biotechnologies with complete and honest disclosure, the public can work to a resolution of the moral status of human embryos and what constitutes responsible and ethical conduct regarding research with them (Fig. 3). As knowledgeable experts in this area of investigation, it is our responsibility and our

obligation to rectify misinformation that now contaminates the public conscience and pollutes public debate. Vigilant education is the key that can enable society to treat human embryos humanely. When the dignity and the sanctity of the weakest member of our human family are valued, acknowledged, defended, and protected, we are all, each and every one, enriched.

REFERENCES

- Hoffman DI, Zellman GL, Fair CC, Mayer JF, Zeitz JG, Gibbons WE, Turner TG Jr (2003) Cryopreserved embryos in the United States and their availability for research. *Fertil. Steril.* **79**, 1063–1069.
- Klimanskaya I, Chung Y, Becker S, Lu S-J, Lanza R (2006) Human embryonic stem cells lines derived from single blastomeres. *Nature* **444**, 481–485.
- Lee H-S, Crane GG, Merok JR, Tunstead JR, Hatch NL, Panchalingam K, Powers MJ, Griffith LG, Sherley JL (2003) Clonal expansion of adult rat hepatic stem cell lines by suppression of asymmetric cell kinetics (SACK). *Biotechnol. Bioeng.* **83**, 760–771.
- Lee H-S, Sherley JL, Chen JJW, Chiu C-C, Chiou L-L, Liang J-D, Yang P-C, Huang G-T, Sheu J-C (2005) EMP-1 is a junctional protein in a liver stem cell line and in the liver. *Biochem. Biophys. Res. Commun.* **334**, 996–103.
- Loeffler M, Potten CS (1997) Stem cells and cellular pedigrees – a conceptual introduction. In: Potten CS, ed. *Stem Cells*, p. 1–28. San Diego, CA: Harcourt Brace & Co.
- McArthur SJ, Leigh D, Marshall JT, de Boer KA, Jansen RP (2005) Pregnancies and live births after trophoectoderm biopsy and preimplantation genetic testing of human blastocysts. *Fertil. Steril.* **84**, 1628–1636.
- Merok JR, Sherley JL (2001) Breaching the kinetic barrier to *in vitro* somatic stem cell propagation. *J. Biomed. Biotechnol.* **1**, 24–26.
- Potten CS, Morris RJ (1988) Epithelial stem cells *in vivo*. *J. Cell Sci. Suppl.* **10**, 45–62.
- Rambhatla L, Bohn SA, Stadler PB, Boyd JT, Coss RA, Sherley JL (2001) Cellular senescence: *ex vivo* p53-dependent asymmetric cell kinetics. *J. Biomed. Biotechnol.* **1**, 27–36.
- Rambhatla L, Ram-Mohan S, Cheng JJ, Sherley JL (2005) Immortal DNA strand cosegregation requires p53/IMPDH-dependent asymmetric self-renewal associated with adult stem cells. *Cancer Res.* **65**, 3155–3161.
- Semino CE, Merok JR, Crane GG, Panagiotakos G, Zhang S (2003) Functional differentiation of hepatocyte-like spheroid structures from putative liver progenitor cells in three-dimensional peptide scaffolds. *Differentiation* **71**, 262–270.
- Sherley JL (2002) Asymmetric cell kinetics genes: the key to expansion of adult stem cells in culture. *Stem Cells* **20**, 561–572.
- Sherley JL (2004) Human embryonic stem cell research: no way around a scientific bottleneck. *J. Biomed. Biotechnol.* **2**, 71–72.
- Sherley JL (2006) Stem cell memory. In: Heard E, ed. *Epigenetics: Concepts, Theories, Paradigms, and Mechanisms* (CD-ROM). London: Henry Stewart Talks.