Delivering on the promise of human stem-cell research

What are the real barriers?

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The therapeutic potential of human embryonic stem cells (hESCs) is one of the most controversial and hotly debated areas of scientific research. The stem-cell debate largely revolves around the ethical implications of two techniques that involve the manipulation of human embryos: the derivation of pluripotent hESC lines from surplus embryos created for the purposes of assisted reproductive technology (ART), and the use of somatic cell nuclear transfer (SCNT) to generate a blastocyst from an enucleated egg and an adult somatic cell in order to produce an hESC line that will be immunologically compatible with the donor of the nucleus.

The most common argument against hESC research is that both techniques involve the destruction of human life, which, according to opponents, begins at conception. Ironically, these same people often support *in vitro* fertilization (IVF) technologies, despite the fact that IVF clinics routinely discard surplus embryos, which are the main source of hESC lines. As this view has rarely been decisive in the public debate, opponents have reinforced their argument by claiming that hESC research is unnecessary because adult stem cells (ASCs) have the same therapeutic potential as hESCs. Advocates of hESC research counter that ASCs will never be pluripotent or sufficiently able to expand into stable cell lines, which are required for both basic and applied research to develop cures against a range of devastating illnesses, such as Alzheimer and Parkinson diseases, or to repair spinal cord injuries.

This ethical controversy has been regarded as a major barrier to research, but here we

argue that its impact has been less damaging than previously thought. In fact, the debate—and the media coverage and public interest that it has created—might have been beneficial for stem-cell research. In addition, the ethical arguments against hESC research have overshadowed other potentially important legal, regulatory, political and economic obstacles that hamper research in stem-cell-based medicine (Fig 1).

Despite much vocal opposition, politicians in the USA seem to be aligning with public opinion on hESC research. Various polls show that 48–73% of Americans approve of the creation of hESC lines for research and therapeutic use, even if it involves the destruction of surplus IVF embryos. US Congress passed the Stem Cell Research Enhancement Act to support hESC research: 55% of Representatives and 63% of Senators voted in favour. A similar trend is evident in Australia, where polls show that 70–82% of Australians approve of hESC research; this support was evident when the Australian Parliament passed the Research Involving Human Embryos Act in 2002.

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in cellular-based therapies. In the USA, this has led to strong support for the National Institutes of Health (NIH; Bethesda, MD) to fund stem-cell research. In 2006, the NIH spent US\$200 million on human ASC research and US\$273 million on non-human ASC research compared with only US\$38 million on hESC research. Australian scientists have also received substantial federal funding: A\$43.5 million in 2001 for the creation of a national Australian Stem Cell Centre at Monash University (Clayton, VIC; Commonwealth of Australia, 2005), an additional A\$55 million granted in 2004 to extend this support to 2011 (Australian Stem Cell Centre, 2004), and A\$22 million for a specialized ASC research centre in 2006 (Abbott, 2006).

It is not clear whether different legislative and regulatory frameworks have made as much difference to scientific progress as is often believed. In 2001, US President George W. Bush vetoed the use of federal money to support the creation of new hESC lines. The NIH was—and still is—allowed to fund research on cell lines that already existed at the time of the announcement, but the viability, genetic stability and pluripotency of most of these lines has since been questioned (Abbott *et al*, 2006). In July 2006, President Bush also vetoed the Stem Cell Research Enhancement Act, which would have allowed the derivation of new hESC lines. As a consequence of Bush's vetoes, there is no consistent national legislative framework on hESC research in the USA.

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Fig 1 | Factors influencing progress in stem-cell research

Embryos Act to allow the creation of hESC lines if they were derived from embryos collected before April 2002, if the parents of the embryo consent, and if the investigator is licensed to perform such research. State governments passed equivalent legislation, thereby creating a consistent national regulation of hESC research in Australia. The more liberal and nationally consistent Australian legislation should have reduced any legal uncertainties and thus paved the way for scientific progress. However, three years later, Australian regulators have issued only four licenses for the derivation of hESC lines. It is not clear how many new lines have been successfully created, although a recent report suggested that Australia has developed 30 hESC lines, including 10 lines that were available before 2001 (Abbott *et al*, 2006). By contrast, more than 100 hESC lines have been derived in the USA (Abbott *et al*, 2006).

A similar situation is evident in countries with even more liberal regulatory regimes. In 2001, amendments to the UK's Human Fertilisation and Embryology Act legalized the creation of hESC lines both from surplus

IVF embryos and through SCNT. Although there have reportedly been applications to obtain a license to create stem-cell lines using SCNT, there are as yet no published reports of such attempts in the UK. SCNT has also been legal in Israel, Singapore and South Korea for some time; however, only one report of a hESC line created using SCNT has been published (Hwang *et al*, 2004), and it has since been discredited for ethical problems and scientific misconduct.

The situation in the USA might be seen as more restrictive. The President's vetoes have created logistical nightmares for the NIH and research organizations. Investigators must show clear separation from NIH and non-NIH funds for any research that aims to create new hESC lines. However, the lack of regulation in the private sector coupled with considerable private investment has facilitated the creation of many new stem-cell lines by US researchers. Furthermore, in the absence of federal legislation, several US states, including California, Massachusetts, New Jersey and Connecticut, have legalized the derivation of new hESC lines. In most cases, these decisions have been motivated by the

belief that the technology has extensive potential for medical applications, but there are also economic considerations; in Massachusetts, the relevant legislation was suggested by the Commonwealth of Massachusetts Joint Committee on Economic Development and Emerging Technologies. As a result, one research team has generated 17 new hESC lines using private funding (Johannes & Regalado, 2004).

Another, albeit much less appreciated, consequence of the debate is the high level of public and media interest. As a result, increased scrutiny of hESC research—and demands for transparency and accountability—are hindering progress. For example, in 2004, Californians voted in favour of Proposition 71, a measure supporting and funding hESC research at the state level. The legislation created the California Institute for Regenerative Medicine (CIRM) to distribute US\$3 billion in grants over 10 years, but legal challenges from opponents have prevented researchers from accessing these funds. In the meantime, some supporters of Proposition 71 are querying how the money will be spent and demanding greater public scrutiny of CIRM's administration. Although accountability by organizations supporting and funding hESC research is to be expected, onerous regulatory requirements might prove counterproductive.

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The Australian Stem Cell Centre—a government-funded Biotechnology Centre of Excellence—has also been criticized by the media and Parliament, and its activities are now scrutinized more closely than any other federally funded Centre of Excellence in the country. Australian scientists are already required to account for their activities under various human and animal ethics, occupational health and safety, and genetic manipulation regulations. The addition of new requirements and the need to respond immediately to queries from the general public, politicians and the media have presented another barrier to the progress of hESC research in Australia, and have probably contributed to the recent departure of several senior scientists to the USA.

As the debate moves away from more extreme views, the political and scientific landscape is changing accordingly. During the past few years, several conservative politicians have moderated their opposition after considerable lobbying from, and consultation with, scientists, clinicians and their constituents. In the USA, they have attempted to pressure the NIH to fund research into methods of stem-cell derivation that do not involve the “destruction of human life”. These alternatives were proposed in May 2005 by the US President’s Council on Bioethics in a white paper entitled *Alternative Sources of Pluripotent Stem Cells* (President’s Council on Bioethics, 2005).

One such method is altered nuclear transfer, which involves the deliberate mutation of an embryo to prevent its proper development (Hurlbut, 2005). This seems a rather dubious solution given that there is ethically no difference between destroying an embryo and genetically engineering an embryo such that it will be unable to survive.

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It has also been suggested that researchers can remove a single blastomere from an eight-cell embryo to create a hESC line while allowing the seven-cell embryo to develop normally. This has been successfully carried out in mice (Chung *et al*, 2006) and might be possible for early human embryos (Klimanskaya *et al*, 2006), although this latter research does not show the survival of the remaining embryo but merely states the feasibility of this process. Some have suggested that this approach could be carried out routinely to create a ‘repair toolkit’ for individual patients. However, the feasibility of such an approach is low and it is unlikely to be adopted by couples requiring ART in whom no specific genetic risk has been identified, because they would undoubtedly opt to implant an embryo with all its blastomeres. It is also doubtful whether it will satisfy all opponents of hESC research, as it can be argued that the blastomere is still a totipotent cell that could develop into a human.

A third approach seeks to re-programme ASCs to become totipotent. Researchers recently reported the generation of an ESC from a fibroblast by the enforced expression of four genes (Takahashi & Yamanaka, 2006). If this re-programming truly changes the epigenetic status of the cell and can be replicated, it might obviate the need to destroy an embryo. However, even if this solution proves possible, other barriers remain.

The battle over the benefits of ASC research compared with ESC research has also produced extravagant public claims about the potential uses of both cell types. Although it has been claimed that 70 clinical conditions can be treated using ASCs (Brownback, 2006), the only ASCs that are approved for clinical use at present are the haematopoietic stem cells for bone marrow transplants—now more commonly delivered as peripheral blood rather than as bone marrow. This cell population shows the characteristics of self-renewal, clonogenicity and multipotentiality, and can repopulate its organ of origin; however, it cannot be cultured in isolation and can only give rise to haematopoietic cells.

By contrast, the pluripotent hESCs that are derived and cultured from the inner cell mass of an embryo normally disappear during further development. However, they can be extensively cultured in defined media (Yao *et al*, 2006) and increasingly directed along specific lineage pathways (Trounson, 2006), albeit not yet with complete or accurate control. Despite attempts by proponents of hESC research to highlight potential therapies against a range of serious diseases—to gain both public support and funds for research—opponents note that there have been no clinical trials using hESCs and no clinical applications are planned (Brownback, 2006; Magnus & Cho, 2005). The lack of success in producing hESCs using SCNT—and the fraudulent claims to have done so—have also been used by opponents to promote the use of ASCs instead.

These competing claims create a major challenge for an expectant public to distinguish fact from fiction. It is appealing to think that this would be less problematic if people were better educated about stem-cell science. The main obstacle, however, is the lack of consensus within the research community on where the science should be going. The rate of information propagation also makes it difficult for most scientists to keep up, let alone the general public.

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The formulation of public policy on stem-cell research usually competes for attention with a multitude of other pressing issues, such as terrorism, climate change and oil prices. To make decisions on issues for which they do not have the time or inclination to conduct the necessary research, people generally use heuristics or cognitive short cuts (Nisbet, 2005). Moreover, the time that the media allocates to the discussion of any topic is generally brief, and so the debate is often conducted in key phrases that lend themselves to sound bites. Scientists have long lamented the impossibility of conveying the necessary technical information, and all the qualifications, to the public through sound bites in the mass media. The result is an extremely varied level of understanding among the public and politicians of the science of stem-cell biology.

Apart from the legislative, ethical and political issues, one of the main challenges in realizing the benefits of stem-cell research is to attract private investment. It is an enormously costly enterprise to develop a new therapy from basic research and to move it through development, regulatory approval and clinical trials. These immense investments are often covered initially by the venture capital sector, and subsequently by the biotechnology and pharmaceutical sector. However, investors have so far been reluctant to make such investments into cellular therapies for a number of good reasons.

First, there is scepticism about the likely success of stem-cell research, on the basis of the historical experience of the hyperbole surrounding gene therapy since the early 1970s (Friedmann, 2005). As a result, the market has become more cautious about the promises of new technologies.

Second, some companies are sensitive to the public debate and are unwilling to perform or support hESC-based research, in part to avoid damaging their brand name. A company such as Johnson & Johnson Pharmaceutical Research (La Jolla, CA, USA)—which is highly visible to the public and whose parent company markets, among

other things, products for infants—is vulnerable to public pressure and negative media coverage. In fact, Johnson & Johnson states on its website that the company does not perform or support research on hESCs.

Third, there is uncertainty about whether the technology will produce defendable and exploitable intellectual property. If, for example, a company has a product based around the isolation of stem cells from a specific organ in which adhesion to plastics is the key criteria of isolation, will this be enough to generate a defendable patent? Would a more tightly defined or more cost-effective methodology to isolate the same cell type from the same organ override the previous patent? Furthermore, given that the US and the European patent offices have become more averse to granting patents on individual genes or proteins, the question remains whether they would grant patents on specific cells.

Fourth, there are regulatory questions that cannot yet be answered because the field is still developing. For example, how would drug approval agencies regulate a therapy that involves cells, medical devices and biochemical factors?

Fifth, and probably the largest barrier from an investor's point of view, are doubts about whether a marketable product can be defined. Much of the rhetoric implies that some cell types will be used therapeutically. But what will the product be? Will it be the cell or the way in which the cell is isolated, expanded or delivered? What else will be necessary for a therapeutic product?

Sixth, the most economically successful products are those that can be widely distributed and do not require individualization for each patient. Despite the alleged advantages of generating autologous cells from ASCs, such treatments would undoubtedly be less economically feasible. By contrast, products

such as the mesenchymal stem cells of Osiris Therapeutics (Baltimore, MD, USA) might be applicable to all patients: these cells are immunomodulatory, will not be rejected and have broad plasticity (Taupin, 2006). The increasing availability of efficacious immunosuppressant drugs will also make non-autologous treatments more acceptable and probably more cost-effective in the future.

But there are already some promising developments. A research team at the University of Düsseldorf, Germany, has developed a therapy, on the basis of ASCs, in which autologous bone marrow cells are injected into the hearts of infarct patients. Results show that, after several months, the therapy leads to myocardial regeneration and neovascularization, thus improving cardiac function in both acute and chronic heart disease (Brehm & Strauer, 2006; Strauer *et al*, 2002).

However, until more pharmaceutical companies make bold attempts to develop successful stem-cell-based therapies, risk aversion among potential investors is a real barrier to realizing the benefits of this research. Despite the ethical, legal and regulatory uncertainty, most large biotechnology and pharmaceutical companies are watching this space closely and have, or are developing, in-house research teams to evaluate stem cells as a potential product.

The final two barriers that are often overlooked are people and time. Why has there been such little progress despite the fact that it is legal to derive hESC lines and use SCNT in the UK, South Korea and Israel? The reasons become clear if we take a closer look at hESCs. The equivalent murine cell type has been available for some 25 years, primarily as a research tool to recreate models of human disease rather than as a way to develop cellular therapies (Evans & Kaufman, 1981; Martin, 1981). Nonetheless, the derivation and manipulation of murine stem cells was an elite skill for many years. It is less than a decade since the first derivation of a hESC line (Thomson *et al*, 1998), and the difficulties of culturing these cells to maintain their pluripotency—as can be done for mouse ESCs (Gearing *et al*, 1987; Gough *et al*, 1988)—has made the manipulation of hESCs an even more highly skilled art and one that few scientists have yet mastered. A major limitation on the field of hESC research is, therefore, a shortage of human research skill that can only be overcome slowly.

In the area of ASCs, 35 years of research into haematopoietic stem cells have now defined the questions that must be answered to decide whether an adult cell is a stem cell. Each new potential ASC source will need to be similarly assessed for self-renewal, long-term genetic stability, multipotentiality and potential to regenerate its own organ of origin. This will require the development of novel assays specific to that cell or organ. It is therefore unrealistic to imagine that advances in the understanding of new sources of ASCs will occur within a few years, when it has taken so long to characterize the few ASCs that we use at present. Progress in this field will take time and considerable investments in human resources.

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In conclusion, it is still unclear which human stem cells—whether embryonic or adult—will be developed and for which conditions. Given this, the focus of the NIH in the USA, and research organizations in other countries, should be on developing human research capacity in both ASCs and ESCs. Each type of research will take time to mature. The ethical debate will need to produce acceptable policy and regulatory compromises so that the regulatory burden can be reduced and investors' risk aversion can be overcome. If these things happen, the major remaining barrier to realizing the medical benefits of stem-cell research might be the lack of skilled scientists in the field.

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