Bioethics Briefing

Number 5: Stem Cells

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Introduction

According to Paul Simon, '*These are the days of miracle and wonder ... Medicine is magical and magical is art ... These are the days of miracle and wonder And don't cry baby, don't cry.*' Based on the almost daily reporting in the media of yet another 'breakthrough' or 'miracle cure' we may be very inclined to agree with him – baby certainly should not cry because modern medicine will surely come to her aid. In recent weeks, for example, we have had the 'pioneering' transplant of a beating heart, heralding a 'new era' in transplant surgery (Randerson, 2006) and the use of testicles as a source of stem cells, paving the way for 'powerful new therapies.' (Sample, 2006). While some may be tempted to dismiss the latter as more media hype about stem cells (perhaps in more colourful language!), the report represents the continuing focus, both in modern western medicine and in the media, on repair of worn out or damaged tissues and organs (or Regenerative Medicine as it is frequently termed).

Stem cells, cells which have the potential to develop into the different cell types that are found in the human body, have been and continue to be a key element in the research on tissue repair. There are two main types of stem cells. The first are embryonic stem cells, located in the early embryo, which in normal development give rise to all of the 200+ cells types found in the fully formed human. The second are adult stem cells, located in various places in the body, which in nature have a relatively limited developmental potential, that potential being determined by the tissue in which the stem cells are located.

The point must also be made that the intense interest in this work, coupled with the desire to succeed, brings its own problems. It has been suggested that some scientists have been tempted to exaggerate their successes. Indeed, in the most extreme case, involving Professor Hwang Woo-suk in South Korea, results were not just exaggerated, but were actually falsified (see, for example, BBC news, 2006). So what then is the current situation in stem cell research and what are the associated bioethical issues?

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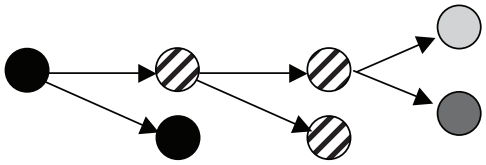
The Science of Stem Cells

The term 'stem' cell gives an idea of what they are; cell populations from which other cell types arise, often in a branching pathway of increasing specialisation. However, in order to maintain that potential, it is clear that not all the cells in the population can develop into specialised cell types. Some stem cells must remain as stem cells in order to continue to feed the developmental pathways. Stem cells are thus defined by two clear characteristics. Firstly, they **self-renew**: when a stem cell divides, at least one of the daughter cells is also a stem cell, thus maintaining the population. Secondly, they give rise to **differentiated cells**. This starts to happen when a daughter cell arising from division of a stem cell becomes, not a new stem cell but a precursor cell that is committed to a pathway of development (Figure 1). These precursor cells also undergo division before particular daughter cells start to move along their determined developmental pathway. What we see therefore, and this is beautifully illustrated by the formation of all the different types of blood cell in bone marrow, is an increasing restriction of developmental potential from the stem cells through to the range of terminally differentiated cell types arising from the stem cell population.

Figure 1: Cartoon to show a very simple sequence from stem cell to precursor cell to two differentiated cell types.



1. Stem cell divides to give one new stem cell and one precursor cell
2. Precursor cell divides
3. One precursor cell divides to give two new (differentiated or partly differentiated) types of cell

Embryonic Stem Cells:

The zygote, which is the single cell that arises from fertilisation of the egg by a sperm, contains all the genetic information necessary for the complete development of the adult mammal: it is genetically and developmentally **totipotent**. The totipotent state is retained by all cells only during the first few cell division cycles. Indeed, it is this that makes it possible to remove a single cell for genetic biopsy at the 8-cell stage (as described in Bioethics Briefing 3: Preimplantation Genetic Diagnosis); the resulting 7-cell embryo goes on to develop normally. However, after few days of cell division and growth, the developmental totipotency is lost. At the **blastocyst** stage, the embryo is a hollow ball into which projects an inner mass of cells. In natural fertilisation it is at about this stage that the embryo attaches to the lining of the uterus and thus establishes a pregnancy. At that time, the outer layer of cells of the blastocyst (the trophoblast) are destined to form the placenta while the inner cell mass will go on to develop into the foetus and thence to the fully formed baby. It is immediately obvious that although the cells of the inner cell mass have lost the potential to form the placenta, they retain the developmental potential to form all the different types of cell that occur in the mammalian body. They are thus described as **pluripotent** stem cells. However, this population is relatively short-lived because, if a pregnancy is established, these cells give rise to the three tissue layers of the embryo, namely the endoderm, mesoderm and ectoderm which themselves go on to form particular tissues and organs as the embryo develops. In terms of self-renewal then, the cells of the inner cell mass are limited but nevertheless they are known as embryonic stem cells (ES cells).

Mouse ES cells were first isolated and cultured in 1981. The maintenance in culture of the self-renewing state means that *in vitro* these cells behave as stem cells for much longer than they would do *in vivo*. In order to keep the cells functioning as stem cells *in vitro* it is necessary to ensure that the gene (or genes) which maintain the stem cell state are active. One of the key genes in this is *Nanog*[1] (reviewed by Yates and Chambers, 2005) which keeps ES cells in their pluripotent state. If *Nanog* is not expressed then the stem cells become much more restricted in their developmental potential. It is presumed that conditions of cell culture allow this gene to remain active and thus maintain the pluripotent state.

[1] In Celtic folklore Tir Nanog is the land of eternal youth

Furthermore, it has proved possible, over recent years, to demonstrate that these cells are genuinely pluripotent by inducing mouse ES cells in culture to differentiate into many of the types of cell found in the adult mouse.

The work with mouse ES cells sets the scene for research on human ES cells. These were first isolated and cultured in 1998 (Thomson *et al*, 1998). Again, it has proved possible to maintain them in the embryonic state and also to induce the formation of a range of specialist types of cell (Odorico *et al*, 2001), leading to the idea that human ES cells may in the future be used to repair tissues and organs damaged by disease or accident. However, a major disadvantage is the culturing of human ES cells has been the presence of mouse fibroblast 'feeder cells' to provide some of the essential nutrients. The use of these feeder cells is regarded as a possible source of contamination, which in turn raises concerns about the therapeutic use of ES cells. The ES research community has therefore welcomed recent reports (e.g. Yao *et al*, 2006) of the growth of human ES cells without the need for feeder cells.

The Human Fertilisation and Embryology (HFE) Act of 1990 brought into being the Human Fertilisation and Embryology Authority (HFEA) and the responsibilities of this body include the regulation of human ES cell experimentation in the UK. The original HFE Act allowed the creation of embryos *in vitro* for specific research projects relating to human reproduction and fertility but not for other purposes. However, in 2001 the Act was amended to extend the research use of *in vitro* embryos to include research on ES cells. This enabled the HFEA to grant a very limited number of licences to particular laboratories for the culture of human ES cells, derived from the blastocyst. Although the granting of these licences permitted the creation *in vitro* of embryos specifically in order to generate ES cells, in practice nearly all this research is carried out with spare embryos from IVF treatments.

As indicated above, one of the main motivations for research on human embryonic stem cells is the generation of particular cell types in order to repair damaged or diseased tissue. However, one of the problems of tissue and organ grafts and transplants is that of immunological rejection. It has therefore been reasoned that in order to avoid rejection it may be possible to use the nuclear transfer technique (where the nucleus of an egg cell is removed and replaced by the nucleus taken from a cell of a different organism) to create embryos that are genetic clones of a particular patient. The use of ES cells derived from these cloned embryos would cause no rejection problems because they are a match to the patient. This procedure is termed **therapeutic cloning** (see also Bioethics Briefing 8, Human Cloning). At the time of writing, the HFEA has granted two licences for this type of research to take place in the UK. To date, however, no ES cultures have been established from cloned embryos in the UK or indeed anywhere else despite, as mentioned briefly already, the claims made by the South Korean research group of Professor Hwang Woo-suk. In fact those claims went as far as to state that ES lines had been established from cloned embryos derived both from healthy subjects and from patients suffering degenerative diseases. The papers containing those claims had been published in *Science* (Hwang *et al*, 2004, 2005), one of the world's leading journals which, following the later admission that no ES lines had been established, published an official retraction of the two papers (Kennedy, 2006). The episode caused embarrassment and anger in the biomedical community and a good deal of questioning about the effectiveness of the peer review process. What emerges from this is that, despite some very optimistic statements by scientists and in the media, the creation of personalised spare parts from human ES cells remains a long way in the future.

Scientific Background: Adult Stem Cells

Stem cells are not confined to embryos; fully formed mammals retain populations of stem cells that are involved in processes such as replacing worn out cells and healing wounds. Examples of adult stem cells that are involved in the ongoing turnover of cells are those in the bone marrow (giving rise to the various types of cell in blood), skin, gut and respiratory tract while populations of stem cells in locations such as the liver and muscle are involved in repairing tissue damage. Further, there is evidence that

dormant stem cells may actually exist in other organs of the body but rarely, if ever, become active, except in *in vitro* culture. The developmental potential *in vivo* of adult stem cells is limited to the few cell types relevant for the particular tissue or organ with which the stem cells are associated. These adult stem cells are therefore described as **multipotent**. For several adult stem cell types, activity declines with age of the organism; no wonder that I complain that athletic injuries take so much longer to clear up than when I was younger!

A number of different therapeutic uses of adult stem cells may be envisaged. Firstly, it may be possible to extend the active life of stem cell populations or to activate stem cell populations that normally remain dormant. Some progress has been made here, for example in understanding what makes certain types of stem cell less responsive as the organism ages (*e.g.* Conboy *et al*, 2005), and in activating or reactivating dormant or semi-dormant stem cells (Ahn and Joyner, 2005). The most spectacular example of the latter is the identification in mouse of mammary stem cells and the induction of the complete growth of a mammary gland (Shackleton *et al*, 2006). Although it is probable that 'unscheduled' mammary stem cell activity is involved in breast cancer, these results also raise the possibility of re-growing breasts after therapeutic mastectomy.

None of the examples mentioned so far involve major changes of cell fate, a phenomenon that would extend hugely the therapeutic potential of adult stem cells. In other words, what is needed is **trans-differentiation**, or switching to a different cell lineage. In stem cell populations that give rise to several cell types, such as those in the bone marrow, there is evidence that the micro-environment of the precursor cells (see above) is one of the factors that regulates the progress of cells into particular cell lineages. A key part of the micro-environment is the stem-cell niche, provided by other cells in the immediate vicinity of the stem cells. It is likely that signalling molecules are exchanged between the stem cells and the cells that constitute the stem cell niche. It is clearly important to understand these signalling mechanisms, particularly if we are to be able to manipulate stem cells to order. So, is it possible, with the limited knowledge we now have, to achieve trans-differentiation by manipulating the culture environment or by placing the cells in a different location *in vivo*? There have indeed been several reports of trans-differentiation of adult stem cells. However, in some of these cases it has not been possible to achieve the results reproducibly and in other cases, what appeared to be trans-differentiation was actually caused by cell fusion (see Raff, 2003, for further details). Nevertheless, there have been some genuine successes. One of the most surprising was the injection of bone marrow cells (which normally give rise to the different types of blood cells) leading to repair of damaged heart muscle (Lovell and Mathur, 2004). Thus, one patient who has received this highly experimental treatment reports that whereas previously he could not walk up more than two stairs without needing to stop, he can now run up the stairs (BBC News 2004). Further, in the UK a clinical trial involving 700 patients was initiated in late 2005 to examine the efficacy of bone marrow stem cells in repairing damaged heart muscle (BBC News 2005).

There has also been a report of bone marrow stromal cells trans-differentiating *in vitro* into skeletal muscle precursor cells which were able to differentiate into muscle fibres and thus repair degenerated muscle when injected into mice or rats (Dezawa *et al*, 2005). Although muscle stem cells do exist *in vivo*, they are very scarce and the authors suggest that in order to bring about effective repair of extensively damaged muscle it may be better to induce trans-differentiation of bone marrow stromal cells rather then relying on activating muscle stem cells. These successes have raised the stakes for research on trans-differentiation of other types of adult stem cell, once again raising the possibility of using a patient's own cells to bring about tissue repair.

Ethical Background

Nearly all the ethical debate around embryonic stem cells focuses on the early human embryo. Whether an embryo is created by IVF or by cloning, it is necessary, if one wishes to establish a culture of ES cells, to stop embryo development. A person's view of the ethical status of the human embryo is a major determinant in whether that person finds this way of using embryos acceptable. It is a topic that has elicited strong words, based on equally strong feelings. Let us then look at the arguments.

Ethical arguments against use of embryonic stem cells

Those who oppose stem cell research often do so because they regard the early human embryo, from the zygote onwards, as a human person (*e.g.* Taylor, 2005; O'Gorman, 2006). They point out that each zygote has a unique human genotype that has never existed before and will never exist again (unless the embryo splits to form identical twins). Further, if the embryo implants into the lining of the womb it will grow into a foetus and thence into a child. It can therefore never be said that an embryo is spare; it would be like saying that a fully formed human was a spare person. The deliberate diverting of embryonic development to establish a stem cell culture is thus regarded as destroying a human person (and some would go as far as defining this act as murder). According to this view, it matters not whether the embryos are 'spare' ones from IVF treatment or have been created specifically for establishing a stem cell culture, their use in this way is wrong. Our desire to end suffering, even potentially the suffering of several people, does not allow us to end the life of another person; embryos are not commodities to be treated as we will and thus the utilitarian view is unacceptable. This is a deontological position based on views of absolute right and wrong (see Bioethics Briefing 1: Ethics and Bioethics).

Opponents of this research usually make two further points. The first is that establishment of embryos by cloning in order to obtain stem cells compounds the wrongness of the procedure. Not only are embryos being created specifically to be destroyed but this will also make it easier to achieve reproductive cloning, a development regarded by most people as undesirable. The second of these ancillary points is that society is not giving enough support to research on adult stem cells which may turn out to have a very promising potential for therapeutic use without the problems of destroying embryos. This argument has been given greater impetus by some recent results (see below).

Ethical arguments for the use of embryonic stem cells

The majority view in the UK does not bestow human personhood on the early human embryo. Thus it is pointed out that in nature, up to 80% of fertilised human eggs / very early embryos do not implant into the lining of the womb and thus do not establish a pregnancy. If all these early embryos are lost then, the argument goes, it is difficult to regard each one as a human person even though each one has a unique set of genes. They also point out the following features of early development. First, it is not until several rounds of cell division have occurred that the allocation of specific cell lineages to placenta and to embryo is made. Second, even after this, the embryo itself may split to form identical twins suggesting that the early embryo cannot yet be regarded as a human individual. Third, studies of genetic mosaicism suggest that, as has been observed in other mammals, two very early embryos may on rare occasions merge to form one that develops normally.

On these grounds, the use of early embryos to create stem cell lines does not mean ending the life of another human. Further, the use of spare embryos may be regarded as an ethical good: unless the 'parents' had given permission for research use these spare embryos, would, after several years of deep-frozen storage, be discarded. Their use for stem cell research can instead bring major benefits to existing humans and thus to society at large. Indeed, again illustrating the strong feelings involved, the late Christopher Reeve[2] (who played 'Superman' in the 1980s films) stated that 'Bigots are delaying my recovery' and by bigots he clearly meant 'pro-life' organisations that support the ban on federally-funded research on

[2] Christopher Reeve suffered a high break of the spinal column in a riding accident; this left him quadraplegic. His eventual death was caused by complications arising from his paralysis.

embryonic stem cells in the USA[3]. Interestingly for observers of the American scene, this became an issue in the 2004 presidential election campaign in which the conservative protestant Christian George W Bush and the Republican party continued to oppose research on ES cells while the Roman Catholic Christian John Kerry[4] and the Democratic party expressed their support for such research.

Most proponents of research on ES cells are equally happy for research on adult stem cells to continue. However, they make the point that since ES cells have in nature a much larger developmental potential than adult stem cells (see below), they are much more likely to bring therapeutic benefits. Finally, on the issue of cloned embryos, supporters of stem cell research may be concerned about the hype surrounding this topic but nevertheless hold that in a country like the UK, where the law forbids reproductive cloning, the latter is not likely to be made more acceptable through the use of therapeutic cloning.

Adult Stem Cells - Ethical Background

It might seem at first sight that the use of adult stem cells carries very little in the way of ethical baggage. However, there are some points to consider. Firstly, there are issues that occur whenever cells or tissues are donated for research or therapy. Although detailed discussion of these issues lies outside the scope of this Briefing, they include informed consent (which may be more complex than appears at first sight, especially if the donor is a child), availability of donors and ownership (or lack of) of any cell lines established from donated cells. Secondly, there are issues around the therapeutic potential of adult stem cells and thirdly ethical comparisons are made with embryonic stem cells.

Ethical arguments against the use of adult stem cells

The main argument against the use of adult stem cells is a consequentialist one: adult stem cells have less developmental potential than embryonic stem cells and, notwithstanding some recent successes, are thus thought to be less useful as a potential therapeutic tool. Based on this argument, society should focus its resources on embryonic stem cells with their much wider developmental potential. In other words, if use of the latter is likely to alleviate more suffering; why bother to spend scarce resources on research involving adult stem cells? On the other hand, it can equally be argued that particular adult stem cells may be very effective if the stem cells in question are used to repair tissue into which they would normally differentiate. There are then no problems with the limited potential of adult stem cells and no need to attempt to induce trans-differentiation.

Ethical arguments for the use of adult stem cells

There are three main arguments in favour of research on and use of adult stem cells. Two of them are based on avoiding activities that many people may find unacceptable. First, if a wide range of cell types can be generated by trans-differentiation of different adult stem cell lines, then the use of embryos is avoided. Secondly, an extension of this is that the generation of stem cells that are immunologically compatible with a patient would not require the use of cloning techniques. In theory at least, adult stem cells could be extracted direct from the patient although it is recognised that this would be difficult for some stem cell populations. The third reason is one of practicality: there has already been some therapeutic success with adult stem cells and continued research should be supported. This is again related to long-standing and oft-debated principles about how scarce resources should be allocated. Readers interested in resource allocation will find it covered in almost any book on medical ethics.

Recent developments: (i) germ-line stem cells from testicles

The ethical debate is no doubt set to continue but some of the heat may be taken out of it by recent results from Gerd Hasenfuss's research group at Göttingen, Germany. They showed that germ-line stem cells (spermatogonial stem

[3] This ban does not apply to commercially funded research. See, for example the web-site of Advanced Cell Technology (http://www.advancedcell.com) which states 'We are a biotechnology company focused on developing and commercializing human stem cell technology in the emerging field of regenerative medicine.'

[4] Kerry's support for stem cell research is actually at odds with the views of the Roman Catholic church

cells, SSCs) from the testes of adult mice will, under appropriate culture conditions 'acquire embryonic stem cell properties' (Guan *et al*, 2006). When injected into a blastocyst, SSCs behave just like the cells of the inner cell mass and contribute to the development of tissues in the embryo/foetus; cells cultured *in vitro* were induced to differentiate into several types of specialised cell. The authors suggested that biopsies from human testes might be used as sources of stem cells thus avoiding the ethical problems associated with extracting them from embryos. Doubtless at this point, many of our male readers have their legs firmly crossed but according to Prof Harry Moore of Sheffield University, the biopsy 'isn't actually as traumatic as it sounds.'

Encouraged by the work with mouse SSCs, a research group in the UK, led by Robert Winston[5] has been granted a licence by the HFEA to compare human SSCs with human ES cells. Initially this will involve response to culture conditions but eventually attempts will be made to induce differentiation of particular cell types as has been achieved with mouse SSCs. If these experiments are successful, Ian Sample envisages that 'in future a man could bank testicular tissue early in life and use it years later to repair damaged or diseased organs, without the risk of rejection.' (Sample, 2006). However, the availability of self-compatible stem cells from testes clearly does not apply to half the human population, namely women. Nevertheless, it has been estimated that only about 150 different SSC lines would need to be established in order to provide acceptable levels of immunological match for 90% of the UK population, both male and female. For the women in the other 10%, creating cloned embryos may be the only option, which brings us back to the ethical dilemmas already discussed. One can only say 'watch this space.'

(ii) Pluripotent cells from tail cells

At the time of going to press, a potentially significant result has just been published in the journal Cell (Takahashi and Yamanaka, 2006). The authors, from Kyoto University in Japan, have studied a number of genetic factors which they believed, on the basis of previous studies, had the potential to be important in the control of stem cell development. After carrying out a series of beautifully designed experiments they have homed in on 4 specific factors – Oct4, Sox2, c-Myc and Klf4. When they added these four transcription factors together to fibroblast cells taken from the tail of an adult mouse, they were able to generate pluripotent cells, which they have termed “induced pluripotent stem cells”. This is an early result, but if correct it may open the door to starting therapies with adult cells which would avoid ethical dilemmas about stem cells and potentially allow a patient to be treated with cells derived from their own tissue.

[5] Who has been very critical of what he regards as the over-optimistic statements about stem cell therapies

Case Study

Read the following article and then write a critical evaluation of it in the light of (a) the current state of stem cell science, as described in this Briefing and (b) the news items and newspaper articles listed in the References or in Suggestions for Further Reading

Has stem cell research been over-hyped?

Ian Sample

Thursday September 8, 2005

The Guardian

'Lord Winston, fertility expert at Hammersmith Hospital in London, thinks so. He kicked off the British Association Festival of Science in Dublin this week by criticising stem cell researchers for making over-the-top claims for the cells' potential. Winston singled out claims surrounding research into embryonic stem cells as being particularly overblown. The danger, he said, was that hype could lead to public expectation becoming unrealistically high, setting up an inevitably painful fall when scientists fail to come up with breakthroughs in the near future.

Richard Ashcroft, a bioethicist at Imperial College London, says the stem cell hype might not be as bad as Winston makes out. "To build public support for what they're doing, scientists are always going to say there is the prospect to cure all these horrible diseases, but they're cautious for the most part in saying when those cures will arrive." But stem cell researchers, especially those working on embryonic stem cells, which must be harvested from early-stage human embryos, may be more prone to hyping their work than others, adds Ashcroft. Because embryonic stem cells are deeply frowned on by many religious groups and others who disagree with the use of human embryos in research, scientists are under greater pressure to extol the potential of their work.

One scientist noticed that Lord Winston made news elsewhere on the day he warned of stem cell hype. *The Scotsman* carried a story highlighting Lord Winston's research into xenotransplants*, modified animal organs that could be implanted into humans. "It's an interesting coincidence, because if you're into finding solutions to the shortage of human organs for transplantation, there are two ways you can go. One is modifying animal organs as Winston is, the other is to try and grow them in labs, and that's the stem cell route," he said.'

*See Bioethics Briefing 4: Xenotransplantation

Questions to consider

Notes for instructors

There are several issues here but the two main ones concern the way that scientists present their work in the light of the need to obtain funding and the way in which the media pick up and present scientists' claims.

It was very clear in 2001 that the Parliamentary Committee on Science and Technology was convinced both of the therapeutic potential of embryonic stem cells and that the UK had a lead in this research. The acceptance of these views led

directly to Parliament modifying the 1990 HFE Act, paving the way for the use of human embryos in stem cell research. However, the general optimism about embryonic stem cells was at that stage based mainly on work with mice plus a few results from human ES cell lines established in the USA. In that sense, both the scientific claims and the news reporting may be regarded as hype. Further, the hype has gone on, with the impression given by some stem cell practitioners that a patient suffering from a degenerative disease would within weeks be cured by stem cells derived from an embryonic clone of themselves.

Concerns about hype and about exploitation of vulnerable patients was also brought into sharp focus in the recent investigation carried out for the BBC's Newsnight programme (Watts, 2006). A company was tracked shipping research grade stem cells via intermediaries to clinics in Europe and Africa where the cells have been injected into patients in unproven and potentially dangerous treatments. Such is the desperation of the sick and such is the hype surrounding stem cells that people are willing to part with thousands of pounds for the chance.

Two further questions then arise. First, is this type of hype confined to stem cells or does it occur with any research that may have a long-term medical potential? Secondly, as has been claimed elsewhere, does the hype actually hinder the research through the withdrawal of support or funding when the promise is not fulfilled as quickly as we were led to believe?

Tutors may also note that the main critic of the hype is involved with another area of speculative biomedical research, namely xenotransplantation and that he his recently moved into research on stem cells from human testes (Sample, 2006).

Video and other media

News reports involving stem cells seem to occur on an almost weekly basis at present. It should therefore prove relatively easy to obtain some recent footage as a means to introduce the topic. If your institution is a member of the British Universities Film and Video Council (BUFVC) it is possible to obtain news clips pertaining to landmark events such as the publication of the Hwang experiments (20th May 2005), and indeed the declaration (15th December 2005) that the data were faked (see Willmott, 2006, for advice on obtaining footage).

A surprisingly helpful clip can be found in "Kenny dies", the closing episode of Season 5 of **South Park** (If your institution is a member of BUFVC they can provide a copy, TRILT identifier 00186929). A 90 second section when Cartman visits the Alder Research Group and asks what stem cell research involves is particularly helpful; severe caution should be observed before showing the rest of the episode to a general audience.

For those willing to embrace new technologies, a special hour-long podcast on stem cells was published by the journal **Nature** on 28th June 2006. This can be found at http://www.nature.com/nature/podcast/index.html where it is available as both the audio file and as a transcript.

A second podcast, this time from the conservative Centre for Bioethics and Human Dignity, offers an alternative view on the implications of the faked Hwang experiments. "The real lesson of the Korean cloning scandal" is a 10 minute podcast presented by Do No Harm: The Coalition for Research Ethics and raises some interesting points. A transcript of the podcast can be found at http://www.cbhd.org/resources/cloning/donoharm_2006-03-10.htm and the audio track can be reached from that page.

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- First report of the cloning of a human embryo. Caused one round of shockwaves as a scientific landmark when initially published. Caused a second wave, when the data were proven to be fabricated!

Hwang W.S., Roh S.I., Lee B.C., Kang S.K., Kwon D.K., Kim S., Kim S.J., Park S.W., Kwon H.S, Lee C.K., Lee J.B., Kim J.M., Ahn C., Paek S.H., Chang S.S, Koo J.J., Yoon H.S., Hwang J.H., Hwang Y.Y., Park Y.S., Oh S.K., Kim H.S., Park J.H., Moon S.Y. and Schatten, G. (2005) Patient-Specific Embryonic Stem Cells Derived from Human SCNT Blastocysts *Science* **308**:1777-1783

- A second paper from the Hwang group, describing the production of patient-specific stem cells, i.e. therapeutic cloning. The data in this paper were also, however, later declared fake, and both this and the proceeding paper were retracted.

Kennedy D. (2006) Editorial Retraction *Science* **311**:335

- Official retraction of the fraudulent papers from the Hwang group

Lovell M.J. and Mathur A. (2004) The role of stem cells for treatment of cardiovascular disease. *Cell Proliferation* **37**:67-87

Odorico J.S., Kaufman D.S. and Thomson J.A. (2001) Multilineage differentiation from human embryonic stem cell lines *Stem Cells* **19**:193-204

O'Gorman M. (2006) PDG, patients and 'public debate' (available online at http://www.bioethics.ac.uk/commentary/2006-01.shtml)

Raff M. (2003) Adult stem cell plasticity: Fact or artefact? *Annual Review of Cell and Developmental Biology* **19**:1-22

- Despite the fact that several breakthroughs have occurred since the publication of this review, it nevertheless remains a very helpful introduction to stem cell plasticity

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- An excellent piece of investigative journalism, which uncovered a trail of evidence associated with the use of substandard stem cells for clinical therapies. A streamed version of the documentary (26 mins) can be reached from this URL.

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Other suggestions for further reading

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- Commentary on the House of Lords' ruling to permit limited work on human cloning

BBC News (2005b) Call for £100m UK stem cell fund (available online at http://news.bbc.co.uk/1/hi/sci/tech/4248079.stm)

- Includes a link to a streamed clip (1 minute) explaining some of the potential benefits of stem cell research

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- Chapter 9 "Cloning and Stem Cells" is particularly relevant

Jha A. (2004) The Guardian profile: Alison Murdoch (available online at http://education.guardian.co.uk/academicexperts/story/0,,1338793,00.html)

- A pen portrait of Prof Alison Murdoch, the first person in the UK granted a license for therapeutic cloning

Parliamentary Office of Science and Technology (2004) Regulating Stem Cell Therapies (available online at http://www.parliament.uk/documents/upload/POSTpn221.pdf)

Picoult, J. (2002) *My Sister's Keeper* Atria Books (Simon & Schuster), New York.

- A poignant and moving novel about the life of a child, created by *in vitro* fertilisation in order to be a stem cell donor for an older sibling

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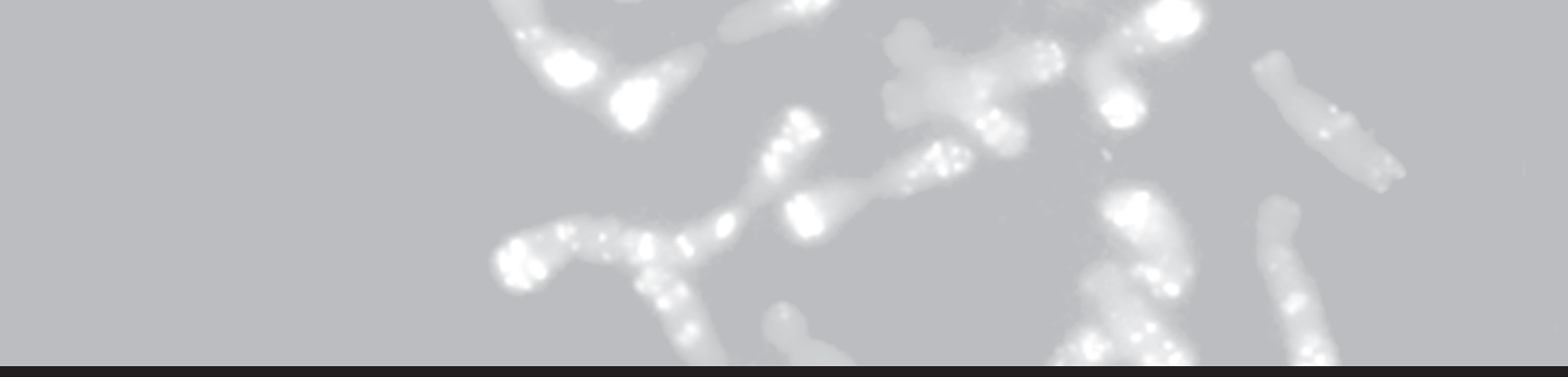

List of available Bioethics Briefings

The following Bioethics Briefings are freely available at
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