SUBMISSION

TO THE

LOCKHART LEGISLATION REVIEW COMMITTEE

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SUMMARY

Southern Cross Bioethics Institute (SCBI) supports the medical scientific enterprise in working towards treatments for debilitating conditions when that work is founded on sound ethical principles.

The Australian community responded to the proposal to allow access to excess IVF embryos on the grounds that their use would be for pursuing cures for diseases like Parkinson’s, diabetes and spinal cord injury. They were also led to believe that cures were imminent and would come from embryonic stem (ES) cells. Since passage of the legislation, not only have there been no treatments, clinical trials or even solid research indicating the clinical application of ES cells in the foreseeable future, but also the majority of embryos licensed for use have been for purposes unrelated to ES cells or cures. The public might justifiably feel misled.

The community also made it clear that embryos should not be deliberately created for research. However, with the lapse of the sunset clause, it would be possible in principle for the de facto creation of human embryos in IVF programmes deliberately for research. Moreover, if the creation of cloned human embryos were permitted, the community’s wishes in this regard would likewise have been disregarded. Any suggestion, as some have proposed, that cloned human embryos are not really human embryos, is semantic game playing at best and outright deception at worst.

At the time of the 2002 debate, there was ample evidence to suggest that the use of ES cells was unnecessary given advances using adult and cord blood stem cells. Since then the disparity is even more acute and work using non-ES cells has far outstripped that using ES cells in animal research, clinical trials and direct therapeutic application.

SCBI recommends that the ban on human cloning be maintained and that no research that is detrimental to human embryos be permitted.
INTRODUCTION

SCBI was heavily involved in the public debate at the time of the tabling of Australia’s *Prohibition of Human Cloning Bill 2002* and the *Research Involving Human Embryos Bill 2002*. We were, and remain, seriously concerned about the central ethical question surrounding the destruction of embryonic human life, considering it unacceptable. We also think that crossing this ethical line will make it difficult to restrict later calls for unethical practices, as well as have a corrosive effect on the broader ethical framework that underpins research involving human life.

We argued that there was no immediate need for access to human embryos, that the hoped-for results could be obtained in other ways, that the claims of benefit coming from ES cell research were overstated, that the interest in human embryos actually had more to do with generalised access for other purposes than with ES cell extraction, and that calls for cloning human embryos would intensify.

Since that time, ES cell research has not produced what was claimed, alternative research on other types of stem cells has proven even more promising with the passage of time, researchers have been more interested in using human embryos for purposes other than ES cell extraction, and the desire to create cloned human embryos has grown stronger with a shift from interest in therapeutic doning to the intentional creation of defective cloned human embryos.

The case for medical advance using ES cells has been overstated, a reality recently admitted to by one of the key figures in the field, the UK’s Lord Winston.

> The potential benefits of embryonic stem cell research have probably been oversold to the public, fertility expert Lord Winston says. He fears a backlash if science fails to deliver on some of the “hype” around the cells - as he believes may happen. He says the notion that a host of cures for serious, degenerative disorders are just around the corner is fanciful.¹

If that is the case with existing ES cells, it is even more the case with ES cells derived from cloned human embryos.

Furthermore, in a recent paper in *Nature Genetics*, fresh concerns have been added to those already raised over the genetic stability of ES cells.²

We believe it is time to consider repealing the legislation permitting research involving the destruction of human embryos.

IS ACCESS TO HUMAN EMBRYOS MORE ABOUT OTHER RESEARCH INTERESTS THAN ABOUT ES CELLS AND CURES?

In 2002, SCBI produced a booklet entitled *Human Embryos: a Limitless Scientific Resource? What the Research Involving Embryos and Prohibition of Human Cloning Bill 2002 really allows*. In that booklet we sought to identify all the uses to which human embryos were being put worldwide in legislatures that allowed their use in research involving their destruction. If the legislation was passed, we believed more embryos would be used for purposes separate from stem cell extraction even though the public debate in 2002 was framed entirely around potential cures coming from ES cells. As it turns out, nine licenses to use human embryos in research involving their destruction have been issued in Australia since 2002, and approximately 70% of the embryos are being used for purposes that have nothing to do with stem cells. The community believed they were agreeing to

¹ Amos J, Winston warns of stem cell 'hype'. BBC News, see [http://news.bbc.co.uk/1/hi/sci/tech/4213566.stm](http://news.bbc.co.uk/1/hi/sci/tech/4213566.stm)
² Maitra A et al., Genomic alterations in cultured human embryonic stem cells. *Nature Genetics* Sep 4 2005 Epub, see [www.nature.com/ng/journal/vaop/ncurrent/abs/ng1631.html?jsessionid=9C69C46F50B41E272E5C76CA12C5803E](http://www.nature.com/ng/journal/vaop/ncurrent/abs/ng1631.html?jsessionid=9C69C46F50B41E272E5C76CA12C5803E)
the use of human embryos for possible medical cures via ES cells. At the time of the public debate, there was no suggestion that human embryos would be used to train IVF practitioners, develop new culture media, or refine preimplantation genetic diagnostic tests. Therefore, with regard to community expectations if not standards, they might justifiably feel misled.

SHOULD EMBRYOS BE DELIBERATELY CREATED FOR RESEARCH?

One of the key principles in the Research Involving Human Embryos Act, 2002, again reflecting a community standard expressed at the time of the 2002 public debate, was that no embryos should be deliberately created for research. Many of those who felt that access to excess IVF embryos could be justified, nevertheless drew the line at access to embryos created expressly for the purpose of research. There is no evidence to suggest that this community standard has changed. Thus the Acts state that no embryos should be created for any other purpose than for the treatment of infertility.

This was also an attempt to keep research interests separate from clinical practice, particularly because the patients providing the embryos may be vulnerable to influence in what should be a decision as free as possible from influence. There is broad agreement among ethical commentators that decision making in clinical practice ought to be as separate from research or other interests as is reasonably possible. Otherwise decisions to act in the best interests of the patient have the potential to be undermined.

Those involved in clinical treatment as IVF practitioners may also be the ones involved with research on embryos, or be closely connected with researchers. This connection could mean that clinical judgments about how many eggs to collect and fertilise may be influenced by the desire to ensure adequate numbers of embryos for research. Importantly, the number of eggs collected has a direct impact on the woman involved. This problem has been highlighted with the lapse in the sunset clause that previously limited research on embryos to those created before 5th April 2002.

Moreover, it would now be possible in principle even if not in practice yet, for embryos to be created, developed to the blastocyst stage, declared excess and consent given for their use in research while still fresh. This could amount to the de facto production of embryos for the purpose of research. There would be no way of determining whether more embryos were created than required for infertility treatment. Furthermore, whether genuine informed consent under these circumstances can be obtained is questionable.

Additionally, if therapeutic cloning were to be allowed, the deliberate creation of cloned human embryos for the express purpose of their destruction would immediately undermine the community standard that embryos only be created for infertility treatment.

IS HUMAN CLONING NECESSARY OR DESIRABLE?

Whilst the current legislation prohibits the creation of cloned human embryos, the review has raised this issue for consideration. In addition to those comments already made about therapeutic cloning, there are several additional points.

First, there is no doubt that the creation of cloned human embryos and the refinement of techniques associated with their production will make it easier for reproductive cloning to occur. Those who ignore the strong negative sentiment about reproductive cloning will be eager to replicate the techniques developed by those who pursue therapeutic cloning. This is a reality that must be faced squarely by those who advocate therapeutic cloning rather than simply denying the strength of the connection. Of greater concern is that key figures in the field have already changed or softened their previous opposition to reproductive cloning. Thus, Baroness Mary Warnock has endorsed
reproductive cloning under some circumstances\(^3\), and Ian Wilmut has softened his position by considering various regulatory models for access to human cloning technology\(^4\).

Second, some think therapeutic cloning is a non-starter anyway, having changed their previously enthusiastic views. Jose Cibelli from Michigan State University says, “I can predict that therapeutic cloning is going to be obsolete.” Australia’s Alan Trounson, speaking to the journal *Nature Medicine* says, “so-called therapeutic cloning to my mind is a non-event … it is just not realistic.”\(^5\)

Third, if the interest in therapeutic cloning is primarily of a research nature, perhaps involving the deliberate creation of defective cloned human embryos, then that research should first be conducted in animals to obtain proof of principle. An enormous amount of cloning work has taken place in animals and none of it yet indicates that therapeutic cloning is feasible. If anything that work has served to highlight the technical problems.

Fourth, the Korean human cloning work was strongly criticized by two bioethicists, who warned in the journal *Science* about the exploitation of young women who were used as egg donors. As the journalist Michael Cook noted,

> after scrutinizing the experiment and the informed consent forms, they concluded that there was abundant potential for abusive exploitation of vulnerable patients and their friends and family members.\(^6\)

The point is, this problem will remain as long as human eggs are required, which is a necessary element of therapeutic cloning.

There is one final point regarding cloning that bears upon community standards of integrity, and that is that accurate language be used to describe what is actually being undertaken. The terms “therapeutic cloning” or “non-reproductive cloning”, neither of which accurately describes the procedure, serve to confuse the public’s perception of this application of human cloning. Likewise, cloned human embryos cannot simply be redefined as ‘activated oocytes’ ‘proto-embryos’ or the long since discredited ‘pre-embryos’. Trying to do so should be seen for what it is, that is, an attempt to reduce the moral status of human embryos by definitional sleight of hand.

**HOW DOES RESEARCH ON HUMAN EMBRYOS SQUARE WITH THE AGREED PROGRESSION OF MEDICAL RESEARCH?**

The accepted mode of progression of medical research has been sidestepped under this legislation. One of the basic guidelines of medical advance is the proof of principle that typically takes place in animal studies. New findings or theoretical work ought to be proven in animal studies before any consideration of its application in humans. However, human embryos have been destroyed, ES cells extracted and possible therapeutic applications explored without prior proof of principle. This problem is even more acute when it comes to therapeutic cloning. Human cloning experiments that have produced blastocysts from which stem cells have been extracted have been undertaken despite significant problems identified in animal studies. Proof of principle is important because it protects humans from what may be futile experiments. And whilst it is true that some view human embryos as mere research material, and therefore not the subjects of legal protection, it is likely that failure to prove the principle of therapeutic cloning in animal studies could lead to the premature utilisation of cloned human ES cells in patients, risking serious negative consequences.

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WHAT ARE THE ALTERNATIVES TO DESTROYING HUMAN EMBRYOS TO OBTAIN ES CELLS?

Southern Cross Bioethics Institute has recently undertaken a literature review (see Appendix) that provides a reasonable coverage of research on embryonic, umbilical and adult stem cells. It is clear that of the advances that have taken place in the last 5 years or so, by far the majority have been with umbilical or adult stem cells. These cells have been and continue to be used in therapeutic application, so far without any indication of teratogenic behaviour. By contrast, work using ES cells lags far behind and one wonders about the wisdom of huge financial investment in ES cells when the clinical applicability of adult stem cells seems to stare us in the face. Add to this the teratogenic behaviour of ES cells, risk of their immune rejection, and community concern over the ethical issues, and at the very least adult stem cell research should be strongly supported financially, and if necessary at the expense of ES cell research.

CONCLUSION

In conclusion, these practical issues are important, but Southern Cross Bioethics Institute is primarily concerned about bioethics. And we are primarily concerned about bioethics because in the final analysis, it is the choices of the community with regard to matters such as these that define us. We believe that sanctioning the destruction of human life at its earliest stages will have a damaging effect in the long run. The protection of human life is fundamental to liberal democracies and when some members of the human family are subject to expedient utility at the hands of others, the effect is corrosive and will impact upon the ability to protect all other members of the human family, particularly the weak, frail and disabled. We also consider it crucial that at this early stage in the growth of biotechnology the ethical underpinnings be sound. It is already beginning to look as if the biotechnological enterprise is taking charge of us, rather than us taking charge of it.

APPENDIX

BRIEFING NOTE ON STEM CELLS

Introduction

In the last five or so years there have been rapid advances in primary research and in therapeutic application using cellular technology based upon the use of stem cells. Stem cells may be divided into three primary types depending upon their origin - embryonic, umbilical and adult. However, this is probably an oversimplification. This perspective may change in recognition of the fact that a plethora of stem cell types with varying properties exist in human tissues from conception to adulthood. This diversity is likely to introduce a new level of complexity. Furthermore, just as the ethical issues surrounding the derivation and use of the various types of stem cells are profoundly different, the possible therapeutic applications to which various stem cells may be put are likewise different. Moreover, the finding that adult stem cells are more plastic than previously thought opens exciting possibilities for future treatments. However, that plasticity may also create a new problem. For if stem cells from the adult body can be shown to behave like those from the early embryo, perhaps the time will come when adult stem cells can go one step further and produce a zygote and hence an embryo directly, even without the need for a cloning step via a human egg cell. Recent experiments in mice have already shown that egg cells can be produced from a form of adult stem cell7. If applicable in humans, such a discovery would not only raise interesting and ethically

challenging possibilities, it would also raise the theoretical question whether a zygote and hence embryo might likewise be produced directly.

The purpose of this briefing note is to review the basic research and therapeutic application resulting from the use of all types of stem cells under the broad categories of embryonic, umbilical and adult.

**Sources of Stem Cells**

Stem cells have been derived from pre-implantation human embryos at approximately 5-6 days of age and grown in culture. Many groups have prepared ES cell lines from different blastocysts and there are now many human ES cell lines worldwide. How many of these cell lines are suitable for either research or therapy is debatable.

ES cells have also been derived from cloned human embryos, parthenogenetically produced embryos and hybrid embryos. A form of ES cell has also been isolated from the gonads of aborted fetuses, although this could perhaps be described more accurately as a foetal stem cell or even an adult stem cell.

Umbilical cord blood is a rich source of stem cells of varying types. British researchers have recently isolated a novel type of cord blood stem cell with properties that are very similar to ES cells, and can also be grown in large numbers. Most recently, a type of stem cell has been isolated from the human placenta, with properties that appear to be very similar to ES cells. A team from Vienna also reported the isolation of stem cells from amniotic fluid that have characteristics similar to ES cells.

Adult stem cells have been found in a wide variety of sites in the adult body, and may be present in every major tissue type. They have been isolated from brain, pancreas, liver, skin, fat,

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14. Researchers at Advance Cell Technology in the USA fused a human cell with an enucleated cow’s egg to produce an embryo that developed to the 32-cell stage. Stem Cell Sciences in Victoria, Australia conducted a similar experiment using a pig’s egg to produce a 32-cell embryo that was destroyed before further development could take place.
19. Miki T et al., Stem Cell Characteristics of Amniotic Epithelial Cells, first published online in *Stem Cell Express* on 4 August 2005. The full article can be located at [http://stemcells.alphamedpress.org/cgi/content/abstract/2004-0357v1](http://stemcells.alphamedpress.org/cgi/content/abstract/2004-0357v1)
Embryonic Stem Cells

The isolation and culturing of ES cells has led to several studies that have attempted to direct their differentiation into specific mature cell types. ES cells have been directed into several types of neural cells, cardiac muscle cells, pancreatic cells, and mesenchymal precursors (an adult stem cell). It has also been claimed that directed differentiation to additional cell types has been achieved, but some of these have yet to be reported separately.

Where ES cells were directed into pancreatic cells, the initial interpretation that the pancreatic cells were able to produce insulin, thereby being candidates for transplantation to correct diabetes, was later shown to be flawed.

ES cells have also been used in various animal models to treat Parkinsonian symptoms, with varying degrees of success. In some cases however, tumour formation has also resulted.
In a rat model for cardiac damage, work at the Mayo Clinic involved directed differentiation of ES cells into functional cardiac cells that were able to improve cardiac function when injected into damaged regions.\(^{48}\)

Mouse ES cells have also been shown to occasionally differentiate into skeletal muscle cells when injected into mdx mice (a model for human muscular dystrophy)\(^{49}\).

The use of ES cells in therapy has been hampered by concerns over the formation of cancers, specifically teratomas\(^{50,51}\). At this point of time there are no human therapeutic applications in which ES cells have been used. Furthermore, the genetic stability of ES cells has been called into question\(^{52,53,54}\), raising concerns over their behaviour once transplanted.

### Umbilical Cord Blood Stem Cells

One of the more promising developments in stem cell technology involves umbilical cord blood. This small amount of blood is rich in stem cells and has already been used to treat many diseases. The number of cord blood banks worldwide is increasing steadily as it becomes apparent that this source of stem cells can be therapeutically valuable.

The capacity of cord blood stem cells to differentiate into other cell types has only recently been explored and so far they have been shown to differentiate into neural progenitors\(^{55}\) and a variety of other cell types including bone, cartilage, fat and blood\(^{56}\). In the latter of these papers, the authors call the cells “unrestricted somatic stem cells” and also note that they displayed no risk of tumour formation. While only a limited amount of research has been invested in directed differentiation of cord blood cells, their capacity to differentiate widely into many different cell types is implied by the fact that they are effective in the treatment of many diseases that involve diverse cell types.

Direct clinical application using cord blood cells has been extensive\(^{57,58,59,60}\). Conditions ranging from leukemia and lymphoma to genetic and immune system disorders have been treated\(^{61}\).

In particularly novel developments, cord blood has been used to treat conditions that are removed from disorders of the blood or immune system. For example, in a study using rats, researchers have used umbilical cord blood to treat spinal cord injury. The rats showed improvements even when

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\(^{50}\) Wakitani S \textit{et al.}, Embryonic stem cells injected into the mouse knee joint form teratomas and subsequently destroy the joint; \textit{Rheumatology} \textbf{42}:162-165, January 2003.


\(^{61}\) For examples of the types of clinical application see \url{http://www.biocellaustralia.com}
treated days after the injury. In a human case study, a Korean team reported that they had treated a 37-year-old woman with a spinal cord injury sustained in 1985 with a cord blood transplant. What is particularly promising about this result is that the treatment took place 19 years after the injury.

In another application, cord blood cells have been used in a rat model to alleviate some of the effects of stroke. In a recent Chinese study, clinicians used cord blood in an attempt to treat a boy with muscular dystrophy, noting increased dystrophin production and slightly improved muscular condition.

In a quite different disease, Krabbe's disease, an inherited degenerative disorder that affects the nervous system, researchers used cord blood from unrelated donors that “favorably altered the natural history of the disease.”

At present there are numerous clinical trials underway that are assessing the ability of cord blood to treat a wide range of conditions. While these trials utilise cord blood without attempts to direct the differentiation of specific stem cells into other more mature cells, the future is likely to see more studies on directed differentiation of cord blood or similar cells following the discovery of placental stem cells that exhibit properties very similar to ES cells. Furthermore, the recent commercial availability of another novel stem cell line isolated from cord blood is likely to further add to the research interest.

Adult Stem Cells

The term ‘adult stem cell’ applies to precursor cells that have been found primarily in the tissues of adults. However, the term is often more broadly applied to cells that are located in the body after birth. Hence, where humans are concerned, young children possess ‘adult stem cells’. Furthermore, some refer to umbilical cord blood stem cells as a form of adult stem cell. These categories are not only loosely applied, but as noted earlier they do not do justice to the reality that cellular development is a continuum from zygote to mature organism, nor to the discoveries of recent years about cellular plasticity. This is perhaps the most interesting finding about adult stem cells; that is their capacity to be plastic and transdifferentiate into cells they would not normally become.

Adult Stem Cell Transdifferentiation

The normal function of adult stem cells - keeping in mind the limitations of current knowledge about them – is to produce new mature cells within their tissue of origin. Hence, liver stem cells give rise to mature liver cells, skin stem cells in the basal cell layer give rise to a range of cells located within the skin, blood stem cells typically give rise to a variety of mature red and white

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65 Dystrophin is the protein damaged or missing in muscular dystrophy.
68 The details of these trials can be accessed at http://www.clinicaltrials.gov
blood cells, and so forth. When a bone marrow transplant is carried out, the bone marrow stem cells repopulate the blood cells that were destroyed as part of the treatment.

But perhaps this is not the only function of stem cells, and they may be able to travel more widely and become mature cells in different locations. This transdifferentiation is increasingly being explored in the context of possible therapy, but it may also be found that various stem cells are normally active in body repair at sites far distant from their origin.

If that is the case, then adult stem cell versatility as part of normal function makes them stronger candidates for manipulation in a therapeutic context. The manner of manipulation has so far been primarily to transplant adult stem cells rather than to attempt directed differentiation in the laboratory prior to infusion. This is not only because of the large body of research that will be required before directed differentiation is achievable, but also because adult stem cells are stable and able to be directly applied clinically without risk of tumour formation or fears about genetic instability. Furthermore, autologous adult stem cell transplantation by definition achieves immunocompatibility.

With regard to their versatility, some argue that adult stem cells,

… perhaps in some cases have a developmental repertoire close to that of embryonic stem cells$^{71}$.

In studies conducted by Catherine Verfaillie at the University of Minnesota, Minneapolis, mesenchymal stem cells have been shown to specialise into neural, cartilage, bone, fat, and muscle cells$^{72}$. Verfaillie considers the cells to be “ … almost like ES cells”, but “better behaved”.

In 2001, Verfaillie isolated a multipotent adult progenitor cell from human volunteers. The journal New Scientist dubbed this cell the ‘ultimate stem cell’$^{73}$.

There have been numerous studies showing that adult stem cells can transdifferentiate to become other types of cells. These include several types of bone marrow stem cell becoming a wide variety of cell types$^{74,75,76,77,78,79,80}$; nasal stem cells differentiating into cardiac, liver, kidney, nerve and muscle$^{81}$; pancreatic stem cells becoming nerve, muscle and pancreatic beta cells$^{82}$; inner ear stem cells showing pluripotency$^{83}$; blood stem cells forming the three major tissue types$^{84}$; various stem cells specialising into numerous other cell types$^{85}$; neural stem cells coerced into becoming blood cells, including cells carrying out an immune function such as B and T lymphocytes$^{86}$; and,

76 Morisot C et al., Human bone marrow mesenchymal stem cells can express insulin and key transcription factors of the endocrine pancreas developmental pathway upon genetic and/or microenvironmental manipulation in vitro. Stem Cells **23**:594-604, 2005.
78 Mezey E et al., Transplanted bone marrow generates new neurons in human brains. Proc Natl Acad Sci USA **100**:1364-1369, 4 February 2003.
84 Zhao Y et al., A human peripheral blood monocyte-derived subset acts as pluripotent stem cells. Proc Natl Acad Sci USA **100**:2426-2431, 4 March 2003.
haematopoietic stem cells differentiating into a variety of nerve cells. The environment in which stem cells find themselves located has a bearing upon the cell type into which they will differentiate.

Some concerns have been raised about some of these reports that adult stem cells were fusing with other cells rather than transdifferentiating. It appeared as if fusion was occurring for about one in every 10,000 to 100,000 cells, and in very specific culture conditions. The results of these experiments have been variously interpreted, but it is possible that cell fusion may occur in a limited number of applications. Moreover, if it does occur, it could operate in parallel with transdifferentiation to achieve a therapeutic effect.

**Parkinson's Disease**

Most of the research on Parkinson's disease has utilised neural stem cells or bone marrow stem cells. Neural or bone marrow stem cells have been isolated and reimplanted, but specific agents have also been applied to stimulate the neural stem cells to proliferate in situ.

Neural stem cells have been grafted into a specific brain site in rats that have been developed as a model of human Parkinson's disease. Some time later, Parkinsonian symptoms diminished, leading to a limited recovery of function. This type of cell has recently been isolated in humans and behaves similarly to its equivalent in rodents.

Neural stem cells seem to be able to form many types of neurons and migrate throughout the brain to repair damage and prevent the loss of dopaminergic neurons that is the hallmark of Parkinson's disease.

The use of factors that might stimulate neural stem cells to proliferate in situ and migrate to the sites of damage is a particularly interesting and potentially most promising development. In a rat study, researchers injected a growth protein into the brains of Parkinson's rats and found that neural stem cells migrated to the site of damage and repopulated the region with cells. Moreover, 80% of the rats benefited from the treatment.

There are at least two examples of Parkinson's treatments in humans using neural stem cells. In one case, researchers isolated a patient's own neural stem cells, directed their differentiation and reimplanted them. One year later the patient's Parkinson's symptoms were reduced by 80%.

The researchers involved are now undertaking a clinical trial of the procedure.
Using a different approach, British researchers treated five Parkinson’s patients with a cell-derived growth factor that stimulated neuronal sprouting in the brain, leading to a 61% improvement in motor function\textsuperscript{102}. Presumably the growth factor was stimulating neural stem cells to differentiate\textsuperscript{103}.

**Diabetes**

Adult stem cells from several different sources have been used in attempts to produce insulin secreting pancreatic islet cells. Most studies have been in mice, with some preliminary studies in humans, and involve either transdifferentiation in vitro before implantation or direct implantation of stem cells that then differentiate into pancreatic beta cells producing insulin. There have been varying successes in terms of the reversal of diabetes.

Researchers have used bone marrow derived stem cells to effect the partial reversal of diabetes in mice\textsuperscript{104,105,106}, splenic cells to permanently reverse autoimmune diabetes in mice\textsuperscript{107}, liver stem cells to reverse diabetes within 10 days in mice\textsuperscript{108}, and pancreatic stem cells to reverse diabetes in mice\textsuperscript{109}.

Researchers have also shown that hematopoietic stem cells from blood are able under certain conditions to prevent the development of autoimmune diabetes in mice that normally develop it\textsuperscript{110}.

*In vitro* studies looking at the isolation, culturing and differentiation of pancreatic stem cells or intestinal epithelial cells have shown that pancreatic insulin producing beta-like cells can be produced\textsuperscript{111}.

In a recent interesting development using human liver cells, Israeli researchers found that the cells could be converted into functional insulin producing cells that reversed hyperglycemia in diabetic mice\textsuperscript{112}. The authors surmise that if this were fully applicable to humans, patients could therefore become their own donors. It is noteworthy that these liver cells were not specifically identified as stem cells.

\textsuperscript{100} For the patient’s testimony to the US Senate Committee on Science, Technology, and Space Hearing: Adult Stem Cell Research, Wednesday, 14 July 2004 by Dennis Turner, see http://www.leaderu.com/science/stemcelltestimony_turner.html

\textsuperscript{101} See evidence given by Dr Michel Levesque at the Science, Technology, and Space Hearing Adult Stem Cell Research, Wednesday, 14 July 2004, SR - 253. Dr. Levesque states “Under the guidance and supervision of the Food and Drug Administration (FDA) office of Cellular, Tissues and Gene Therapies and the Center for Biologics Evaluation and Treatment (CBER) we are about to begin Phase II trials using this promising cell therapy”.


\textsuperscript{107} Kodama \textit{et al.}, Islet regeneration during the reversal of autoimmune diabetes in NOD mice. \textit{Science} \textbf{302}(5648):1223-7, 14 November 2003.


\textsuperscript{110} Steptoe RJ \textit{et al.}, Transfer of hematopoietic stem cells encoding autoantigen prevents autoimmune diabetes. \textit{J Clin Invest} \textbf{111}:1357-1363, May 2003


Spinal Cord Repair

The use of stem cell therapy for spinal cord repair has advanced rapidly in the last five years. Neural, bone marrow stromal, olfactory and hematopoietic stem cells have all been used to promote neuronal regrowth and hence spinal cord repair in animal models and for at least one of these, in patients.

In several studies using rats, neural stem cells have been shown to promote spinal cord regeneration leading to some degree of functional recovery\(^\text{113}\), although at the same time concern has been raised over side effects which may limit neural stem cell applications in some settings\(^\text{114}\). Several studies on spinal cord repair have utilised different types of bone marrow stem cell. For example, bone marrow stromal stem cells have been shown to partially repair cord damage in various rat models of spinal cord injury\(^\text{115,116,117,118}\).

In an unexpected development, it seems one of the better adult stem cells for cord repair so far is a form of nasal cell called the olfactory ensheathing cell. Several studies in rats with spinal injury have shown significant improvements in function following injection of these cells\(^\text{119,120,121}\). In other experiments, the olfactory cells appear to stimulate injured spinal cells to undergo long-distance regeneration\(^\text{122}\). Moreover, the treatment of patients with spinal cord injury using these cells has resulted in some improvement\(^\text{121}\). The recent isolation and purification of these cells in humans represents a promising development in spinal cord repair\(^\text{124}\).

A different type of human bone marrow derived stem cell, the hematopoietic stem cell, has recently been shown to differentiate into fully-fledged neurons in the developing spinal cord of the chicken embryo\(^\text{125}\). The authors determined that these human cells did not fuse with chicken cells in the process of differentiation.

Stroke

Following stroke-like injury in rats, the stimulation of circulating hematopoietic stem cells by granulocyte colony-stimulating factor causes a reduction in the volume of the damaged site,


\(^\text{118}\) Sasaki M et al., Transplantation of an acutely isolated bone marrow fraction repairs demyelinated adult rat spinal cord axons. Glia 35, 26-34, July 2001.


\(^\text{120}\) Lu J et al., Olfactory ensheathing cells promote locomotor recovery after delayed transplantation into transected spinal cord. Brain 125:14-21, 2002.


\(^\text{125}\) Sigurjonsson OE et al., Adult human hematopoietic stem cells produce neurons efficiently in the regenerating chicken embryo spinal cord. Proc Natl Acad Sci USA 102:5227-5232, 5 April 2005.
improved blood vessel ingression, and increased neural plasticity. In similar experiments, this treatment led to improved function. In a separate study using human bone marrow stromal cells to treat stroke in rats, the intravenous injection of the cells produced a neurological benefit.

In an earlier study it had already been shown that stroke injury itself causes endogenous neural stem cells to proliferate in an attempted repair process. If neural stem cells are added directly to the mouse brain following stroke-like brain injury, they proliferate, differentiate into neurons and glial cells and lead to a partial recovery of motor function.

**Cardiac Damage**

Numerous clinical examples exist of patients injected with their own bone marrow stem cells following severe heart failure. There was a significant improvement in cardiac function, ability to exercise, and regeneration of myocardial cells. The reparative effect may be due in part to improved blood perfusion through angiogenesis, which is the creation of new blood vessels.

In experiments using a novel type of human bone marrow stem cell that could differentiate widely into cells of the 3 major lineages, engraftment into rat myocardium led to improvement in overall cardiac function. The researchers also showed that these cells had extensive capacity for expansion without loss of multipotency and achieved their effect by creating new cardiomyocytes as well as fusing with existing cells.

The activation of endogenous bone marrow stem cells by specific biochemical agents is also a promising putative therapy for cardiac failure. In experiments using mice, researchers were able to activate bone marrow stem cells to migrate to damaged myocardium and effect repair by reducing the area of damage.

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There has also been considerable interest and work using myoblasts, which are muscle stem cells. These cells, like bone marrow stem cells, are able to improve cardiac function when infused\textsuperscript{142,143,144}.

Another form of muscle stem cell, taken from cardiac tissue itself, has been the subject of a recent study in rats\textsuperscript{145}. Significant improvements in cardiac function were shown following infusion of the cells without any evidence of cell fusion.

\textbf{Other Conditions}

Considerable research has been undertaken to see whether adult stem cells are able to regenerate the muscle loss that accompanies muscular dystrophy, but with limited success. Several groups have reported partial restoration of dystrophin, the missing protein in affected muscle.

The use of bone marrow stem cells has a long history in the treatment of various blood disorders, most notably the leukaemias. However, the repertoire of these cells as well as those from peripheral blood has increased dramatically recently with applications in the treatment of brain tumours (in combination with high dose chemotherapy)\textsuperscript{149,150}, localized retinoblastoma\textsuperscript{151}, solid tumours\textsuperscript{152}, breast cancer\textsuperscript{153}, and autoimmune diseases like multiple sclerosis\textsuperscript{154}, systemic lupus erythematosus\textsuperscript{155} and rheumatoid arthritis\textsuperscript{156}. This by no means a complete list.

\textbf{Concluding Remarks}

Stem cells hold enormous promise in the development of new therapies for a wide range of conditions. At this point in time stem cells derived from adult tissues or umbilical cord blood show the greatest clinical application and a rapidly growing repertoire of capacity for transdifferentiation. Coupled with the possibility for autologous transplant (and hence immunocompatibility), their stability, and recent expansion in quantities sufficient for therapy, adult and cord blood stem cells must be considered the most feasible options.

\textsuperscript{142}Menasché P et al., Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. \textit{J Am Coll Cardiol.} \textbf{41}(7):1078-83, 2 April 2003.
\textsuperscript{145}Dawn B et al., Cardiac stem cells delivered intravascularly traverse the vessel barrier, regenerate infarcted myocardium, and improve cardiac function. \textit{Proc Natl Acad Sci USA} \textbf{102}:3766-3771, 8 March 2005.
\textsuperscript{146}Gussoni E et al., Dystrophin expression in the mdx mouse restored by stem cell transplantation. \textit{Nature} \textbf{401}(6751):390-394, 23 September 1999.
\textsuperscript{148}Torrente Y et al., Human circulating AC133(+) stem cells restore dystrophin expression and ameliorate function in dystrophic skeletal muscle. \textit{J Clin Invest} \textbf{114}(2):182-95, July 2004.
\textsuperscript{150}Abrey LE et al., High dose chemotherapy with autologous stem cell rescue in adults with malignant primary brain tumors. \textit{J Neurooncol} \textbf{44}:147-153, September 1999.
\textsuperscript{151}Hertzberg H et al., Recurrent disseminated retinoblastoma in a 7-year-old girl treated successfully by high-dose chemotherapy and CD34-selected autologous peripheral blood stem cell transplantation. \textit{Bone Marrow Transplant} \textbf{27}(6):653-655, March 2001.
\textsuperscript{152}Waldmann V et al., Transient complete remission of metastasized merkel cell carcinoma by high-dose polychemotherapy and autologous peripheral blood stem cell transplantation. \textit{Br J Dermatol} \textbf{143}:837-839, October 2000.
\textsuperscript{156}Burt RK et al., Autologous hematopoietic stem cell transplantation in refractory rheumatoid arthritis: sustained response in two of four patients. \textit{Arthritis & Rheumatology} \textbf{42}:2281-2285, November 1999.
In contrast, progress using ES cells has been slow and hampered by the risk of tumour formation and immune rejection. The potential use of ES cells derived from human cloned embryos is even more problematic - especially considering that their application as a therapy tailored for one patient would be inordinately expensive.