Southern Cross
BIOETHICS INSTITUTE

SUBMISSION

TO THE

LOCKHART LEGISLATION REVIEW COMMITTEE

Dr Gregory K Pike, PhD, Director
Ms Selena Ewing, BHSc, Research Officer
Mr Zac Alstin, BA(Hons), Research Officer

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

[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

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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[3] Warnock M, *Making Babies: Is there a right to have children?* Oxford University Press, Oxford, 2002.

[4] McGee G & Wilmut I, A Model for Regulating Cloning, In: *The Human Cloning Debate*, Ed. McGee G, Berkeley Hills Books, Berkeley, 2000.

[5] Mandavilli A, Scientists seek simple remedies to cloning conundrums. *Nature Medicine* **11**:459, 2005.

[6] Cook M, False dawn for stem cell cures. *MercatorNet* 27 May 2005, www.mercatornet.com/content/view/85/0/

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 cell[7]. If applicable in humans, such a discovery would not only raise interesting and ethically

[7] Johnson J *et al.*, Oocyte Generation in Adult Mammalian Ovaries by Putative Germ Cells in Bone Marrow and Peripheral Blood. *Cell* **122**:303-315, 29 July 2005.

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[8]. 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[9,10,11,12], parthenogenetically produced embryos[13] and hybrid embryos[14].

A form of ES cell has also been isolated from the gonads of aborted fetuses[15], 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[16]. 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[17,18]. 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[19]. A team from Vienna also reported the isolation of stem cells from amniotic fluid that have characteristics similar to ES cells[20].

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[21], pancreas[22], liver[23], skin[24], fat[25],

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[8] Thompson JA *et al.*, Embryonic stem cell lines derived from human blastocysts. *Science* **282**:1145-1147, 6 November 1998.

[9] Hwang WS *et al.*, Evidence of a pluripotent human embryonic stem cell line derived from a cloned blastocyst. *Science* **303(5664)**:1669-74, 12 March 2004.

[10] Hwang WS *et al.*, Patient-Specific Embryonic Stem Cells Derived from Human SCNT Blastocysts. *Science* 308:1777-1783, 2005.

[11] Hwang WS *et al.*, Human embryonic stem cells and therapeutic cloning. *J Vet Sci* **6(2)**:87-96, June 2005.

[12] Highfield R, Scientists take a giant step forward in human cloning. *UK Telegraph*, 10 May 2005.

[13] Advanced Cell Technology in the USA recently announced production of a parthenogenetically derived human embryo by manipulation of a human egg to develop as an embryo without fertilisation or cloning. See Cibelli JB *et al.*, The first human cloned embryo. *Sci Am* **286(1)**:44-51, January 2002, and Cibelli JB *et al.*, Somatic cell nuclear transfer in human: Pronuclear and early embryonic development. *J Regen Med* **26**, 25-31, 2001.

[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.

[15] Shamblott MJ *et al.*, Derivation of pluripotent stem cells from cultured human primordial germ cells. *Proc. Natl. Acad. Sci. USA* **95**:13726-31, 1998.

[16] Lu S & Ende N, Potential for clinical use of viable pluripotent progenitor cells in blood bank stored human umbilical cord blood. *Life Sciences* **61**:1113-1123, 1997.

[17] McGuckin CP *et al.*, Production of stem cells with embryonic characteristics from human umbilical cord blood. *Cell Prolif* **38(4)**:245-55, August 2005.

[18] McGuckin CP *et al.*, Thrombopoietin, flt3-ligand and c-kit-ligand modulate HOX gene expression in expanding cord blood CD133 cells. *Cell Prolif* **37(4)**:295-306, August 2004.

[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

[20] Prusa A-R *et al.*, Oct-4-expressing cells in human amniotic fluid: a new source for stem cell research? *Human Reprod* **18**:1489-1493, 2003.

[21] Uchida N *et al.*, Direct isolation of human central nervous system stem cells. *Proc. Natl. Acad. Sci. USA* **97:**14720-14725, 19 December 2000.

[22] Bonner-Weir S *et al.*, In vitro cultivation of human islets from expanded ductal tissue. *Proc Natl Acad Sci USA* **97**, 7999-8004, 5 July 2000.

[23] Malouf NN *et al.*, Adult-derived stem cells from the liver become myocytes in the heart in vivo. *Am J Pathol* **158**:1929-1935, June 2001.

muscle[26], blood[27], bone marrow[28], lung[29], and tooth pulp[30]. The majority of the studies cited have isolated adult stem cells from humans.

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[31,32,33], cardiac muscle cells[34,35,36], pancreatic cells[37,38], and mesenchymal precursors (an adult stem cell)[39]. It has also been claimed that directed differentiation to additional cell types has been achieved[40], 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[41,42,43].

ES cells have also been used in various animal models to treat Parkinsonian symptoms, with varying degrees of success[44,45,46,47]. In some cases however, tumour formation has also resulted.

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[24] Toma JG *et al.*, Isolation of multipotent adult stem cells from the dermis of mammalian skin. *Nature Cell Biol* **3**:778-784, September 2001.

[25] Zuk PA *et al.*, Multilineage cells from human adipose tissue: Implications for cell-based therapies. *Tissue Engineering* **7**:211-228, 2001.

[26] Williams JT *et al.*, Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes. *Am Surg* **65**:22, January 1999.

[27] Eglitis MA & Mezey E, Hematopoietic cells differentiate into both microglia and macroglia in the brain of adult mice. *Proc Natl Acad Sci USA* **94**:4080-4085, 1997.

[28] Reyes M *et al.*, Purification and ex vivo expansion of postnatal human marrow mesodermal progenitor cells. *Blood* **98**:2615-2625, 1 November 2001.

[29] Emura M, Stem cells of the respiratory epithelium and their in vitro cultivation. *In Vitro Cell Dev Biol Anim* **33**:3, January 1997.

[30] Gronthos S *et al.*, Postnatal human dental pulp stem cells (DPSCs) *in vitro* and *in vivo*. *Proc Natl Acad Sci USA* 97:13625-13630, 5 December 2000.

[31] Shin S *et al.*, Human motor neuron differentiation from human embryonic stem cells. *Stem Cells Dev* **14(3)**:266-269, June 2005.

[32] Schulz TC *et al.*, Directed neuronal differentiation of human embryonic stem cells. *BMC Neuroscience* **4**:27, 2003. The full text of this article is available at http://www.biomedcentral.com/1471-2202/4/27

[33] Yasushi Takagi *et al.*, Dopaminergic neurons generated from monkey embryonic stem cells function in a Parkinson primate model *J Clin Invest* **115(1)**:102-9, January 2005.

[34] Min JY *et al.*, Long-term improvement of cardiac function in rats after infarction by transplantation of embryonic stem cells. *J Thor Cardiovasc Surg* **125**:361-369, February 2003.

[35] Hodgson DM *et al.*, Stable benefit of embryonic stem cell therapy in myocardial infarction. *Am J Physiol Heart Circ Physiol* **287(2)**:H471-9, August 2004.

[36] Zhang YM *et al.*, Stem cell-derived cardiomyocytes demonstrate arrhythmic potential. *Circulation* **106**:1294-1299, 3 September 2002.

[37] Lumelsky N *et al.*, Differentiation of embryonic stem cells to insulin-secreting structure similar to pancreatic islets. *Science* **292**:1389-1394, 18 May 2001.

[38] Hori Y *et al.*, Growth inhibitors promote differentiation of insulin-producing tissue from embryonic stem cells. *Proc Natl Acad Sci USA* **99(25)**:16105-10, 10 December 2002. Epub 2002 Nov 19. PMID:12441403.

[39] Barberi T *et al.*, Derivation of Multipotent Mesenchymal Precursors from Human Embryonic Stem Cells. *PloS Medicine* 2(6):e161, June 2005.

[40] Trounson A., Human embryonic stem cell derivation and directed differentiation. *Ernst Schering Res Found Workshop* **54**:27-44, 2005.

[41] Rajagopal J *et al.*; Insulin staining of ES cell progeny from insulin uptake. *Science* **299**:363, 17 Jan 2003.

[42] Sipione S *et al.*, Insulin expressing cells from differentiated embryonic stem cells are not beta cells. *Diabetologia* **47**:499-508, 2004 (published online 14 February 2004).

[43] Hansson M *et al.*, Artifactual insulin release from differentiated embryonic stem cells. *Diabetes* **53:** 2603-2609, October 2004.

[44] Ben-Hur T *et al.*, Transplantation of human embryonic stem cell-derived neural progenitors improves behavioral deficit in Parkinson's rats. *Stem Cells* **22(7)**:1246-55, 2004.

[45] Nishimura F *et al.*, Potential use of embryonic stem cells for the treatment of mouse Parkinsonian models: improved behavior by transplantation of in vitro differentiated dopaminergic neurons from embryonic stem cells. *Stem Cells* **21**:171-180, March 2003.

[46] Kim J-H *et al.*, Dopamine neurons derived from embryonic stem cells function in an animal model of Parkinson's disease. *Nature* **418**:50-56, 4 July 2002.

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 cells 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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[47] Bjorklund LM *et al.*, Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. *Proc Natl Acad Sci* **99:** 2344-2349, 19 February 2002.
[48] Hodgson DM *et al.*, 2004, *Op. Cit.*
[49] Bhagavati S & Xu W Generation of skeletal muscle from transplanted embryonic stem cells in dystrophic mice. *Biochem Biophys Res Comm* **333(2)**:644-9, 29 July 2005.
[50] Wakitani S *et al.*, Embryonic stem cells injected into the mouse knee joint form teratomas and subsequently destroy the joint; *Rheumatology* **42**:162-165, January 2003.
[51] Erdo F *et al.*, Host-dependent tumorigenesis of embryonic stem cell transplantation in experimental stroke. *J Cereb Blood Flow Metab* **23**:780-785, 2003.
[52] Cowan CA *et al.*, Derivation of embryonic stem-cell lines from human blastocysts. *New Engl J Med* **350**:13, published online 3 March 2004.
[53] Draper JS *et al.*, Recurrent gain of chromosomes 17q and 12 in cultured human embryonic stem cells. *Nature Biotech* **22**:53-54, January 2004.
[54] Humpherys D *et al.*, Epigenetic instability in ES cells and cloned mice. *Science* **293**:95-97, 6 July 2001.
[55] Sanchez-Ramos J *et al.*, Molecular and cellular evidence for neural progenitors in Human Umbilical Cord Blood. *Neurology* **56**(suppl. 3):S03.001, 2001.
[56] Kögler G *et al.*, A new human somatic stem cell from placental cord blood with intrinsic pluripotent differentiation potential. *J Exp Med* **200**:123-135, 19 July 2004.
[57] Laughlin MJ *et al.*, Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *New Engl J Med* **344**:1815-1822, 14 June 2001.
[58] Ziegner UH *et al.*, Unrelated umbilical cord stem cell transplantation for X- linked immunodeficiencies. *J Pediatr* **138(4)**:570-573, April 2001.
[59] Gore L *et al.*, Successful cord blood transplantation for sickle cell anemia from a sibling who is human leukocyte antigen-identical: implications for comprehensive care. *J Pediatr Hematol Oncol* **22(5)**:437-440, Sept-Oct 2000.
[60] Singapore scores medical first in treatment of thalassaemias. *Agence France Presse*, 14 Aug 2001. For a description of the case see http://www.nuh.com.sg/mediaroom/files/Cord%20blood%20transplant%20-%20Final.pdf
[61] For examples of the types of clinical application see http://www.biocellaustralia.com

treated days after the injury[62]. 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[63]. 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[64].

In a recent Chinese study, clinicians used cord blood in an attempt to treat a boy with muscular dystrophy, noting increased dystrophin[65] production and slightly improved muscular condition[66].

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"[67].

At present there are numerous clinical trials underway that are assessing the ability of cord blood to treat a wide range of conditions[68]. 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[69]. Furthermore, the recent commercial availability of another novel stem cell line isolated from cord blood is likely to further add to the research interest[70].

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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[62] Saporta S *et al.*, Human umbilical cord blood stem cells infusion in spinal cord injury: Engraftment and beneficial influence on behavior. *J Hematotherapy Stem Cell Res* **12**:271-278, 2003.

[63] Reported by Tae-gyu, Kim, Korean Scientists Succeed in Stem Cell Therapy. *Korea Times*, Nov 26 2004. Report can be accessed at http://times.hankooki.com/lpage/200411/kt2004112617575710440.htm

[64] Chen J *et al.*, Intravenous administration of human umbilical cord blood reduces behavioral deficits after stroke in rats. *Stroke* **32**:2682-2688, November 2001.

[65] Dystrophin is the protein damaged or missing in muscular dystrophy.

[66] Zhang C *et al.*, Therapy of Duchenne muscular dystrophy with umbilical cord blood stem cell transplantation. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* **22(4)**:399-405, August 2005.

[67] Escolar ML *et al.*, Transplantation of Umbilical Cord Blood in Babies with infantile Krabbe's Disease. *New Engl J Med* **352(20)**:2069-2081, 19 May 2005.

[68] The details of these trials can be accessed at http://www.clinicaltrials.gov

[69] Toshio Miki *et al.*, 2005 *Op. Cit.*

[70] BioE First to Clone and Commercialize Multipotent Stem Cell Lines Derived from Human Umbilical Cord Blood *Gen Eng News* *http://www.genengnews.com/news/bnitemaspx?name=519610XSL_NEWSML_TO_NEWSML_WEB.xml*

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,

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[71] Clarke DL *et al.*, Generalized Potential of Adult Neural Stem Cells. *Science* **288**:1660-1663, 2 June 2000.
[72] Reported by Gretchen Vogel, Can Old Cells Learn New tricks? *Science* **287**:1418-1419, 25 February 2000.
[73] Sylvia Pagan, Ultimate stem cell discovered. *New Scientist* Jan 2002, for an online copy of this article see: http://www.newscientist.com/news/news.jsp?id=ns99991826
[74] Crain BJ *et al.*, Transplanted human bone marrow cells generate new brain cells. *J Neurol Sci* **233(1-2)**:121-3, 15 June 2005.
[75] Yoon Y-S *et al.*, Clonally expanded novel multipotent stem cells from human bone marrow regenerate myocardium after myocardial infarction. *J Clin Invest* **115**:326-338, February 2005.
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[80] Krause DS *et al.*, Multi-Organ, Multi-Lineage Engraftment by a Single Bone Marrow-Derived Stem Cell. *Cell* **105:** 369-377, 4 May 2001.
[81] Murrell W *et al.*, Multipotent stem cells from adult olfactory mucosa. *Developmental Dynamics* **233:**496-515, June 2005.
[82] Kruse C *et al.*, Pluripotency of adult stem cells derived from human and rat pancreas. *Applied Physics* A **79**:1617-1624, November 2004.
[83] Li H *et al.*, Pluripotent stem cells from the adult mouse inner ear. *Nature Med* **9**:1293-1299, October 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.
[85] Howell JC *et al.*, Pluripotent stem cells identified in multiple murine tissues. *Ann New York Acad Sci* **996**:158-173, 2003.
[86] Bjorson CR *et al.*, Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells *in vivo*. *Science* **283**:534-7, 22 January 1999.

haematopoietic stem cells differentiating into a variety of nerve cells[87]. The environment in which stem cells find themselves located has a bearing upon the cell type into which they will differentiate[88].

Some concerns have been raised about some of these reports that adult stem cells were fusing with other cells rather than transdifferentiating[89,90]. 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[91] 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[92]. 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.[93] This type of cell has recently been isolated in humans and behaves similarly to its equivalent in rodents.[94]

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[95,96,97].

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[98].

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%[99,100]. The researchers involved are now undertaking a clinical trial of the procedure[101].

[87] Eglitis MA & Mezey E, 1997, *Op. Cit*.
[88] Shihabuddin LS *et al.*, Adult spinal cord stem cells generate neurons after transplantation in the adult dentate gyrus. *J Neurosci* **20:**8727-8735, Dec 2000.
[89] Terada N *et al*, Bone marrow cells adopt phenotype of other cells by spontaneous cell fusion. *Nature* **416(6880)**:542-5, 4 April 2002.
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[91] Ianus A *et al*., *In vivo* derivation of glucose competent pancreatic endocrine cells from bone marrow without evidence of cell fusion. *J Clin Invest* **111**:843-850, March 2003.
[92] Mari Dezawa *et al.*, Specific induction of neuronal cells from bone marrow stromal cells and application for autologous transplantation. *J Clin Invest* **113**:1701-1710, 2004.
[93] Studer L *et al.*, Transplantation of expanded mesencephalic precursors leads to recovery in Parkinsonian rats. *Nature Neurosci* **1**:290-295, 1998.
[94] Svendsen CN *et al*., Human neural stem cells: isolation, expansion and transplantation. *Brain Pathol* **9**:499-513, 1999.
[95] Liker MA *et al*., Human neural stem cell transplantation in the MPTP-lesioned mouse. *Brain Res* **971:**168-177, May 2003
[96] Ourednik J *et al.*, Neural stem cells display an inherent mechanism for rescuing dysfunctional neurons. *Nature Biotechnol* **20:**1103-1110, November 2002.
[97] Åkerud P *et al.*, Persephin-overexpressing neural stem cells regulate the function of nigral dopaminergic neurons and prevent their degeneration in a model of Parkinson's disease. *Mol Cell Neurosci* **21:**205-222, November 2002.
[98] Fallon J *et al.*, *In vivo* induction of massive proliferation, directed migration, and differentiation of neural cells in the adult mammalian brain. *Proc Natl Acad Sci USA* **97:**14686-14691, 19 December 2000.
[99] Lévesque M & Neuman T, Autologous transplantation of adult human neural stem cells and differentiated dopaminergic neurons for Parkinson disease: 1-year postoperative clinical and functional metabolic result. *Am Assoc Neurol Surg Ann Meeting* Abstract #702, 8 April 2002.

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[102]. Presumably the growth factor was stimulating neural stem cells to differentiate[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[104,105,106], splenic cells to permanently reverse autoimmune diabetes in mice[107], liver stem cells to reverse diabetes within 10 days in mice[108], and pancreatic stem cells to reverse diabetes in mice[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[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[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[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.

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[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

[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".

[102] Gill SS *et al.,* Direct brain infusion of glial cell line-derived neurotrophic factor in Parkinson disease. *Nature Med* **9**:589-595, May 2003.

[103] Love S *et al.,* Glial cell line-derived neurotrophic factor induces neuronal sprouting in human brain. *Nature Med* **11**:703-704, July 2005.

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[105] Hess D *et al.,* Bone marrow-derived stem cells initiate pancreatic regeneration. *Nature Biotechnol* **21:**763-770, July 2003.

[106] Ianus A *et al., In vivo* derivation of glucose competent pancreatic endocrine cells from bone marrow without evidence of cell fusion. *J Clin Invest* **111**:843-850, March 2003.

[107] Kodama *et al.,* Islet regeneration during the reversal of autoimmune diabetes in NOD mice. *Science* **302(5648)**:1223-7, 14 November 2003.

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[111] Seaberg RM *et al.*, Clonal identification of multipotent precursors from adult mouse pancreas that generate neural and pancreatic *In vitro* lineages. *Nature Biotechnol* **22:**1115-1124, September 2004.

[112] Sapir *et al.*, Cell-replacement therapy for diabetes: generating functional insulin-producing tissue from adult human liver cells. *Proc Natl Acad Sci USA* **102:**7964-7969, 17 May 2005.

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[113], although at the same time concern has been raised over side effects which may limit neural stem cell applications in some settings[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[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[119,120,121]. In other experiments, the olfactory cells appear to stimulate injured spinal cells to undergo long-distance regeneration[122]. Moreover, the treatment of patients with spinal cord injury using these cells has resulted in some improvement[123]. The recent isolation and purification of these cells in humans represents a promising development in spinal cord repair[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[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,

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[113] Han SS & Fischer I, Neural Stem Cells and Gene Therapy: Prospects for Repairing the Injured Spinal Cord. *J Am Med Assoc* **283**(17):2300-2301, 3 May 2000.

[114] Hofstetter CP *et al.*, Allodynia limits the usefulness of intraspinal neural stem cell grafts; directed differentiation improves outcome. *Nature Neurosci* **8:**346-353, March 2005.

[115] Ankeny DP *et al.*, Bone marrow transplants provide tissue protection and directional guidance for axons after contusive spinal cord injury in rats. *Exp Neurol* **190**:17-31, 2004.

[116] Ohta M *et al.*, Bone marrow stromal cells infused into the cerebrospinal fluid promote functional recovery of the injured rat spinal cord with reduced cavity formation. *Exp Neurol* **187**:266-278, 2004.

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[119] Ramon-Cueto A *et al.*, Functional recovery of paraplegic rats and motor axon regeneration in their spinal cords by olfactory ensheathing glia. *Neuron* **25**:425-435, February 2000.

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[122] Ramon-Cueto A *et al.*, Long-distance axonal regeneration in the transected adult rat spinal cord is promoted by olfactory ensheathing glial transplants. *J Neurosci* **18**:3803-3815, 15 May 1998.

[123] Highfield R, New hope for paralysed woman. *UK Telegraph* 12 June 2004. For an online copy of this article see http://www.telegraph.co.uk/news/main.jhtml?xml=/news/2004/12/06/ncell06.xml&sSheet=/news/2004/12/06/ixnewstop.html For the US congressional testimony regarding this case and others by one of the researchers involved, Dr. Jean D. Peduzzi-Nelson, given at a Science, Technology, and Space Hearing: Adult Stem Cell Research on Wednesday July 14 2004 - 2:30 PM - SR - 253 see: http://commerce.senate.gov/hearings/testimony.cfm?id=1268&wit_id=3671

[124] Barnett SC *et al.*, Identification of a human olfactory ensheathing cell that can effect transplant-mediated remyelination of demyelinated CNS axons. *Brain* **123**:1581-1588, Aug 2000.

[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[126]. In similar experiments, this treatment led to improved function[127]. 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[128].

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[129]. 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[130].

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[131,132,133], ability to exercise[134], and regeneration of myocardial cells[135,136]. The reparative effect may be due in part to improved blood perfusion through angiogenesis, which is the creation of new blood vessels[137,138,139].

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[140]. 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[141].

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[126] Shyu W-C *et al.*, Functional recovery of stroke rats induced by granulocyte colony-stimulating factor-stimulated stem cells. *Circulation* **110:** 1847-1854, 2004.

[127] Willing AE *et al.*, Mobilized peripheral blood stem cells administered intravenously produce functional recovery in stroke. *Cell Transplantation* **12**:449-454, 2003.

[128] Li Y *et al.*, Human marrow stromal cell therapy for stroke in rat. *Neurology* **59**:514-523, August 2002.

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[130] Riess P *et al.*, Transplanted neural stem cells survive, differentiate, and improve neurological motor function after experimental traumatic brain injury. *Neurosurgery* **51:** 1043-1052, October 2002.

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[132] Check E, Cardiologists take heart from stem-cell treatment success. *Nature* **428**:880, 29 April 2004.

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[135] Britten MB *et al.*, Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction. *Circulation* **108:** 2212-2218, November 2003.

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[141] Orlic D *et al.*, Mobilized bone marrow cells repair the infarcted heart, improving function and survival. *Proc Natl Acad Sci USA* **98:**10344-10349, 28 August 2001.

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[142,143,144].

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

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.[146,147,148]

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)[149,150], localized retinoblastoma[151], solid tumours[152], breast cancer[153], and autoimmune diseases like multiple sclerosis[154], systemic lupus erythematosus[155] and rheumatoid arthritis[156]. This by no means a complete list.

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.

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[142] Menasché P *et al.*, Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol.* **41(7)**:1078-83, 2 April 2003.

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[145] Dawn B *et al.*, Cardiac stem cells delivered intravascularly traverse the vessel barrier, regenerate infarcted myocardium, and improve cardiac function. *Proc Natl Acad Sci USA* **102:**3766-3771, 8 March 2005.

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[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. *Bone Marrow Transplant* **27(6)**:653-655, March 2001.

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[156] Burt RK *et al.*, Autologous hematopoietic stem cell transplantation in refractory rheumatoid arthritis: sustained response in two of four patients. *Arthritis & Rheumatology* **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.