



Southern Cross
BIOETHICS INSTITUTE

Briefing Note on Adult Stem Cells

(including some comparisons with embryonic stem cells)

24th March 2002

Introduction

Advances in cellular physiology over the past few years have been dramatic to say the least. The traditional concept that cells only proceed from a less specialised or undifferentiated state to a more differentiated state, with no going back, has been turned on its head. This was most spectacularly displayed in the cloning of Dolly in which a mature adult specialised cell was fused with an egg cell that had been emptied of its nuclear DNA, and the new cell behaved like a single cell embryo and began the development of a new individual. Science now recognises the versatility or plasticity of all cells in a new and radically different way.

Cells found within the early embryo, embryonic stem cells, seemed for many years to be the logical choice for a source of cells able to differentiate into all other cells, but in the light of cloning and adult stem cell research that notion has been rapidly overtaken.

When derived from the patient being treated, adult stem cells are by definition compatible for transplant. To obtain similarly compatible embryonic stem cells, cloned embryos of the patient would be required – termed ‘therapeutic cloning’.

There has been more financial investment worldwide in adult stem cells than in embryonic stem cells¹. Of the 15 US Biotech firms looking for stem cell cures, only two focus on embryos².

Sources of Embryonic and Adult Stem Cells

Embryonic stem cells are derived from 5-6 day old embryos by extracting the inner cell mass. The inner cell mass would normally go on to produce the body if development were to continue. Human embryonic stem cells were first extracted and cultured in late 1998³. A similar cell type was extracted from human primordial germ cells of a fetus at about the same time⁴. It is possible that embryonic stem cells may also be derived from cloned embryos⁵, parthenogenetically produced embryos⁶ and hybrid embryos⁷.

¹ Eliot Marshall, The Business of Stem Cells. *Science*, 25 February 2000, **287**:1419-1421.

² Minter, Wall St. Journal; July 23, 2001.

³ Thompson, J.A. *et al.*, Embryonic stem cell lines derived from human blastocysts. *Science*, 6 November 1998, **282**:1145-1147.

⁴ Shambloot, M.J. *et al.*, Derivation of pluripotent stem cells from cultured human primordial germ cells. *Proc. Natl. Acad. Sci. USA* **95**:13726-31, 1998.

⁵ A recent report in *New Scientist* describes work by Chinese researchers who extracted embryonic stem cells from cloned human embryos at the blastocyst stage.

⁶ 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. Published in the *Journal of Reproductive Medicine*.

Adult stem cells have been derived from a wide range of tissues, and may be present in every major tissue type. Adult stem cells have been isolated from brain⁸, pancreas⁹, liver¹⁰, skin¹¹, fat¹², muscle¹³, blood¹⁴, bone marrow¹⁵, lung¹⁶, tooth pulp¹⁷, and umbilical cord¹⁸. The majority of the studies cited have been conducted on human adult stem cells.

Properties of Adult Stem Cells

A recent editorial in the medical journal *The Lancet*, concluded with the following words:

If stem cells do turn out to be a significant source of therapeutic agents they could come not from human embryos but from alternatives such as reprogrammed adult cells.¹⁹

While embryonic stem cells are extremely versatile cells, adult stem cells may also be highly pliable. But too much versatility may be undesirable. Embryonic stem cell versatility has already proven problematic in terms of tumour formation.

Although traditionally thought to be committed to development into a narrower range of cell types, adult stem cells have recently exhibited unexpected flexibility by changing into many different tissue types. The new term “transdifferentiation” is now being used to describe this capacity. Indeed, some argue that adult stem cells “perhaps in some cases have a developmental repertoire close to that of embryonic stem cells.”²⁰

Referring to the malleability of adult stem cells, Malcolm Moore from the Memorial Sloan-Kettering Cancer Center in New York points out:

Lineage-defined progenitor cells in adult tissues [adult stem cells] may be more plastic than hitherto thought. They might have the capacity to de-differentiate, or be reprogrammed, becoming *totipotent* stem cells [italics added].²¹

⁷ 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.

⁸ Uchida N *et al.*, Direct isolation of human central nervous system stem cells. *Proc. Natl. Acad. Sci. USA* 19 December 2000, **97**, 14720-14725.

⁹ Bonner-Weir S *et al.*, In vitro cultivation of human islets from expanded ductal tissue. *Proc Natl Acad Sci USA* July 5 2000, **97**, 7999-8004.

¹⁰ Malouf NN *et al.*, Adult-derived stem cells from the liver become myocytes in the heart in vivo. *American Journal of Pathology* June 2001, **158**, 1929-1935.

¹¹ J.G. Toma *et al.*, Isolation of multipotent adult stem cells from the dermis of mammalian skin. *Nature Cell Biology* Sept 2001, **3**: 778-784.

¹² Zuk, PA *et al.*, Multilineage cells from human adipose tissue: Implications for cell-based therapies. *Tissue Engineering* **7**: 211-228, 2001.

¹³ Williams, JT *et al.*, Cells isolated from adult human skeletal muscle capable of differentiating into multiple mesodermal phenotypes. *Am. Surg.* Jan. 1999, **65**: 22.

¹⁴ Eglitis, M. A. & Mezey, E. Hematopoietic cells differentiate into both microglia and macroglia in the brain of adult mice. *Proc. Natl. Acad. Sci. U.S.A.*, 1997, **94**:4080-4085.

¹⁵ Reyes M *et al.*, Purification and ex vivo expansion of postnatal human marrow mesodermal progenitor cells. *Blood* Nov 1, 2001, **98**: 2615-2625.

¹⁶ Emura, M. Stem cells of the respiratory epithelium and their in vitro cultivation. *In Vitro Cell Dev. Biol. Anim.* Jan. 1997, **33**: 3.

¹⁷ Gronthos, S *et al.*, Postnatal human dental pulp stem cells (DPSCs) *in vitro* and *in vivo*. *Proc Natl Acad Sci USA* Dec. 5, 2000, **97**: 13625-13630.

¹⁸ 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.

¹⁹ Editorial, Overexcitement on embryo stem cells, *The Lancet*, 26 August 2000, **356**(9231):693.

²⁰ Clarke, D. L. *et al.*, Generalized Potential of Adult Neural Stem Cells. *Science*, 2 June 2000, **288**:1660-1663.

²¹ Malcolm Moore, “Turning Brain into Blood” – Clinical Applications of Stem-Cell Research in Neurobiology and Hematology. *The New England Journal of Medicine*, 19 August 1999, **341**(8):605-607.

The United States National Bioethics Advisory Commission (NBAC) concluded:

... it would be far more desirable to explore the direct use of human cells of adult origin to produce specialized cells or tissues for transplantation into patients.²²

Studies at Harvard Medical School have shown that mouse adult stem cells derived from the brain (neural stem cells) can be injected into the brains of other mice with a degenerative disorder, the abnormal cells being replaced by a large number of normal cells.²³ Neural stem cells could also be coerced into becoming blood cells, including cells carrying out an immune function such as B and T lymphocytes.²⁴ In animal studies, neural stem cells have also been shown to promote spinal cord repair.²⁵ It is notable that the most promising example of research into spinal cord repair cited by Christopher Reeves at the March 5 US Senate hearing was carried out with adult stem cells, even though the reference was used as an example of the promise of embryonic stem cells.

Adult neural stem cells have been grafted into a specific brain site in rats that had been developed as a model of human Parkinson's disease. Some time later, Parkinsonian symptoms diminished, leading to a limited recovery of function.²⁶ This type of cell has recently been isolated in humans and behaves similarly to its equivalent in rodents.²⁷

A recent study in mice showed that adult pancreatic stem cells could be removed, grown in culture and then transplanted into a strain of diabetic mice, thereby reversing the diabetic state²⁸. Based upon preliminary experiments with human tissue, the researchers consider it likely that similar results may be obtained in humans. Attempts to form insulin-producing cells from human embryonic stem cells led to cells producing one fiftieth of the normal amount of insulin²⁹.

Research in Sweden has shown that mouse neural stem cells can be nurtured to become heart, liver, lung, intestine, kidney, muscle, and other tissues.³⁰ Speaking of the research, Professor Richard Gardner of Oxford University, who chaired a Royal Society group on therapeutic cloning, said:

I think therapeutic cloning is not terribly realistic. This other approach of reprogramming later cells makes sense.³¹

In studies conducted by Catherine Verfaillie at the University of Minnesota, Minneapolis,³² mesenchymal stem cells have been shown to specialise into neural, cartilage, bone, fat, and muscle cells. Verfaillie considers the cells to be "... almost like ES [embryonic stem] cells", but "better behaved" in that they are more stable than embryonic stem cells and less likely to spontaneously differentiate into a variety of cell types in an uncontrolled fashion. More recently, Verfaillie has isolated a multipotent adult progenitor cell from human volunteers. The journal *New Scientist* dubbed this cell the 'ultimate stem cell'³³, and in subsequent research it has been used to almost completely reverse the effects of stroke induced in rats³⁴.

²² NBAC 1997, 30-31.

²³ Reported by Abi Berger, Neural stem cells successfully transplanted. *British Medical Journal*, 12 June 1999, **318**:1575.

²⁴ Bjorson, C. R. *et al.*, Turning brain into blood: a hematopoietic fate adopted by adult neural stem cells *in vivo*. *Science*, 22 January 1999, **283**:534-7.

²⁵ Steve S.W. Han & Itzhak Fischer, Neural Stem Cells and Gene Therapy: Prospects for Repairing the Injured Spinal Cord. *Journal of the American Medical Association*, 3 May 2000, **283**(17):2300-2301.

²⁶ Studer, L. *et al.*, Transplantation of expanded mesencephalic precursors leads to recovery in Parkinsonian rats. *Nat. Neurosci.* 1998, **1**:290-295.

²⁷ Svendsen, C. N. *et al.*, Human neural stem cells: isolation, expansion and transplantation. *Brain Pathol.* 1999, **9**:499-513.

²⁸ Reported by Abi Berger, Transplanted pancreatic stem cells can reverse diabetes in mice. *Science*, 18 March 2000, **320**:736.

²⁹ Lumelsky, N. *et al.*, Differentiation of embryonic stem cells to insulin-secreting structure similar to pancreatic islets. *Science*, May 18, 2001, 292: 1389-1394.

³⁰ Clarke, D. L. *et al.*, Generalized Potential of Adult Neural Stem Cells. *Science*, 2 June 2000, **288**:1660-1663.

³¹ Cited by Roger Highfield in *Study queries the need for therapeutic cloning*. Daily Telegraph Internet download.

www.telegraph.co.uk

³² Reported by Gretchen Vogel, Can Old Cells Learn New tricks? *Science*, 25 February 2000, **287**:1418-1419.

³³ <http://www.newscientist.com/news/news.jsp?id=ns99991826>

³⁴ Published in the March issue of *Experimental Neurology*.

Haematopoietic stem cells, which typically give rise to blood cells, have been shown to differentiate into a variety of nerve cells³⁵. These well-studied cells have also been injected into mice developed as a model for Duchenne's Muscular Dystrophy, leading to partial restoration of the missing protein in affected muscle.³⁶

If directed differentiation with specific biochemical cues becomes possible, adult stem cells may be able to be persuaded to morph into a desired cell type within a patient's body, obviating the need for extraction and culturing.

Human trials or treatments using adult stem cells

The use of bone marrow stem cells (an adult stem cell) 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 the following conditions (*not a complete list*):

- Brain tumours (in combination with high dose chemotherapy)³⁷
- Localized retinoblastoma³⁸
- Solid tumours³⁹
- Breast cancer⁴⁰
- Autoimmune diseases like multiple sclerosis⁴¹, systemic lupus erythematosus⁴² and rheumatoid arthritis⁴³
- Heart damage⁴⁴

Adult stem cells taken from umbilical cord blood have also been used clinically, and even though the stem cells are not from the patient, rejection did not occur. This suggests that these cells are more 'immuno-naïve' than other cells and may perhaps be suitable for stem cell banks. The following conditions have been treated with cord blood stem cells.

- Blood disorders⁴⁵
- Immunodeficiencies⁴⁶

³⁵ Eglitis, M. A. & Mezey, E. Hematopoietic cells differentiate into both microglia and macroglia in the brain of adult mice. *Proc. Natl. Acad. Sci. U.S.A.*, 1997, **94**:4080-4085.

³⁶ Gussoni, E. *et al.*, Dystrophin expression in the mdx mouse restored by stem cell transplantation. *Nature*, 23 September 1999, **401**(6751):390-394.

³⁷ Abrey, LE *et al.*, High dose chemotherapy with autologous stem cell rescue in adults with malignant primary brain tumors. *J. Neurooncol.* Sept. 1999, **44**:147-153.

³⁸ 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* March 2001, **27**(6), 653-655.

³⁹ Waldmann V *et al.*, Transient complete remission of metastasized merkel cell carcinoma by high-dose polychemotherapy and autologous peripheral blood stem cell transplantation. *Br. J. Dermatol.* Oct 2000. **143**, 837-839.

⁴⁰ Damon LE *et al.*, High-dose chemotherapy and hematopoietic stem cell rescue for breast cancer: experience in California. *Biol. Blood Marrow Transplant* **6**: 496-505, 2000.

⁴¹ Mancardi GL *et al.*, Autologous hematopoietic stem cell transplantation suppresses Gd-enhanced MRI activity in MS. *Neurology* July 10, 2001, **57**: 62-68.

⁴² Wulffraat NM *et al.*, Prolonged remission without treatment after autologous stem cell transplantation for refractory childhood systemic lupus erythematosus. *Arthritis Rheum* March 2001, **44**(3): 728-731.

⁴³ Burt, RK *et al.*, Autologous hematopoietic stem cell transplantation in refractory rheumatoid arthritis: sustained response in two of four patients. *Arthritis & Rheumatology* November, 1999, **42**: 2281-2285.

⁴⁴ Strauer BE *et al.*, Myocardial regeneration after intracoronary transplantation of human autologous stem cells following acute myocardial infarction. *Dtsch Med Wochenschr* Aug 24, 2001, **126**, 932-938.

⁴⁵ Laughlin MJ *et al.*, Hematopoietic engraftment and survival in adult recipients of umbilical-cord blood from unrelated donors. *New England Journal of Medicine* June 14, 2001, **344**: 1815-1822.

⁴⁶ Ziegner UH *et al.*, Unrelated umbilical cord stem cell transplantation for X- linked immunodeficiencies. *J Pediatr* April 2001, **138**(4): 570-573.

- Anaemia⁴⁷
- Thallassaemia⁴⁸

At this stage no clinical treatments have been achieved with embryonic stem cells.

At a June 22, 2001 Workshop entitled “Stem Cells and the Future of Regenerative Medicine” sponsored by the National Academy of Sciences Institute of Medicine in Washington DC, Marcus Grompe, M.D., Ph.D., an expert in cell transplantation to repair damaged livers (Department of Molecular and Medical Genetics, Oregon Health Sciences University) stated that “there is no evidence of therapeutic benefit from embryonic stem cells.” Furthermore, Bert Vogelstein, Professor of Oncology and Pathology at Johns Hopkins University and Chairman of the Institute of Medicine's committee studying stem cell research described all claims of therapeutic benefit from embryonic stem cells as “conjectural”.

Recent experiments on the fusion of adult stem cells and embryonic stem cells.

Two research groups recently conducted experiments to increase understanding of ‘transdifferentiation’^{49,50}. They found that adult stem cells and embryonic stem cells fused to each other, forming cells that could be dangerous and possibly lead to tumour formation. The results of these experiments have been variously interpreted. Dr Peter Mountford, CEO of Melbourne company Stem Cell Sciences, said the research “brings into question the validity” of claims about adult stem cells⁵¹. However, in the same article Dr Rietze of the Walter and Eliza Hall Institute is quoted as saying “They’re suggesting it is a cautionary tale for adult stem cells, but their results argue the exact opposite, that it is with embryonic stem cells that the caution needs to be taken”.

It is important to note that fusion occurs for about one in every 10,000 to 100,000 cells, and in very specific culture conditions.

Summary

Adult stem cells hold enormous promise in the development of cell therapies. The body of basic research and applied clinical research is expanding at an extremely rapid rate and it is expected that standardised treatments will become available in the near future. With the current radical reinterpretation of the behaviour of cells *in vitro* and *in vivo* this field of medical research represents the opportunity for a revolution in medical treatment for some of the most distressing of human ailments including Parkinson’s disease, Alzheimer’s disease, spinal cord repair, diabetes and many more.

Dr Gregory K Pike, PhD
Deputy Director
Southern Cross Bioethics Institute
24th March 2002

⁴⁷ 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* Sep-Oct 2000, **22(5)**: 437-440.

⁴⁸ Singapore scores medical first in treatment of thalassaemias. *Agence France Presse*, Aug. 14, 2001.

⁴⁹ Terada, N. *et al.*, Bone marrow cells adopt phenotype of other cells by spontaneous cell fusion. *Nature*, Advanced Online publication DOI: nature730, (2002).

⁵⁰ Ying, Q-L *et al.*, Changing potency by spontaneous fusion. *Nature*, Advanced Online publication DOI: nature729, (2002).

⁵¹ Debra Smith, Doubts on use of adult stem cells, Sydney Morning Herald, March 14, 2002.