

# Non-haematological uses of cord blood stem cells

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## Summary

Embryonic stem (ES) cell therapies are often promoted as the optimal stem cell source for regenerative medicine applications because of their ability to develop into any tissue in the body. Unfortunately, ES cell applications are currently limited by ethical, political, biological and regulatory hurdles. However, multipotent non-ES cells are available in large numbers in umbilical cord blood (CB). CB stem cells are capable of giving rise to hematopoietic, epithelial, endothelial and neural tissues both *in vitro* and *in vivo*. Thus, CB stem cells are amenable to treat a wide variety of diseases including cardiovascular, ophthalmic, orthopaedic, neurological and endocrine diseases. In addition, the recent use of CB in several regenerative medicine clinical studies has demonstrated its pluripotent nature. Here we review the latest developments in the use of CB in regenerative medicine. Examples of these usages include cerebral palsy and type I diabetes. The numbers of individuals affected with each of these diseases are estimated at 10 000 infants diagnosed with cerebral palsy annually and 15 000 youths diagnosed with type 1 diabetes annually. A summary of the initial results from such clinical studies using autologous cord blood stem cells will be presented.

**Keywords:** umbilical cord blood, stem cells, regenerative medicine, tissue engineering.

Almost 1 in 3 individuals in the United States, or 128 million people, could potentially benefit over their lifetime from regenerative medicine, including therapies for cardiovascular, neurological and orthopaedic diseases (<http://www.dhhs.gov/reference/newfuture.shtml>). Diseases such as type 1 diabetes (T1D), myocardial infarction, stroke and spinal cord injury could be treated with greater efficacy. Most of the current therapies for these diseases are palliative rather than restorative, greatly impacting the quality of life for affected individuals, as well as the medical burden on society. The use of stem cells in regenerative medicine however, holds the promise of replacing or regenerating these affected tissues. However, success will depend upon

selection of the correct stem cell source and proper utilisation (see Table I). Translation of these therapies from the laboratory to the clinic requires the use of stem cells that must be medically and economically feasible. Political and ethical controversy surrounding the use of embryonic stem (ES) cells, as well as significant biological and regulatory limitations to their utilisation (to be discussed later in this review), has spurred a growing interest in the potential of other non-ES sources, particularly umbilical cord blood (CB). For 15 years CB has been used interchangeably for bone marrow in the stem cell transplantation of various malignant and genetic blood diseases. To date, more than 14 000 CB transplants have been performed (Kurtzberg, 2009), generally with fewer side-effects that observed with comparable bone marrow transplants (Rubinstein *et al*, 1993; Wagner *et al*, 1995; Gluckman *et al*, 1997). Recently, the use of CB in several regenerative medicine applications has expanded its clinical utility. Work done by McGuckin *et al* (2004, 2005), Rogers *et al* (2007), Kucia *et al* (2007) and Harris *et al* (2008), (Sunkomat *et al*, 2007) has shown that CB contains a mixture of multipotent stem cells capable of giving rise to cells derived from the endodermal, mesodermal and ectodermal lineages.

It has been shown that CB stem cells have the ability to regenerate numerous tissue types, and when transplanted into animals and humans, have produced measurable functional improvements (Harris & Rogers, 2007; Harris *et al*, 2008). Generally, tissue-derived stem cells have been described for neural (Seaberg & van der Kooy, 2002), muscle (Hill *et al*, 2006), retinal (Tropepe *et al*, 2000), pancreas (Seaberg *et al*, 2004), skin (Toma *et al*, 2001) and liver tissues (Yoon *et al*, 2004) but these tissue-specific stem cells have limited self-renewing capabilities and are unable to reconstitute a whole organ system. However, CB stem cells appear to be unique in their ability to undergo pluripotential differentiation. Thus, CB appears to be a practical substitute for ES cells and is readily available for use in tissue engineering and regenerative medicine. Recently clinical trials have begun using CB stem cells to treat T1D, cerebral palsy and peripheral vascular disease among others (Harris *et al*, 2007; Harris & Rogers, 2007; to be discussed below). This paper also reviews the latest developments in non-haematological use of CB stem cells for regenerative medicine.

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	Advantages	Limitations
Embryonic stem cells	High development potential High proliferative capacity Little risk of viral contamination	Limited supply Ethical issues No clinical data Biological constraints
Newborn stem cells Cord blood	Younger, excellent proliferation and differentiation abilities Immediately available Less stringent HLA requirements Lower risk of GVHD, infections Autologous transplants possible	Delayed short-term engraftment One-time supply
Adult stem cells Bone marrow	Ability to differentiate Rich concentration of stem cells Greater amount of historical data Rapid engraftment	Complex harvest Minimal residual disease (MRD) Increased potential for GVHD
Peripheral blood	Good historical data Less invasive than bone marrow Facilitates easier autologous transplants	

Table I. Not all stem cells are the same.

### Pre-clinical and clinical trials in regenerative medicine

Regenerative medicine applications are different from typical stem cell transplants. These applications do not require the severe pre-conditioning regimes that often lead to a myriad of side-effects, and contribute to morbidity and mortality of the recipient. However, this lack of pre-conditioning does generally require the use of autologous stem cells for the therapy to be successful. Otherwise, immune rejection will most probably occur. Information gained from the laboratory and pre-clinical animal studies are now being translated into clinical applications. CB stem cell infusion has started to make its way into the clinic to treat patients with neurological damage and endocrine disease. With the growth of family CB banks over the past 10 years (estimated total numbers of samples in storage of approximately 500 000) there are currently sufficient numbers of potential patients available for these and other such treatments. For example, recently the Cord Blood Registry has reported a rapidly expanding use of autologous CB stem cell samples in regenerative medicine applications that surpasses the standard use in stem cell transplant (see Fig 1).

#### Stroke and neural injury

Cerebrovascular diseases are the third leading cause of death in the United States, not including the multitudes of individuals who survive only to suffer debilitating lifelong injuries. Cerebral ischemia (CI) is by far the most prevalent cause of stroke (87%; <http://www.americanheart.org>). Approximately 700 000 people in the United States are affected by stroke annually; and 1 in 16 Americans who suffer a stroke will die from it (Furfaro & Gaballa, 2007). The brain is extremely sensitive to hypoxia and some degree of tissue death is likely

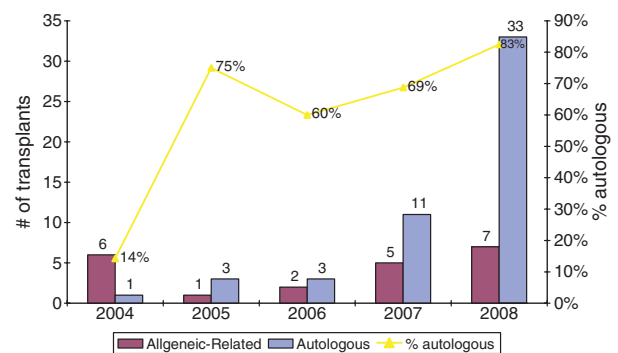


Fig 1. Summary of recent autologous cord blood use at Cord Blood Registry.

from stroke. At a relatively young age the brain loses most of its plasticity so any significant tissue death can be profoundly devastating. Interestingly, in young children the brain is very plastic and very large portions of the brain can be removed (such as removal of tumours or hemispherectomy for severe seizures) with relatively low to no noticeable long term neurological damage. These facts suggest that younger neural cells, which could be generated by differentiation from CB, might have a greater capacity to regenerate the injured brain.

Nowhere has the potential significance of CB stem cell therapy for the treatment of neurological disease been greater than in this area of stroke therapy. As early as 2001, it was demonstrated that the infusion of CB stem cells into rats in the commonly used middle carotid artery occlusion (MCAO) model of stroke could reverse many of the physical and behavioural deficits associated with this disease (Chen *et al*, 2001). Studies demonstrated that direct injection of the stem cells into the brain was not required (Willing *et al*, 2003), and

in fact, beneficial effects could be observed even if the stem cells did not actually home into the target organ (probably via the release of growth and repair factors triggered by the anoxia) (Borlongan *et al*, 2004; Newman *et al*, 2006). The beneficial effects seemed to be dose-dependent and could reduce the size of the infarcted tissue (Vendrame *et al*, 2004). It appeared that multiple progenitor populations in CB were capable of mediating these effects (Xiao *et al*, 2005). Significantly, unlike current pharmacological interventions that require treatment within the first few hours after stroke, CB stem cell therapies were effective up to 48 h after the thrombotic event (Newcomb *et al*, 2006). In fact, administration of CB stem cells immediately after the ischemic event may be detrimental in that the inflammatory milieu may be toxic to the administered stem cells.

The majority of reported studies (Nan *et al*, 2005; Vendrame *et al*, 2005, 2006; Xiao *et al*, 2005; Chen *et al*, 2006; Meier *et al*, 2006; Newcomb *et al*, 2006; Nystedt *et al*, 2006) have shown that CB administration in stroke models resulted in some degree of therapeutic benefit with no adverse effects. Neuroprotective effects (Nan *et al*, 2005; Vendrame *et al*, 2005, 2006; Xiao *et al*, 2005; Mäkinen *et al*, 2006; Newcomb *et al*, 2006) as well as functional/behavioural improvements (Nan *et al*, 2005; Xiao *et al*, 2005; Newcomb *et al*, 2006; Nystedt *et al*, 2006) from CB therapies have been widely reported. Neurological improvement was accompanied by decreased inflammatory cytokines (Vendrame *et al*, 2005), by neuron rescue/reduced ischemic volume (Xiao *et al*, 2005; Newcomb *et al*, 2006; Vendrame *et al*, 2006), as well as by lowered parenchymal levels of granulocytic/monocytic infiltration and astrocytic/microglial activation (Newcomb *et al*, 2006). Thus, the mechanisms behind the observed beneficial effects afforded by CB therapies included reduced inflammation (Vendrame *et al*, 2006), protection of nervous tissue from apoptosis (Xiao *et al*, 2005) and nerve fibre reorganisation (Xiao *et al*, 2005). These observations are particularly encouraging as it implies that CB therapy can mediate both direct restorative effects to the brain as well as tropic neuroprotection. Many of the published studies lend support to this trophic role, in that several investigators reported (Vendrame *et al*, 2005; Xiao *et al*, 2005; Nystedt *et al*, 2006) neural protection with little to no detection of CB cells engrafted in the brain. The level of engraftment in the brain appeared to be a function of the route of CB administration. When CB was administered intravenously (Vendrame *et al*, 2005; Chang *et al*, 2006; Mäkinen *et al*, 2006; Nystedt *et al*, 2006), little or no CB migration to the brain was found. However, when CB was given intraperitoneally (Chang *et al*, 2006) there was evidence of neural restorative effects. Early studies have also shown benefit in animal models of haemorrhagic (as opposed to embolic) stroke (Nan *et al*, 2005). For additional information, the reader is referred to the recent review on cell therapies for stroke found in reference (Bliss *et al*, 2007).

In addition to stroke, CB stem cells have been used in other nervous system injury models, two of which have now

instigated clinical trials. Lu *et al* (2002) have demonstrated that intravenous administration of CB mononuclear cells could be used to treat traumatic brain injury in a rat model. In this model the CB cells were observed to enter the brain, selectively migrate to the damaged region of the brain, express neural markers and reduce neurological damage. Similarly, CB stem cell transplant could also alleviate symptoms of newborn cerebral palsy in a rat model, with improved neurological effects (Meier *et al*, 2006). These observations have now been turned into clinical therapies (see below). Cord Blood Registry (a private family CB bank) has released 50 CB stem cell units for autologous use in the treatment of cerebral palsy, anoxic and traumatic brain injury (<http://www.cordblood.com>) in a clinical study at Duke University. Early, albeit anecdotal, reports have indicated beneficial effects from the CB mononuclear cells infusions (Kurtzberg, 2009). Several investigators have begun planning clinical trials to treat children with hypoxic/ischaemic and traumatic brain injury by utilising autologous CB stem cell infusions.

The observation that CB stem cells can become different types of nervous cells extends its utility to other areas of neurological damage, including spinal cord injury. Spinal cord injured rats infused with CB stem cells have shown significant improvements 5 d post-treatment compared to untreated animals. The CB stem cells were observed at the site of injury but not at uninjured regions of the spinal cord (Chen *et al*, 2001). This finding is supported by another study demonstrating that CB stem cells transplanted into spinal cord injured animals differentiated into various neural cells, improving axonal regeneration and motor function (Kuh *et al*, 2005). Significantly, in a recently reported clinical use of CB stem cells to treat a patient with a spinal cord injury (Kang *et al*, 2005) it was stated that transplantation of CB cells improved her sensory perception and mobility in the hip and thigh regions. Both computed tomography and magnetic resonance imaging studies revealed regeneration of the spinal cord at the injury site. Since the CB stem cells were allogeneic in origin it will be significant to determine if immune rejection or other immune-mediated problems occur that might jeopardize the early improvement. Neither additional patients nor additional studies in this area have been reported. However, the use of CB stem cells for spinal cord injury seems to be the next logical clinical trial. Large numbers of children are unfortunate enough to suffer a spinal cord injury at an early age (e.g. diving into a pool, car accidents, falls, etc) and it would be expected that a significant number would have autologous CB banked and available for treatment.

#### *Orthopaedic applications*

The potential of CB stem cells to generate bone and cartilage has been recently examined. It is estimated that more than 10<sup>6</sup> individuals in the USA annually suffer from articular joint injuries involving cartilage, ligaments and/or tendons, as well as difficult to heal bone fractures (<http://www.arthritis.org>).

CB contains both ES-like and mesenchymal stem cells (MSC) capable of differentiating into both bone and cartilage (Wang *et al*, 2004). In fact, when CB stem cells were placed into animals with fractured femurs there was significant bone healing. Work from the laboratories of Szivek *et al* (2006) and (D. T. Harris, unpublished observations) have also examined the ability of CB stem cells to become cartilage in comparison to tissues derived from bone marrow MSC and adipose stem cells, with early encouraging results.

### *Epithelial tissue applications*

Cord blood contains stem cells capable of giving rise to epithelial tissue, making it amenable in applications for the eye (cornea), skin (wound healing) and other such tissues (e.g. gut and lung). In terms of the eye, the cornea appears to be suitable for routine clinical applications. The outer layer of the eye is made up of the central cornea, the limbus and the sclera. The cornea epithelium is a rapidly self-renewing tissue; implicated to have its own source of stem cells (the limbus) specialized for this purpose. Corneal epithelial stem cell deficiency is an important cause of visual disability, resulting from alkali injury, Stevens–Johnson syndrome, ocular cicatricial pemphigoid, aniridia, chronic rosacea keratoconjunctivitis and iatrogenic causes. Without a normal corneal epithelium, a clear image cannot be focused on the retina. Autologous corneal epithelial stem cell grafts have been successful for patients with unilateral disease. However, harvesting cells from the functional eye places the healthy eye at risk for vision loss. Additionally, in bilateral conditions, autologous grafts are not available. The best current solution for bilateral disease is a corneal epithelial stem cell allograft. Allografts require chronic anti-rejection therapy with possible systemic side effects. In addition, the average survival of allografted corneal stem cells is 2 years. Further, severe corneal wounds requiring intervention are not uncommon in clinical practise. In fact, corneal wounds make up 37% of all visual disabilities and almost a quarter of all medical visits for ocular problems in North America (Germain *et al*, 1999, 2000).

Work from the group of Nichols *et al* (2005) (Harris *et al*, 2008; Harris, unpublished observations) have used CB stem cells as a viable therapeutic modality for ocular surface disease, and as a source of tissue for ocular surface reconstruction. Preliminary laboratory and animal data is supportive of this hypothesis (Harris *et al*, 2008). Histological and immunohistochemical analyses of differentiated CB stem cells revealed that epithelial cell sheets produced *in vitro* were morphologically indistinguishable from corneal epithelial cell sheets. Differentiated CB stem cells were capable of expressing the corneal epithelial specific cytokeratin, k3. Further, when New Zealand White rabbits were transplanted with the differentiated cell sheets it could reconstitute the cornea, forming an optically clear surface. Other investigators have demonstrated that MSC are also capable of reconstituting the cornea in a rat model (Ma *et al*, 2005). As CB contains MSC, this observation may

partially explain the mechanism of action of CB stem cells described above.

Based on the above observations, CB stem cells should also be able to differentiate into skin epithelial cells and thus be useful in facilitating wound repair (e.g. for diabetic ulcers). Work from the Harris (unpublished observations) and Ablin laboratories (R. Ablin, Department of Immunobiology, University of Arizona, personal communication) has begun to investigate this premise, knowing that previous studies have demonstrated a bone marrow stem cell contribution to wound healing in mice (Badiavas *et al*, 2003). In support of this hypothesis, there was an initial report in 2004 of the use of allogeneic CB progenitor cells in two patients to promote skin wound/lesion repair (Valbonesi *et al*, 2004). Progenitor cells were admixed with an autologous fibrin matrix and  $3 \times 10^4$  cells were injected in a volume of 3 ml into the margins of the lesions. At 3–7 months follow-up there was evidence of significant healing in both patients. To date, no other reports have been published.

### *Juvenile diabetes*

Approximately 15 000 youth in the US are newly diagnosed with T1D annually (<http://www.diabetes.niddk.nih.gov/dm/pubs/statistics/#youngpeople>) and 5–10% of all adults living with diabetes display the T1D phenotype (<http://diabetes.niddk.nih.gov>). Considering that 23.6 million people in the US are believed to be living with diabetes, one can estimate that 1–2 million of these individuals have T1D, which results from destruction by the immune system of the beta cells in the pancreatic islets responsible for insulin production. The end result is uncontrolled blood glucose levels. Diabetic complications include cardiomyopathy, coronary artery disease, peripheral vascular disease and neurological complications. In an effort to treat T1D, surgical procedures have been developed to transplant islets across histocompatibility barriers with limited success due to immune rejection and the lack of cadaver donors. Investigators have tried to address the issue of T1D through the use of stem cells and regenerative medicine (VOLTARELLI *et al*, 2007; US Institutes of Health, September 2006).

Currently, autologous CB mononuclear (stem) cells are being evaluated in a clinical trial to treat T1D in children (<http://www.clinicaltrials.gov/ct/show/NCT00305344?order=1> Accessed 20 September 2006; Haller *et al*, 2008). To date, 23 children have been treated, and the first child treated under the study protocol showed significant improvement in glucose control and was able to produce insulin much longer than children with a similar prognosis (Willing *et al*, 2003). Most of the treated children have reported enhanced blood glucose control and management. In addition, it appeared that there was retention of endogenous insulin production as assessed by stimulated C-peptide secretion. Although the mechanism of action is not yet known, there is data to support both islet maintenance/regeneration as well as a resetting of the aberrant immune system. Similar results have been reported in animal

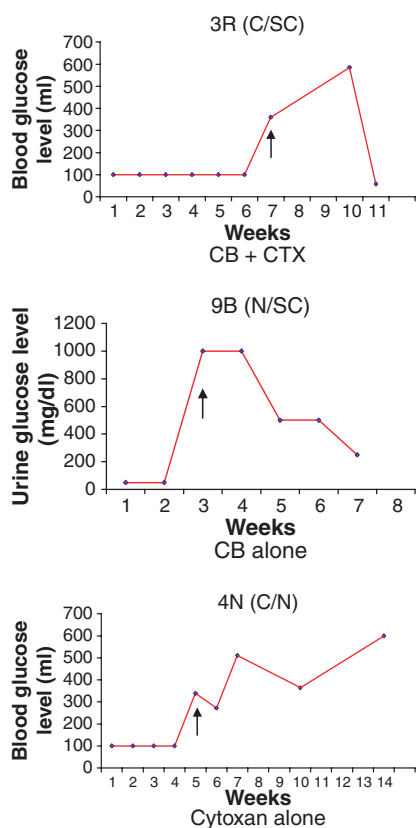


Fig 2. Representative examples of blood glucose levels observed in diabetic mice with cord blood stem cells and cytoxin (CB + CTX), cord blood stem cells alone (CB), or cytoxin alone.

studies set up to simulate the experimental conditions (see Fig 2). Animals with T1D and treated with CB stem cells had lower blood glucose levels, reduced insulinitis and increased lifespan compared to control diabetic animals (Ende *et al*, 2004, 2002; D.T. Harris, M. Badowski & S.M. Harman 2009, unpublished observations), confirming the patient findings. It is postulated that, once *in vivo*, the infused CB stem cells differentiate into new islet cells and mediate an immune tolerance to the new derived islet cells. *In vitro* CB stem cells can be driven to become insulin secreting islet cells, as indicated by the production of C-peptide, an offshoot of the *de novo* secretion of insulin (Denner *et al*, 2007; Sun *et al*, 2007), making this a rational hypothesis.

### Cerebral palsy

Cerebral palsy (CP) is a devastating brain disorder that affects many children worldwide, with 10 000 infants diagnosed annually ([http://www.ucp.org/uploads/cp\\_fact\\_sheet.pdf](http://www.ucp.org/uploads/cp_fact_sheet.pdf)), and stem cells ultimately have the capacity to generate new cells to replace those lost through injury or disease. Umbilical CB stem cells have shown promise in the treatment of CP in both animal models and early human trials. Recently, considerable excitement has been generated by anecdotal reports of

improvement after umbilical CB stem cell infusions in children treated in a clinical study at Duke University. Although not a randomized trial, this treatment has been used to treat more than 50 children with cerebral palsy. Preliminary observations have been encouraging (see <http://www.msnbc.msn.com/id/23572206/>), and many additional patients are being enrolled. Similar results for children with cerebral palsy have been reported recently by investigators treating children in Europe and Asia (C. McGuckin, Novussanguis Foundation, Paris, France, May 2008, personal communication). It should be noted that not all children have benefited to the same extent, and it appears that the younger the patient the more significant the benefits that have been observed. However, the optimal therapeutic regime and the mechanism(s) behind any beneficial effects have yet to be determined.

### Traumatic brain injury

The University of Texas at Houston is to begin a FDA-submitted clinical trial to treat children with traumatic brain injury utilising autologous CB stem cell infusions (C.S. Cox and J.E. Baumgartner, 2008, UT Health Sciences Center, Houston, Texas, personal communication), based on the successful results obtained with a similar autologous bone marrow stem cell study and numerous animal studies demonstrating the efficacy of stem cell treatments in models of traumatic brain injury (Harting *et al*, 2008).

### Hearing loss

A recent animal study demonstrated that CB stem cells might have clinical utility to repair inner ear damage and restore hearing (Revoltella *et al*, 2008). Human CB stem cells were intravenously injected into immunodeficient mice made deaf by exposure to kanamycin, high intensity noise, or a combination of these insults. The study showed that the CB stem cells migrated and engrafted into the cochlea of the deaf mice and that the levels of engraftment correlated with both the severity of damage and the treatment dose. Analysis at 60 d post-treatment showed that the mice in the CB treatment group had well-repaired cochlea with dramatic hair cell regrowth, while control mice showed no sign of repair or hair cell regeneration. This study has led to discussion and enthusiasm to translate these promising findings into a clinical trial to investigate autologous CB infusions for childhood hearing damage.

### Comparison to embryonic stem cells

Embryonic stem cells are touted as the holy grail of regenerative medicine therapies, while other viable alternatives have been overlooked and disregarded. Therefore, with many political and funding obstacles recently removed from the scientific arena, is there a significant role for CB in such therapies? One should be cognizant of the fact that ES cells



have numerous biological roadblocks and limitations that prevent their trek to the clinic and rapid access to patients. These limitations include the inherent allogenicity for many versions of this stem cell source and the accompanying threat of immune rejection. As life-long immunosuppression is neither desirable nor therapeutically possible in many instances, there comes a need to create patient-specific (i.e. 'tissue-matched') ES cells either by therapeutic cloning or by use of induced pluripotency methods (i.e. induced pluripotency stem (iPS) cells) (Byrne *et al*, 2007; Park *et al*, 2008). Although the threat of immune rejection can be overcome in this fashion, the threat of teratoma formation is omnipresent (Amariglio *et al*, 2009) in any type of ES cells when these cells are directly used in patients without first differentiating the ES cells into the desired tissue (which involves large amounts of time and monies, as well as invoking regulatory issues posing such problems that there is insufficient space in this review to fully do the discussion justice). The requirement for 'autologous' stem cells and the inability to derive differentiated cell lines or tissues from newly created patient-specific ES cells in time to meet the treatment 'window' required for successful therapies to be realized does not seem to have an answer at this time. It must be remembered that when a patient suffers a heart attack or a stroke, these patients require therapy within days if not hours. As most patients will present with a limited time to treat, and as creation of patient-specific ES cell lines can be expected to require months at best, such an ES-based therapy should have significant limitations. Finally, the overall costs of overcoming each of these limitations must be passed on to either the patient or third-party payers (and which is conservatively estimated at approaching \$50 000 per derivation of each patient-specific ES cell line/differentiated tissue), which ultimately will be the major limiting factor for the progress of ES cell therapies to the clinic and access to the population in general. In order for regenerative medicine therapies to be successfully transitioned to the general public, one must identify a source of stem cells that is derived from the patient, is easily and economically harvested, and contains large numbers of stem cells. Finally, the stem cell based therapy must be as successful as current therapy and must be significantly less expensive. CB stem cells and CB therapies seem to be the ideal solution to these requirements. We believe that CB stem cells are the best alternative to ES cells in that they appear capable of being utilized in many of the same applications claimed for ES cells, including cardiac, neurological, orthopaedic and ophthalmic applications.

## Conclusions

Regenerative medicine has the ability to treat many of the conditions discussed above by replacing or repairing malfunctioning tissues. By the year 2040, the population of senior citizens in the United States will be double today's number, a total of 70 million, and as much as 25% of the US gross

domestic product could be devoted to healthcare. Because regenerative medicine focuses on functional restoration of damaged tissues, not just the abatement or moderation of symptoms, this field has the potential to cut healthcare costs significantly. In the United States, 950 000 people die of heart disease or stroke each year, at an annual cost of \$351 billion. Almost 21 million patients live with diabetes and its complications, at a cost of \$132 billion annually. However, in order for the promise of regenerative medicine to be realized, it is necessary to identify optimal stem cell sources for particular disease states, and make efforts to inform the lay and medical communities as to their options.

Already, in examples of T1D and neurological (cerebral palsy and brain injury) applications, CB has transitioned from the laboratory to the clinic and numerous patients are currently being treated in clinical trials. Other trials will surely rapidly follow, including therapies for the eye, joints, wound healing and spinal cord. The key to these advances lies in the pluripotency of CB stem cells and their ability to be used in many instances under the practise of medicine, as it appears in many instances that it is possible to merely infuse the stem cells directly without timely and costly *in vitro* culture and differentiation. Whether the beneficial effects are due to stem cell differentiation into new tissues, or due to release of trophic factors, are not yet known. However, the assertion that CB stem cells are amenable to regenerative medicine applications today is supported by the clinical trials for T1D and cerebral palsy discussed above. We believe that research and clinical trials conducted now and over the next several years will demonstrate that CB stem cells are capable of performing most if not all of the functions of ES cells, and that CB stem cells may eventually render the current ES cell debate mute; not for political but for scientific reasons.

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