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Cell Therapy and Stem Cells for Brain Repair: Towards a Cord Blood Therapy

Paul R. Sanberg, Ph.D., D.Sc.
Distinguished University Professor
Associate Vice President
Director, Center of Excellence for Aging & Brain Repair
University of South Florida – College of Medicine

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HONORS EXCELLENCE OCCASIONAL PAPER SERIES

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PAUL R. SANBERG, PH.D., D.SC.
DISTINGUISHED UNIVERSITY PROFESSOR
ASSOCIATE VICE PRESIDENT
DIRECTOR, CENTER OF EXCELLENCE FOR AGING & BRAIN REPAIR
UNIVERSITY OF SOUTH FLORIDA – COLLEGE OF MEDICINE

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Biographical Note

As with the music that he plays as an avocation, guitarist Paul Sanberg also puts deep commitment into his true vocation: leading a team of researchers in finding ways to repair the brain and spinal cord. Sanberg is chief executive of a developmental Tampa company, Saneron C Cell Therapeutics, which operates out of the University of South Florida, and distinguished professor of neuroscience there.

Sanberg was born in Coral Gables, Fl. His family moved to California when he was five and stayed there through his high school years. He enjoyed his biology class above all others, so he studied biology at York University in Toronto, then attended the University of British Columbia to study medical sciences. After that, he was off to Australian National University to get his doctorate in neurological science. He was the only college graduate in his family.

After a fellowship at Johns Hopkins Medical School in Baltimore, he moved to Ohio to serve as a professor of neuroscience at the University of Cincinnati. Sanberg then became vice president and scientific director for a small startup company in Providence, R.I., Cytotherapeutics Inc., a cellular therapy company spun out of Brown University’s incubator, which uses animal cells for therapy. He came to USF some twelve years ago to become the research director of neurosurgery and director of the Center of Excellence for Aging and Brain Repair. Now one of the country’s leading experts on stem cell research, he is also recognized internationally for his work on Tourette Syndrome and other neurological problems.

Founded in October 1999, Saneron Therapeutics began as an incubator company based on university research at USF. In 2001, it merged with CCell Biotherapies Inc. of Clearwater. Fueled by research at USF, Saneron continues its close relationship with USF. Sanberg serves as chairman and acting CEO. When he is not playing guitar or flying his own plane, he devotes most of his time to doing research at the university. “I want to develop therapies for chronic degenerative disorders which we have no treatments for,” he said.

A portion of this text is paraphrased from a Powerezine.com article.
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Introduction to Stem Cells

The last few years have witnessed an expansion in stem cell research and its potential for therapy following the revolutionary mammalian cloning experiments. In addition to the controversial embryonic stem cell research, adult stem cell sources like hematopoietic stem cells, mesenchymal stem cells, epidermal stem cells, pancreatic stem cells, and several other organ stem cells are currently identified and characterized in laboratories all over the world. Clinical stem cell therapy dates back to the first bone marrow transplant experiments in the middle of the past century. Most stem cell biologists would agree that Artur Pappenheim (1870 – 1916) was the first to propose the concept of a common ancestral stem cell (Lajtha, 1980). Till and McCulloch (1961) were the first to demonstrate the ability of transplanted bone marrow cells to form colony-forming units (CFU) on the spleen of lethally irradiated mice in vitro. Their initial studies measured the proliferation potential of bone marrow cell colonies and led to the developing hypothesis of hematopoietic stem cells (Potten, 1983; Till and McCulloch, 1961). Since then much confusion has occurred in the meaning and usage of the words stem, progenitor, and precursor cells.

In an attempt to unify terminology in this field, a workshop in 1978 comprised mostly of hematologists (Lajtha, 1979; Lajtha, 1983) defined stem cells as “cells with extensive self-maintaining (self-renewal) capacity, extending throughout the whole (or most) of the life-span of the organism. Differentiation potential is a property of some types of stem cells but is not an essential feature of stemness.” Differentiation has been defined as “cells becoming specialized for particular functions” (Lackie and Dow, 1999) and as “the change in genetic expression patterns” (Lajtha, 1979). Therefore, any cell that replicates its own numbers
throughout most of the organism’s life is considered a stem cell, regardless of whether the cell differentiates further. As Lajtha (1983) has pointed out, “every cell in the body except for the zygote is already differentiated;” the question is whether a cell is capable of further differentiation. More recently however, other scientists, mostly in the neuroscience and transplantation field, have defined a stem cell as an undifferentiated cell that is capable of self-renewal and proliferation, and can asymmetrically divide to generate differentiated cells or multipotent cells (Rao and Mattson, 2001; Shihabuddin, et al., 1999; Gage, 2000). At this time there seems to be a consensus regarding the terminology of stem cells, although there has been no formal establishment of a nomenclature. Please refer to the following papers for their discussion of this topic: Potten, 1983; Metcalf, 1984; Gage, 1998; NIH, 2001; Marshak, et al., 2001; Blau, et al., 2001; Rao and Mattson, 2001.

The endogenous factors that trigger proliferation and differentiation of stem cells and their progenies are just beginning to be determined and understood. It is known that the proliferation, expansion, and differentiation of stem cells are regulated through intrinsic cellular factors, extrinsic cellular factors (cytokines/growth factors, cell adhesion molecules), and cell-to-cell interaction (Rao and Mattson, 2001). For example, embryonic stem cells can be maintained in vitro in the presence of Leukemia Inhibitory Factor (LIF) and these cells will produce neural stem cells when supplemented with fibroblast growth factor (FGF) in culture (Tropepe, et al., 2001). Both epidermal and basic fibroblast growth factors (EGF, bFGF) will keep neural stem cells in a proliferative state (Gritti, et al., 1999), while brain derived neurotrophic factor (BDNF) will direct neuronal progenitors to differentiation (Eaton and Whittemore, 1996). Some stem cells have been reported to transdifferentiate; that is, to give rise or transit to a different stem cell with distinct properties. Kondo and Raff (2000) have shown that oligodendrocyte progenitor cells may transdifferentiate to pluripotent stem cells and give rise to neurons. However, caution should be employed when determining the ability of a cell to transdifferentiate. Progenitor cells that were obtained from muscle and thought to be of muscle origin were reported to transdifferentiate into hematopoietic stem cells. Upon further investigation, these stem cells were, in fact, determined to be hematopoietic stem cells residing within the muscle (Ogawa, et al., 2002). While it is possible in vitro to direct the differentiation of pluripotent stem cells and lineage restricted progenitor cells, we are only at the initial stages of learning how to direct stem cells to phenotypes that might be useful in vivo.
Umbilical Cord Blood Stem Cells

Over the past two decades, human umbilical cord blood (HUCB) has emerged as a novel valuable source for stem cells next to bone marrow and peripheral blood. Only 20-25% of patients are expected to find an HLA-matched sibling from the bone marrow donor pool. Since its first successful transplant for Fanconi’s anemia in 1988, HUCB was found to be a highly enriched source for immature stem and blood cells that are less immunogenic than adult marrow and blood cells. Compared with bone marrow recipients, cord blood recipients from related or unrelated donors experience a decreased incidence of acute graft-versus-host disease and a rather delayed hematopoietic recovery (Wagner, et al., 1995; Rocha, et al., 2001; Vaziri, et al., 1994). Lower immunogenicity of cord blood is credited to abundant immature progenitors with longer telomeres than adult marrow stem cells (Ridson, et al., 1994).

In preclinical studies, cord blood transplantation has rescued lethally irradiated mice and reconstituted their bone marrow (Broxmeyer, HE, 1996; Yao, et al., 2004). Following these leading experiments, clinical trials using cord blood transplantations have been applied to more than 2500 patients, mostly children, thus far. An insufficient number of stem cells obtained from a single cord has hampered extensive applications in adults, which require compilation of blood cells from several umbilical cords. Predictably, a primary goal in the field of cord blood transplantation has been ex vivo expansion and amplification of its stem cell content by various manipulations.

Several successful CBTs have been performed for malignant and non-malignant diseases of blood and other organs (Mansergh, et al., 2000). Diseases of the nervous system are an especially attractive target for stem cell therapy, since neurodegeneration is considered an end-stage illness and treatment for the most part is symptomatic. In addition, the discovery of neural stem cells and the potential of other stem cells to transdifferentiate into neural tissues have expanded neuroscience research in that direction. Studies that showed differentiation of embryonic stem (ES) cells in vitro into all neurons and glia (Mansergh, et al., 2000) generated justifiable excitement about their therapeutic potential to replace degenerating neural cells. Ethical and medical concerns have directed stem cell research nationwide to alternative sources for plastic stem cells, including HUCB stem cells. Many reports have followed from our laboratories and several others that show that HUCB stem cells could differentiate across tissue lineage boundaries into neural and other tissue lineages.
We have demonstrated that cultured mononuclear fraction of HUCB in a proliferating medium supplemented with all-trans-retinoic acid (RA) and nerve growth factor (NGF) promoted the expression of Musashi-1 and TUJ-1 neural markers and the GFAP astrocyte marker (glial fibrillary acidic protein). In addition, mRNA for neuronal markers nestin and necdin was detected (Sanchez-Ramos et al., 2001). Likewise, Ha, et al., (2001) have shown that HUCB cultured in Beta mercaptoethanol differentiated into neural phenotype, as determined by positive immunocytochemical expression of neural nuclear antigen (NeuN), neurofilament, and GFAP, and by RT-PCR mRNA for nestin, neurofilament and microtubule-associated protein (MAP2). McGuckin, et al. (2004) have demonstrated that HUCB cells could expand in liquid culture supplemented with thrombopoietin, flt-3 ligand, and c-kit ligand (TPOFLK) into both hematopoietic and neuroglial progenitors.

Experiments with Selected Cord Blood Stem Cells

In most of the aforementioned studies, the mononuclear fraction of cord blood cells was used in the initial culture, without prior purification or selection of a precursor cell of interest. Whether neural differentiation of cord blood cells is the progeny of neural progenitors or hematopoietic, mesenchymal, or other stem cells within the cord blood graft was not clear. It became important to characterize a specialized cell fraction or population within the cord blood that is enriched for neural precursors for purposes of targeted therapy and genetic manipulations, and to further understand stem cell biology.

Bicknese, et al. (2002) purified a multipotent HUCB cell subset that is negative for the CD14 monocyte marker and the CD34 hematopoietic progenitor marker. The culture was supplemented with basic fibroblast growth factor (bFGF) and human epidermal growth factor (hEGF). Immunohistochemistry and Western Blot analysis showed differentiation into cells that expressed both GFAP and TUJ1 astrocyte and neural markers after seven days in culture. In another study, a different HUCB cell fraction that is positive for both CD34 and the leukocyte marker CD45 was isolated using magnetic cell sorting (Buzanska, et al., 2002). These clonal cells were, however, incapable of forming hematopoietic colonies. Upon culture in DMEM and hEGF, cells positive for nestin were produced. After further exposure to retinoic acid and BDNF, cells were immunopositive for TUJ1, MAP2, GFAP, and Gal-C (galactocerebroside) oligodendrocyte marker.

In view of available literature on cord blood stem cells, it is premature to define...
the cord blood cell fraction most enriched for neuroprogenitors. Further studies that include clonal analysis of transfected cells, neural and glial functional assays, and in vivo transdifferentiation are required before defining and isolating plastic cord blood cell populations. Most ongoing research is influenced by the bone marrow system, which may be similar to cord blood in terms of hematopoietic reconstitution, but significantly different in both cellular structure and content.

Preclinical Studies Utilizing HUCB Cells

In vitro plasticity studies strongly suggest that cord blood stem cell therapy may represent a viable alternative for brain repair. Preliminary in vivo investigative studies examined homing, migration, and differentiation of HUCB cells into normal brains (Irons, et al., 2004). HUCB mononuclear fraction was transplanted into the subventricular zone of neonatal rat pups. Thirty days after transplantation, the pups were euthanized and brains dissected for human cells. HUCB cells were detected in the subventricular zone, the overlying cortex, and corpus callosum. Immunohistochemical phenotyping showed GFAP and TUJ1 positive cells of donor HUCB origin in the developing brain, indicating differentiation into glial and neural phenotypes. The safety of this form of xenogenic transplantation was determined by the absence of histological abnormalities or behavioral deficits in the transplanted rats. In both allo- and xeno-transplants, however, the use of immune suppressive therapy enhanced, and at times was necessary to maintain, the survival of donor cells (Kogler, et al., 2004).

HUCB Cell Therapy for Stroke

Stroke, one of the leading causes of death worldwide, is produced by focal ischemia to the brain and subsequent neural degeneration and damage. The basis for the use of cellular therapy in animal models for stroke is to stimulate neural regeneration and limit further damage. The beneficial effect of HUCB transplantation in stroke animals has challenged the dogma of neural rejuvenation and offered a viable system to analyze the cellular and molecular events involved in this regeneration.

There seems to be a consensus that ischemic injury in vital organs like the heart and the brain promotes cell migration to the site of injury to initiate the process of repair. Stimulation of endogenous stem cells that are activated and mobilized
in response to various injuries seems to be an exciting strategy to promote endogenous repair of the adult CNS. However, the capacity of these progenitors to migrate and to differentiate into neural or glial cells differs according to the lesion-type and the germinative zone from which they arise (reviewed by Picard-Riera, et al. 2004). Studies in rodent models of stroke suggested that this process may be maintained by intrinsic stem cells that reside in the subventricular zone. Similar stem cells depicted as subventricular astrocytes have been recently proposed as a source for neural stem cells in adult humans (Chen, et al., 2001).

Ischemic neural injury stimulates inflammatory processes associated with recruitment and release of mediators crucial for initiating repair and supporting regeneration. This was demonstrated by in vitro studies using migration assays, in which extracts of ischemic tissues promoted migration of HUCB, as compared to healthy controls (Chen, et al., 2001). Neurotransmitters involved in this inflammatory process included NGF (neurotrophic growth factor), BDNF (brain derived neurotrophic factor), EGF (epidermal growth factor), FGF-2 (fibroblasts growth factor-2), IGF, erythropoietin, and SCF (stem cell factor), (reviewed by Peterson, 2004).

The evidence for the effect of HUCB transplantation on neural recovery after stroke first came from studies of our laboratory in collaboration with Michael Chopp’s laboratory (Chen, et al., 2001; Lu, et al., 2002) where rats were subjected to middle cerebral artery occlusion (MCAO) to induce focal ischemia-like pathology. Systemic delivery of HUCB via lateral tail vein injection helped improvement in the transplanted animals and was detected in the affected cortex, subcortex and striatum of the damaged brain. Immnuohistochemical phenotyping showed positive staining for neuronal markers (NeuN and MAP-2), astrocyte marker GFAP, and endothelial marker FVIII. Homing studies showed that tissue damage induced by traumatic brain injury stimulated migration of infused cord blood to the parenchyma of the affected brain tissue. Expression of neural and astrocyte markers was associated with functional improvements and reduction of motor and neuronal deficits.

Studies in stroke models from our laboratories have suggested that this improvement is linked to several factors, including the site and extent of the neural damage, timing of the transplant, and the route of cellular administration. In the studies by Willing, et al., (2003), stroke was similarly induced in rats by MCAO. Transplantation of HUCB into the striatum or the femoral veins of rats resulted in improved behavioral deficits. Nonetheless, this improvement was not associated with detection of donor HUCB cells in the brain by immunostaining meth-
Cellular administration via the femoral vein was less invasive and associated with recovery of the forelimb. A subsequent study in our laboratories (Vendrame, et al., 2004) has shown significant improvement in behavioral recovery four weeks after MCAO occlusion in these rats. Migration of HUCB was observed only in the injured hemisphere, and better recovery was correlated with higher doses of infused cord blood.

Another study by Saporta, et al., (2003) tested the effect of intravenous injection of cord blood on the recovery from spinal cord injury. HUCB was injected into rats one and five days after compression spinal cord injury. HUCB cells were localized around the site of injury, but not in the healthy spinal cord tissues. Behavioral open-field test scores were improved in the rat group transplanted five days after the injury. All of these studies have demonstrated that tissue injury is a critical factor in attracting donor cord blood cells and initiating the process of repair. Release of trophic factors at the site of injury may simultaneously promote selective migration of donor stem cells and also accelerate healing and tissue repair.

Despite detection of donor cells at the site of injury, which cells within the cord blood graft contribute to the observed recovery and how this repair is achieved remain critical questions in neural transplantation. In a recent study from our labs, Borlongan, et al., (2004) were not able to detect HUCB in the brains of rats transplanted via the intravenous route after stroke induction. Despite the fact that a blood brain barrier permeabilizer (mannitol) was co-infused with the cord blood cells, human cells were not engrafted. Reduced cerebral infarct size and increased levels of neuroprotectant factors led the authors to suggest that the observed recovery after stroke was mediated by molecules induced by the cord blood cells, regardless of the availability of these cells at the site of the damage. A different mechanism was suggested by a study by Taguchi, et al., (2004), who used the CD34+ cells within the cord blood to study the effect of this stem cell-enriched population on recovery from stroke. Immunocompromized mice were transplanted intravenously with CD34+ cells forty-eight hours after the induction of stroke. Recovery was associated with enhanced neovascularization on the borders of the ischemic zone. Interestingly, when this neovascularization was suppressed by antiangiogenic agents, neurogenesis was impaired. This study suggests that systemic administration of cord blood CD34+ cells stimulated neovascularization, which in turn stimulated endogenous neurogenesis. Despite these encouraging data, the role of stem cell therapy in stroke is still elusive. Several factors like the type of injected cells (whole cord blood versus purified stem cells), the route of transplantation (systemic versus local, and intra-arterial ver-
sus intravenous), and most importantly, the time window for successful therapy (less than thirteen hours to up to one week), remain to be determined.

Clinical Studies with Cord Blood

An expanding list of disorders currently treated with cord blood transplantation include hemoglobinopathies like sickle cell anemia and thalassemia, leukodystrophies, severe combined immune deficiency, aplastic anemia, Fanconi’s anemia, glycogen storage diseases like Hurler syndrome and Hunter syndrome, erythrocyte enzyme deficiencies and errors of metabolism. Additionally, cord blood cell therapy was promising in the treatment of acute lymphoblastic leukemia (Luan, et al., 2004; Wang, et al., 2004) and acute myeloid leukemia (Berger, et al., 2004). One hundred percent donor engraftment and five years disease-free survival was accomplished in a two-month old infant suffering from beta-thalassemia after transplantation of partially MHC-matched HUCB from unrelated donor (Hall, et al, 2004).

Progress of cell therapy applications for neurological disorders has been slower. Wenger, et al., (2000) have utilized cord blood transplantation to treat Krabbe disease. This enzymatic disorder is caused by deficiency of galactocerebrosidase (CAL-C), which results in deficiency of myelin formation in both the central and the peripheral nervous system. Prognosis of this disease is grave in infants, but better in older patients. Cord blood transplantation improved the disease manifestations, but cure was not achieved.

Another metabolic disease that seriously affects the nervous system is Hurler's syndrome. It is a severe form of mucopolysaccharidosis type I that affects children, and causes progressive deterioration of the central nervous system that leads to death. In a study by Staba, et al., (2004), cord blood transplantation from unrelated donors was used to treat young children with Hurler's syndrome. A myeloablative preparative regimen that did not involve total-body irradiation was followed by cord blood transplantation. The children showed a high survival rate and were durably engrafted with donor cord blood.

Conclusion and Future Perspectives

Human umbilical cord blood is a highly promising source for cell therapy in a variety of diseases currently treated with bone marrow transplantation. This
promise is particularly valuable for patients suffering from neural disorders for which no cure is available. In vitro studies that showed plasticity of cord blood cells, and in vivo studies that achieved not only delay or halt of neural degeneration but also active restoration of neural functions, have created justifiable excitement in neural research. Unique qualities of HUCB like availability, immature cellular phenotype, enrichment for hematopoietic progenitors, plasticity, and lower incidence of graft-versus-host disease all appropriate its use as an ideal source for cell therapy (reviewed by Newman et al., 2004).

HUCB transplantation is a particularly attractive strategy for neurological disorders because of the grave prognosis and current absence of cure for most of these diseases, and the promising data from basic research and preclinical studies. Many practical factors influence the outcome of therapy with CBT. For example the route of cord blood infusion is particularly critical in the CNS when we consider the blood brain barrier. In animal models, intra-bone transplantation of cord blood has shown higher seeding efficiency than the intravenous route (Castello, et al., 2004). This strategy could be especially beneficial when the number of cord blood stem cells is limited, or when direct delivery of stem cells to the site of damage is believed to initiate earlier repair within the critical hours after the ischemic or traumatic damage.

The abundance of in vitro data showing differentiation of various cord blood stem cells into neural and glial cells have tempted researchers to suggest that cord blood-induced brain repair is mediated by a transdifferentiation process. Plasticity of stem cells, however, has been a subject of intense debate (Verfaillie, et al., 2002). Despite evidence for neural differentiation both in vitro and in vivo, limited evidence suggests that this phenotypic delineation involves functional neural cells. This lack of functional assays has directed most preclinical studies to gauge improvement by behavioral testing.

The promising data of improved behavior, delayed disease onset and prolonged survival, coupled with an immense desire to find a cure for debilitating and devastating CNS diseases, has stimulated a renewed interest in stem cell therapy for neural disorders. The critical question to be pursued by researchers is what possible mechanisms are involved in neural repair by cell therapy. Replacement of diseased cells with functional “new” stem cells may be an accepted resolution for cases like leukemia cured by bone marrow transplantation; however, the available evidence in neuroscience studies suggests that other mechanisms are involved.
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Disclosure: Paul R. Sanberg is Chairman & Co Founder of Saneron CCEL Therapeutics, Inc., A University of South Florida spin-out company developing cord blood related cell therapy products. He is also an inventor on related patent applications by USF.

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