Human Umbilical Cord Blood Treatment of United States Soldiers following Neurological Injury

I.   TBI and Iraq and Afghanistan: the need for treatment

Traumatic Brain Injury (TBI) has emerged as the distinguishing injury of the Iraq War (Warden, 2006). Distinct military conflicts produce a characteristic injury; World War Two veterans had increased radiation-induced cancer, while the Vietnam War led to Post Traumatic Stress Disorder and exposure to Agent Orange. Medical experts are witnessing an emerging increase in TBI. 21st century soldiers are protected better than ever before from bullets and bombs, but in surviving extreme blasts symptoms of brain damage seem unavoidable (Okie, 2006).

According to the National Institute of Neurological Disorders, disabilities resulting from a TBI depend upon the injury's severity, location, and general health of the individual. Among surviving soldiers wounded in combat in Iraq and Afghanistan, TBI appears to account for a larger proportion of casualties than it has in other recent U.S. wars (Okie, 2005). According to the U.S. Army Institute of Surgical Research, 22 percent of the wounded soldiers from these conflicts who passed through the military's Landstuhl Regional Medical Center in Germany had injuries to the head, face, or neck. According to November 2006 issue of the *New England Journal of Medicine*, the true proportion is probably higher, since some cases of closed brain injury are not diagnosed promptly (Okie, 2005). In the Vietnam War, by contrast, 12 percent of all combat casualties had a brain injury, according to Ronald Bellamy, editor of the *Textbooks of Military Medicine*. Mortality from brain injuries was 75 percent greater in Vietnam than Iraq or Afghanistan, making brain injury survivors a larger fraction of war veterans than previously seen (Okie, 2006)

Some common disabilities include deficient memory, reasoning, sensory processing, understanding, depression, anxiety, aggression and social inappropriateness. More serious head injuries may result in stupor, coma and vegetative states. One Washington medical centre reported 83% of wounded marines and sailors suffer from temporary or permanent brain damage.

II.   Infant and fetus display increased ability to heal neurological damage

Thompson SN, Gibson TR, et al. showed how injury affects axonal growth and synaptogenesis following traumatic brain injury in young mice. Their data highlight the adult brain's ability for axonal and synaptic plasticity following a brain injury, but that repair may diminish with age. Similarly, memory loss in humans begins early in adulthood. Rex and Kramar reported that memory loss during aging results from declined plasticity (Rex et al., 2005; Rex et al., 2006; Thompson et al., 2006). Neuroplasticity is greater in the first four to five years of life, suggesting that interventions could be more effective when applied at this

time. Increasing evidence suggests that stem cells have tremendous potential to support repair of damaged brain tissue (El-Badri et al., 2006; Newman et al., 2004; Savitz et al., 2003). Their capacity to migrate to damaged tissue and either replace tissue or deliver protection suggests that they might have unrivalled therapeutic potential in perinatal medicine (Garbuzova-Davis et al., 2003; Goldstein et al., 2006).

III. Evidence that cord blood can produce neurological cells

a. InVitro

Buzanska and Jurga have developed a body of literature describing in vitro neuronal differentiation of human umbilical cord blood (Buzanska et al., 2005; Buzanska et al., 2006a; Buzanska et al., 2006b; Jurga et al., 2006a; Jurga et al., 2006b). Mononuclear cells isolated from whole human umbilical cord have been able to develop neural precursors in vitro (Kogler et al., 2004). Interestingly, Sun reports that he can develop neural cells by invitro culture of the nonhematopoietic fraction of human umbilical blood (Sun et al., 2005).

b. In Vivo, animal models

The transplantation or infusion of cord blood cells in various animal models, such as ischemia/stroke, traumatic brain injury, Parkinson's disease, and amyotrophic lateral sclerosis has resulted in amelioration of behavioral deficits, and with some diseases, a prolonged lifespan. The migration of HUCB cells to ischemic brain supernatant (tissue extracts) is time-dependent, and the expression of specific chemokines responds to this migration pattern, which may provide insights into the functional improvements seen in the animal models. In 2000, it was first suggested that immature stem cells (Berashis/ Beginning Cells) existing in HUCB might have an ameliorating effect in the neurodegenerative disease amyotrophic lateral sclerosis, ALS. HUCBC were shown to prolong lifespan and delay onset of clinical findings in the ALS mouse SODG93A mice (Bendotti and Carri, 2004; Ende et al., 2000; Garbuzova-Davis et al., 2003; Gurney et al., 1994). Motor function improvement and symptom onset delay following cord blood transplantation, in animals experiencing muscle weakness to paralysis; have garnered attention from scientists interested in treating neurological disorders. Embryonic stem cells pose a therapeutic risk unlike umbilical cord stem cells, without the ability to control up and down regulating proteins or growth factors, embryonic stem cell's immortality is a risk of developing a neoplasm or tumor. Unencumbered by ethical objections, Human Umbilical Cord Blood (HUCBC) has presented itself as an abundant, alternative stem cells. Life span improvement in mouse models of ALS, Parkinson's, Huntington's, and Alzheimer's have all been shown using mononuclear cell fraction from HUCB (Chen et al., 2001; Chen and Ende, 2000; Ende and Chen, 2001; Ende and Chen, 2002; Ende et al., 2000).

IV. Evidence that cord blood has produced improvement in animal neurological damage.

a. Brain

The ability of stem cells to participate in brain repair has been increasingly demonstrated. Most investigations have aimed to replace damaged neurons by direct transplantation or recruitment of newly generated cells in the adult. However, the extent of improvement seen in animal models of stroke, Parkinson, ALS, etc have far outweighed the presence of HUCB cells at the location of injury. Therefore, it has been widely accepted that functional improvements seen in animal models were often a result of cord blood cell-induced self-repair and neuroprotection, rather than cell replacement (Borlongan et al., 2004; Chen et al., 2001; El-Badri et al., 2006; Ende and Chen, 2001; Ende and Chen, 2002; Ende et al., 2000; Escolar et al., 2005; Fu et al., 2006; Garbuzova-Davis et al., 2003; Goldstein et al., 2006; Newman et al., 2004; Savitz et al., 2003). Thus, a far more pragmatic approach in the short term might be to use stem cells as chaperones for degenerating nervous tissues particularly post trauma.

It should be noted that following marrow ablation in mice, human cord blood cell administration has not only produced a transplant but also accelerated endogenous marrow recovery (Czarneski et al., 1999; Rameshwar et al., 1999).

b. Spinal Cord

The use of HUCB cells has been reported to improve recovery in cases of CNS injuries such as stroke, traumatic brain injury, and spinal cord injury. At the University of South Florida, CD34-positive stem cells isolated from HUCB were intravenously transplanted into the injured spinal cords of rats one week after injury; recovery of motor functions was seen (Saporta et al., 2003). Cells from HUCB reduced the area of the cystic cavity at the site of injury, increased white matter, and promoted the regeneration of axons in the injured spinal cord. Immunohistochemical examination revealed that transplanted human cells survived in the host spinal cord for at least 3 weeks after transplantation but had disappeared by 5 weeks. There was no evidence of an immune reaction at the site of injury in either group. These results suggest transplantation of the CD34-positive fraction from HUCB may have therapeutic effects for spinal cord injury. Other work has corroborated these findings on cord blood as a beneficial treatment for spinal cord injury (Bambakidis and Miller, 2004; Nan et al., 2005; Nishio et al., 2006; Roussos et al., 2005; Xiao et al., 2005; Zhao et al., 2004).

c. Cord blood effects on neurological illness in animals, with and without immunosuppressant

There have been multiple studies showing neurological improvement following administration of HUCB cells with immunosuppressant (Ende et al., 2000; Escolar et al., 2005) and without immunosuppressant (Ende and Chen, 2001; Ende and Chen, 2002; Garbuzova-Davis et al., 2003; Saporta et al., 2003; Vendrame et al., 2004; Vendrame et al., 2005; Willing et al., 2003b; Xiao et al.,

2005; Zhao et al., 2004). Therefore, currently we do not advocate any immunosuppression.

## V.	Blood transfusion from adult donors in trauma cases produces chimera with no evidence of negative effect

The recent works of Utter and Lee have shown that trauma patients are good candidates to develop micro chimera while showing no evidence of graft versus host disease.   For many years we have known that routine blood transfusions would occasionally produce micro chimera and graft versus host disease in patients with a diminished immune system (HIV patient receiving immunosuppressant, etc). If routine transfusions can produce micro chimera in trauma patient, cord blood matched only for blood groups could be very beneficial to treat trauma injuries. Utter and Nathens reported transfusion-associated microchimerism in trauma patients as well as that microchimerism in transfused trauma patients is associated with diminished donor-specific lymphocyte response. Lee and Paglieroni corroborated these findings by reporting frequent long-term microchimerism in severe trauma patients without evidence of negative effects. The microenvironment of trauma may induce a temporary engraftment of cord blood mononuclear cells.

## VI.	Possible cons to cord blood treatment

The only contradictory article we have identified is Makinen, et al., which reported human umbilical cord blood cells do not improve outcome following middle cerebral artery occlusion in rats (Makinen et al., 2006).   Adult male rats were subjected to MCAO and HUCB was administered intravenously after 24 h recovery. The limb-placing test, beam-walking and cylinder tests were used to assess function, and water-maze to assess cognitive performance. MCAO rats showed partial spontaneous recovery in sensorimotor function however, the recovery was similar to control. Only few human nuclei positive cells were detected in rats brains that received HUCBC. Imaging indicated uptake in lung, liver, spleen, and kidney, but not in the brain immediately after administration or 24 h post-administration, suggesting that HUCB cells do not improve recovery because of limited migration of cells to the ischemic brain.

Conversely, in 2001, University of South Florida reported HUCB cells administered intravenously 5-7 days **after** a MCAO reliably produce recovery and protect neural tissue (Chen et al., 2001). Cells do not exert their effects by engraftment in the infarct region, even though they migrate to the site of injury. Sanberg et al., used a combination of in vivo and in vitro studies to show that HUCBCs decrease inflammation in the brain after stroke and thereby enhance neuroprotection (Borlongan et al., 2004; Vendrame et al., 2005; Willing et al., 2003a; Willing et al., 2003b). In addition to modulating the inflammatory response, the cord blood cells increase neuronal survival through non-immune mechanisms. Once thought of as "cell replacement therapy," some propose cord

blood treatment reduces inflammation and provides neuroprotection. The authors noted a disproportionate clinical improvement to the number of human cells present.

In our evaluation of this article, we concluded that injecting cord blood day 1 post occlusion may account for poor recovery due to acute inflammation. The studies by University of South Florida indicated that their best results were seen when HUCBC were administered on day 5-7 post occlusion. It should be noted that acute inflammatory responses are decreased in utero, therefore it would be logical to assume cord blood will not respond appropriately under acute inflammation (Maley et al., 2006; Sammin et al., 2006).

VII.   Suggested Treatment Proposal

The dosage and therapy time course can only be estimated. Two cord blood units (two billion cells) can support leukemia patients following marrow ablation and the results are superiors to marrow replacement in terms of engraftment and declined graft versus host disease. In addition, our animal studies have shown a direct correlation between cell dose and clinical improvement. Therefore the recommendation would be to administer three units of cord blood (3 billion cells), partially HLA matched, blood type specific given 5-7 days post trauma.

The Landstuhl Regional Medical Center in Germany has access to German cord blood banks with fresh and frozen specimens that could be typed and made readily available for administration within 5-10 days of a neurological injury.

VIII.   Safety

From 1964-1974, one of the authors of this report administered multiple units of cord blood (139) to 15 patients. No adverse effects were noted except one case of cold antibody. Recently, Dr. Bhattacharya published 2 articles reporting the use of multiple units of cord blood without immunosuppressant for non-neurological problems (Bhattacharya, 2005; Bhattacharya, 2006). In one instance, 2-6 units were given to 28 patients without producing any clinical graft versus host disease symptoms. Bhattacharya 2005 reported in the *Journal of Americas College of Surgeons* that when 413 units of cord blood were given to 54 men and 26 women in an under-resourced country, the researchers did not encounter "a single case of immunologic or nonimmunologic reaction so far."

IX.   Conclusion

There is solid evidence that cord blood cells can both produce neural cells in vitro and provide protective support following neurological trauma. Furthermore, there is strong evidence that cord blood cell transfusions, frozen or fresh, are safe or safer than blood transfusion from an adult donor.

With the larger number of neurological injured marines and soldier, <u>failure to attempt</u> to improve their recovery via a <u>very safe procedure</u> could be considered a tragedy.

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