Autologous Umbilical Cord Blood Treatment for Autism: Rationale and Potential Goals of Treatment

Could autologous umbilical cord blood (AUCB) offer stem cells that could alter functionality of aberrant immune or nervous system cells affected by some environmental factor in patients with negative genetic screening for autism?

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Autism is now the leading cause of childhood neurodevelopmental morbidity, recently analyzed to be about 1:88 children in the United States. This condition has many theoretical causes, and many suggest a “multi-hit” mechanism, implying that more than just a genetic predisposition is required. The majority of clinical autism is classified as idiopathic type. This is important for the reasoning behind our current study using autologous umbilical cord blood stem cells (AUCB) in autism. For patients with negative genetic screening using today’s microarray technology, AUCB could potentially alter functionality of aberrant immune or nervous system cells that may have been affected by some environmental factor.

BACKGROUND
Autism is now the leading cause of childhood neurodevelopmental morbidity, recently analyzed to be about 1:88 children in the United States. This condition has many theoretical causes, and many suggest a “multi-hit” mechanism that suggests more than just a genetic predisposition. Genetics plays a role in the development of autism and many genes have been identified that can increase the risk for autism, however not everyone who carries a genetic predisposition develops symptoms of autism. Maternal in utero environment, family history of psychiatric disorders and/or autoimmune disease are all risk factors for autism. With new genetic screening with microarrays and, soon, the whole human genomic exome studies that are available, more genes associated with autism will be discovered. At this time, the majority of autism lacks a genetic linkage; approximately 15-20 percent of patients have a genetic abnormality detected with current chromosomal microarray technology. The majority of clinical autism is still classified as the idiopathic type, which is an important fact to the reasoning behind our current study using autologous umbilical cord blood (AUCB) in autism. For a subset of patients with idiopathic autism, AUCB stem cells may alter functionality of aberrant immune or nervous system cells that may have been affected by some environmental factor.

DEFINING AUCB
Autologous umbilical cord blood (AUCB), a rich source of stem cells, is available through collection of umbilical cord blood from the umbilical cord at birth. The processing and
cryogenic storage of cord blood has become more common in the past two decades. As scientific understanding of stem cell-based medical interventions expands, having available umbilical cord blood allows access to a mixture of stem cells including a small subset comprised of pluripotent stem cells, cells capable of becoming many different types of tissues, although there is debate about the relative concentration of pluripotent stem cells in cord. Other types of stem cells found in the cord blood include hematological and immune system precursors, and mesenchymal stem cells. The use of hematopoietic stem cells, administered through peripheral infusions is an established treatment option for hematological disorders.

AUCB contains a heterogeneous cell population including multiple types of stem cells: hematopoietic stem cells which are precursors of blood and immune cells; mesenchymal stem or stromal cells, which are precursors of connective tissue; and pluripotent fetal stem cells, primitive stem cells with characteristics of embryonic stem cells, that are the smallest population of stem cells in AUCB. The aforementioned stem cells may act in any infusion, including a peripheral infusion into a vein where they migrate to the bone marrow and lymphatic regions initially, and later through circulation stem cells can reach the blood brain barrier and central nervous system. In animal models stem cells have been observed to migrate into the CNS, where they seem to congregate near sites of injury, which may include regions in the CNS containing endogenous stem cell populations. The infused cells do not persist and suggesting that observed benefits are due to endogenous stem cells stimulated by their exposure to the external, infused stem cells. The mechanisms that work in human conditions such as cerebral palsy or autism are not clearly understood.

Today less than 20 percent of cord blood is banked in the United States. It is important to identify local resources for public or family banking as this easily obtained, non-controversial source of stem cells should not go to waste. Patients giving birth should be educated about the options to save and bank later use privately or donate cord blood to public banking for use by an unknown patient requiring a transplant or research purposes.

**POTENTIAL MECHANISMS IN AUTISM**

The use of AUCB or allogeneic cord blood stem cells as a potential treatment for neurological developmental disorders such as cerebral palsy and ischemia is being studied. Pooled umbilical cord stem cells have been used in autism and other disease states, such as multiple sclerosis. Autism represents another developmental heterogeneous disorder that has multiple mechanisms behind the development of the condition. Although numerous genetic studies have been done in autism, there are few subgroups of autism with known predisposing genetic factors that increase the risk. Therefore, the cause of autism is more than genetic for the majority of cases, currently estimated at 1 in every 88 children. One theory for the cause of autism is that aberrant immune activation may lead to neuronal dysfunction in a subset of patients with autism. It is possible that a predisposition to autoimmune activation or other environmental stressors may lead to changes in growth and maturation of the infant nervous system causing the autistic symptoms to appear sometime between 12-24 months of age. The possible mechanisms and the manner that AUCB may help are discussed below.

In autism, glial cell activation is present in many studies. Elevated cytokines or direct in vivo or post-mortem brain studies have shown increased glial cell activity. Cytokine elevation has also been described in CSF and blood of autistic patients. Maternal autoantibodies are associated with increased risk of autism in subsequent children. Autistic features are also seen in laboratory offspring exposed to anti-CNS antibodies when maternal serum is given to pregnant animals. Serum from autistic children has shown autoantibodies to brain derived neurotrophic factor (BDNF) and capillary endothelial cells that line the blood brain barrier. Children with autism have also been found to have elevated levels of tumor necrosis factor-alpha (TNF-). A small pilot study demonstrated a reduction of TNF- with 2.5 mgs lenalidomide over 12-weeks. Elevated glutamate and anti-oxidant protection in autism may be a secondary effect from chronic inflammation.

Epilepsy or abnormal EEG findings in autism may reflect dysfunctional neurotransmitter function, although these
findings could be induced by chronic inflammation, similar to glial activation seen in epileptic patients. Glial activation in epileptic patients involves many of the same mechanisms studied in autism research focused on glial and cytokine activity.\textsuperscript{18,28} Up to 50 percent of autistic patients, especially in children under five years of age, may have abnormal EEG patterns with epileptic potentials seen.\textsuperscript{29} Throughout their lifespan, autistic patients have a 10-30 percent risk of developing clinical epilepsy with active convulsions as well. Therefore, this activity may also occur from history of chronic inflammatory issues in autistic patients.

Umbilical cord blood stem cells have been shown to alter glial activation in animal models, and may alter T and B cell pro-inflammatory activity.\textsuperscript{30} Additionally, it is possible that AUCB stem cells, including any neuronal precursors, may alter dysfunction via cellular messaging, as has been seen in use of stem cell supernatant from adipose stem cell cultures in animal models of epilepsy or inflammation.\textsuperscript{31}

Pooled stem cell studies using non-autologous cord blood samples in autism have shown some findings with clinical improvement.\textsuperscript{9} However, risks associated with the use of pooled cord blood include host immune rejection and graft versus host disease, both complications not applicable to the use of AUCB.

**DESIGNING A PRACTICAL STUDY**

Our study is the first of its type to be done in the United States using AUCB for autism. The study is designed as a double-blinded placebo controlled trial. Participants must have negative genetic testing, including a chromosomal microarray. This ensures, to the best of our ability, that the study population is similar to the general population of patients with idiopathic autism. Because most autism is thought to be more than genetic in origin, AUCB may help by reversing the theoretical environmental factors that may have been part of what caused that patient’s autistic condition to evolve. In an exploratory study, we will also measure serum cytokine markers to see if there is an underlying autoimmune activity before or after cord blood administration.

We chose to use children under seven years of age to optimize the measurement of the primary outcome: improved language and communication as measured by the standardized one word vocabulary receptive and expressive speech instruments. In addition, we are measuring global clinical improvement, consisting of a 7-point Likert scale and measures of functionality. Infusion groups will cross over after six months to allow adequate response time and measure duration of any observed affects. Clinicians involved with measurement of outcomes are blinded.

Potential limitations of our study include a small sample size, which may not show a statistical difference between infusion groups, especially if we find crossover effect. If there is a crossover effect, once patients receive the infusion of cord blood, their language does not return to baseline after the washout period. Additionally, our measurements may not be sensitive enough to measure differences between the two groups. However, based on limited anecdotal reports of pooled non-autologous cord blood use in children, the positive observations seen in cerebral palsy treated with AUCB, and the animal model research described above, we expect to see a response in our study. If we find that only a subset of patients responds, we will attempt to analyze differences in that group.

We expect that it may take 18-24 months before results from this study are available, however if major differences are obvious we can obtain partial analysis from the unblinded clinician. Patience for our results is needed, as this therapy is still only an exploratory study to evaluate the safety and efficacy of AUCB in autism.

**CONCLUSION**

Autism affects 1:88 children in the United States and has become the leading cause of developmental disability. Etiology remains unclear and no specific core treatments exist to modify or reverse the course of this lifelong neurological condition. Heterogeneity and multifactorial risks make any one treatment unlikely to help all cases. AUCB offers a safe source of stem cells that may be able to alter underlying immune or acquired risk factors. Our current study offers an initial practical application for this concept. Results will be analyzed to determine what role AUCB has in affecting the course of autism in our patient population.

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For more information on the current study, visit http://www.cordblood.com/en/stem-cell-research/cord-blood-research/autism

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