THEA
Center for Regenerative Medicine

Stem Cell Therapy

While stem cell therapies may seem to have appeared overnight, they have been practiced for decades. The most recent developments in stem cell science have brought exciting new opportunities for improving patient outcomes - especially over the long term.

What are Stem Cells?

Stem cells are primitive cells in our body serving as a reservoir, able to replenish itself and differentiate into a wide range of specialized cells, in order to replace damaged cells and regenerate tissue. They have innate intelligence, able to home in to injured areas, secrete bioactive molecules that exert local and systemic effects, reduce inflammation, and recruit local cells to assist in the healing process.

Every cell in our body can trace its origin to the ultimate stem cell – a fertilized egg. Each cell division moves the cells down a path to their final cell type such as cells of muscle, nerve, or liver. All along this journey cells make commitments that are typically irreversible. This implies that any tissue in our body may require stem cells for regeneration. Properly harnessed, stem cells have the potential to repair or reverse an incredibly broad range of conditions, such as musculoskeletal injuries, autoimmune diseases, wounds, and lung conditions.

Where are these Stem Cells in the body?

Stem cells exist in varying forms in numerous places throughout the body, although with a tendency to decline in number and quality throughout our life cycle. Adult stem cells are most abundant in bone marrow, fat tissue, and blood; it is from these sources the body often recruits stem cells when they are needed. Bone marrow transplant has been a routine treatment for decades.

Stem cells are especially abundant at birth, in umbilical cord and placenta, which is why many parents choose to privately store umbilical cord blood/tissue when their babies are born. Membranes from placenta have been used to treat burns and other wounds for over a century.

What is Stem Cell Therapy?

Stem cell therapy utilizes stem cells to help with various health conditions. There are many types of stem cells, some more primitive than others, thus with more potentials to differentiate. Embryonic stem cells have the most potential to differentiate, but science has not yet found a way to safely harness these cells for use in clinical settings. We are all born with a reservoir of stem cells, but their numbers and quality decline significantly as we age. Stem cell therapy hopes to benefit people's health using these cells' innate intelligence, their ability to home in to areas

needing repair, and their ability to send out signal and recruit other cells to participate in such repair.

Adult Tissue as Stem Cell Source

More recently, stem cells from a patient's own fat, bone marrow, and circulating blood have been used to treat a variety of common conditions. For example, in the case of joint problems that require replacement or repair of cartilage, concentrated and directed doses of one's own stem cells have been shown to be more effective and long-lasting than widely practiced alternatives using PRP (platelet rich plasma) or cortisol injections.

Acquiring stem cells from an adult's blood requires many sessions and expensive processing, to harvest a useful number of therapeutic cells. Using bone marrow increases yield and requires only one session. Harvesting stem cells from fat has exciting applications and has shown efficacy for treating a variety of conditions.

However, adult stem cells from a patient's old body are as old and as diseased as the patient himself, thus affecting their therapeutic potential, leading to inconsistent treatment results.

Birth Tissue as Stem Cell Source

Tissues typically discarded at birth (e.g. placenta, umbilical cord) is another rich source of stem cells that boast some unique properties that set them apart from adult stem cells. While adult stem cells need to be a match (much like blood transfusions) to avoid rejection by the recipient's immune system, stem cells of umbilical cord and placental origin do not need to be matched. This is because the young cells present in birth tissues have not fully developed the surface proteins ("HLA markers") found on the outer membranes of adult cells, and thus are able to "fly under the radar" of the recipient's immune system. This immune-privileged status makes the transplant an easier task: instead of harvesting the cells from the patient that carries surgical risks, the doctor can now open the stem cell "medicine cabinet" to administer precise doses.

Stem cells of birth tissue origin have another unique advantage: These cells are young and have been shown to be therapeutically more active. While we do not yet know all of the mechanisms by which stem cells promote healing, we do know that these cells produce cytokines and growth factors, and recruit local cells to perform work of repair and regeneration. When birth tissue stem cells are compared to adult stem cells, they demonstrate higher level of secretion of cytokines and growth factors, higher speed of differentiation, slower cellular aging, stronger anti-inflammatory effects, and higher number of future cell divisions before eventual cell death. Also, studies have shown that umbilical cord stem cells have greater neuro-protective and neuro-restorative properties compared to adult bone marrow stem cells.

Yet, it may not simply be the cells that are exerting therapeutic benefits. Recent study out of Stanford University showed that umbilical cord blood contains an abundant supply of a valuable protein called TIMP-2, which has shown to improve memory and learning, through improving hippocampal function.

Birth Tissue - Amniotic Membrane

Amniotic membrane products have been rapidly advancing in quality and popularity in the last few years. They show greater long-term efficacy over PRP (platelet rich plasma) or cortisol injections. Using these products does not require matching, because while the chorionic (maternally facing) membrane presents HLA markers, the fetal-facing membrane (amnion) is immune-privileged and can be used in allogeneic applications (transplantation into a different individual).

Birth Tissue - Umbilical Cord Blood

Umbilical cord blood contains hematopoietic CD34+ stem cells, which for decades have been used to treat the same panel of conditions for which bone marrow transplants were used for. Hematopoietic stem cells also help with angiogenesis (generating blood vessels) thus help ensure blood supply to the repaired tissue. There is also evidence, that a more naïve progenitor cell is present exclusively in cord blood. Recently, a valuable protein TIMP-2 was found to be abundant in the umbilical cord blood, and TIMP-2 was shown to promote memory, learning and hippocampal health.

Birth Tissue - Umbilical Cord Tissue

Umbilical cord tissue is a dense source of MSC's, mainly from a gelatinous material surrounding the blood vessels of the cord, called Wharton's jelly (WJ). MSC's (mesenchymal stem cells) were shown to have the capacity to differentiate into bone, cartilage, fat, skeletal muscle, cardiac muscle, and even neurons, or cells of the kidney, liver and pancreas. MSC's from umbilical cords are more primitive than MSC's derived from more mature tissue sources, and have intermediate properties between embryonic and adult stem cells. They have anti-inflammatory, immune-modulating, antimicrobial and anti-tumorigenic properties, are able to home in to sites of injury, and send out signals to recruit local cells to participate in rescue and repair. MSC's from WJ may also be particularly helpful in the treatment of neurodegenerative conditions.

In Conclusion

Non-embryonic stem cells can be harvested from various sources including bone marrow, adipose tissue, blood, amniotic fluid and birth tissue (such as umbilical cord and placenta). Among these, birth tissue-derived cell products offer many advantages, including abundance of stem cells, youthfulness of cells with higher metabolic activities, richness of cytokines and growth factors, easy harvesting, lack of need for HLA matching, excellent safety record, superior ability for replication and differentiation, higher anti-inflammatory and robust angiogenic potentials.

Although autologous stem cell transplantation (using a person's own stem cells) is currently the most utilized form of stem cell therapy, as it avoids the risk of graft vs. host immune response, this method has significant drawbacks in the aging and chronically ill populations. Besides

requiring invasive procedures to harvest the cells, in the older and chronically ill population, both the number and quality of stem cells have declined, limiting their regenerative capabilities.

Even among the young and healthy adult population, stem cells obtained from a person's bone marrow or adipose tissue still produce less cytokines/growth factors, with lower anti-inflammatory potentials, lower rate of growth & differentiation, shorter telomeres (end sequences that protects the chromosomes), more rapid cellular aging, and less remaining generations of offsprings, when compared to the stem cells of birth tissue origin.

Choosing Stem Cells

And as one can see, stem cell products available to physicians for treating patients can be obtained from a variety of sources and manufacturers. There are differences in quality of the source material and the manufacturing process. It is important to investigate the purity, quality, and viability of the stem cell product to achieve the best results.

While some products like amniotic membranes used for dressing burns can benefit a patient even when there are no living cells present (due to the scaffolding effect) other products like injectable stem cells used for treating joints or stroke are more effective when the donor cells are living and healthy.

Some stem cell companies provide cell assay results that define the product and verify the presence of healthy living cells. Some products that have been freeze-dried, are stored at room temperature, or are suspended in solutions that aren't conducive to cell stability may contain scaffolding, growth factors, and other things but are less likely to provide any living cells.

Your doctor is likely to have more information about the emerging stem cell therapies and can guide you in your search for the best that modern medicine has to offer. More developments and more successes are being reported everyday in this rapidly progressing area of medicine. It is a wonderful time to be alive when so many of the things that could rob us of our vitality can now be treated in effective and often lasting ways.

For further info please contact **info@theacrm.com**

FAQ's

1. *Where does your clinic get your stem cells?*

We believe that the best source of stem cells as of date are of birth tissue origin, thus we provide treatment using cells derived from birth tissue including the umbilical cord and placenta.

While in the mother's womb, a fetus receives nourishment and oxygen from the mother's blood. These essential substances pass to the fetus through the placenta and umbilical cord, which

connect the mother and fetus. The blood found within the umbilical cord is the baby's, not the mother's.

Typically, the umbilical cord and placenta are discarded after birth. But researchers have discovered that umbilical cord tissue and blood are rich in stem cells, such as mesenchymal stem cells and hematopoietic stem cells, and they are the best source of stem cells when comparing various factors, such as the youth of the cells, safety, convenience, low potential for adverse immune rejection, not requiring enzymatic manipulations, high cell viability and differentiation potential, and low potential to cause tumors, as well as lack of ethical controversy.

We also believe that the stem cells derived from a combination of umbilical cord tissue, cord blood as well as amniotic membrane offer the most complete array of therapeutic benefits.

We use products from Chara Biologics, who is the leader in the regenerative medicine field, and a company that emphasizes integrity, innovation and highest quality.

2. What makes Chara products different from other stem cell products?

*Chara products are **neonatal-**sourced regenerative medicine products.*

1) *When **Compared to Autologous Stem Cell Sources** (using a person's own fat, bone marrow or blood, etc.), Chara products are:*

   - *Obtained from **healthy newborn babies***
   - *Cells are **more primitive**, **metabolically more active**, with **faster rate of self-renewal,** and **wider range of differentiation***
   - *Secrete **more growth factors**, have **longer telomeres**, **senesce** (get old) **slower***
   - ***Lack the accumulation of lifelong cellular damages** of adult stem cells, which have gone through oxidative stress, radiation, or other toxic exposures associated with living and aging*
   - ***Highly rich in cytokines & growth factors**, many of which are no longer present in adult tissue sources*
   - *Have **more anti-inflammatory** and **neuro-protective** effects.*

- *Using Chara products **avoids invasive procedures** involved in autologous stem cell harvesting, thus avoiding the risks of **infection**, **scarring**, and **decline in a person's own stem cell pool**.*

- *Even someone who is **more advanced in age** or **more ill** can obtain high quality stem cells to help their body heal and regenerate.*

- *Allows for **repeated dosing** at **precise concentrations** in regular intervals to target various conditions.*

- *Chara products are processed in a **FDA-registered and inspected** laboratory that adheres to **cGMP** guidelines, which means it provides much **more quality assurance** compared to the tissue-processing in a physician's office.*

*2) When **Compared to Other Neonatal Allograft Stem Cell Sources**:*

*Chara products are all **highly rich in MSC's**, with **20-30% of the total cell populations being MSC's**.*

*MSC's have been proposed to be renamed as **Medicinal Signaling Cells** by its discoverer Dr. Arnold Caplan. These cells are located throughout the body, hovering around blood vessels and communicating with local stem cells, serving as the orchestrators of regeneration. Countless research studies have been conducted, which demonstrated the beneficial effects of MSC's in a multitude of illnesses.*

MSC's:

  - *exert **paracrine** effects: induce changes in nearby cells by secreting cytokines/ growth factors, to promote cellular proliferation, differentiation & angiogenesis (making new blood vessels)*
  - *have powerful **anti-inflammatory** effects*
  - *have **immune-modulating** effect - able to modify and regulate the immune system, such as in autoimmune disorders*
  - *have **anti-microbial** properties, helpful in fighting acute, chronic or systemic infections, and have been shown to be effective against protozoa (as in Lyme's disease)*
  - *have **anti-apoptotic** properties - can rescue injured cells (due to trauma, hypoxia, chemical/mechanical damage, radiation, etc.) from programmed cell death*
  - *have **angiogenic** properties - help promote new vascularization to provide blood supply to newly formed tissue*
  - *have **anti-fibrotic** properties - can help break down scar tissue, such as in the case of liver cirrhosis and scarring after myocardial infarction ("heart attack")*

- *Chara Biologics is the first in the industry to achieve a positive **CFU assay** result, demonstrating **MSC colony formation** -- a definitive test for MSC presence and their viability & health.*
- *Chara products are produced by laboratories with **perfect safety records**, even after a total of over 30,000 doses being administered.*
- *All donors are U.S.-based, and selection criteria are highly stringent.*
- *CharaCore provides the **highest cell concentration & viability** compared to other cord tissue-based products in the U.S., and provide **more complete cell types, abundant cytokines/growth factors,** due to its **delicate extraction process** which allows for more therapeutic agents to be preserved.*

- *CharaCore is the only product in the industry that it is processed from the **cord tissue**, **cord blood** and **amniotic membrane**, allowing it to harness the regenerative potential of all 3 birth tissue compartments.*

- *In CharaCore, serum from cord blood is carefully added back to the final product. Cord blood serum contains valuable proteins/growth factors, such as **TIMP-2 protein**, which has been shown to **promote memory and learning**. (Many stem cell companies throw away the serum or put it in cosmetic products to sell at high prices.)*

3. How would Chara products help me?

***CharaCore** is a pre-mixed cell suspension that contains cellular material, collagens, growth factors, and other key biologic components. They are all intended for homologous use for the repair, replacement, reconstruction, or augmentation of human tissue.*

FOUNDATION FOR REGENERATION

The birth tissue ECM contains Collagens I, III, IV, V, VI, VII, fibrous proteins that provide a structural scaffold to support cellular migration. Fibronectin, integrins, laminins, and hyaluronons also play a key role in proliferation, differentiation and adherence to the scaffold.

MODULATE CORRECT TISSUE REPAIR

Growth factors contained in the birth tissue ECM, including PDGF, VEGF, EGF, FGF and TGF-B, support cell proliferation and migration across the defect. This combination of proteins works with the body's own cells to modulate correct tissue reconstruction rather than scar tissue. Cellular components, especially MSC's, further deliver targeted signals to promote tissue repair.

REGULATE INFLAMMATION, SCARRING & PAIN

Birth tissue products have been shown to reduce inflammation, fibrous tissue growth, and potential scar tissue formation.

NON-IMMUNOGENIC

Birth tissue-derived stem cell products are 'immune-privileged', possessing little or no risk of foreign body reaction, which can lead to fibrosis and graft failure.

ANTI-MICROBIAL

Application of birth tissue products has been shown to reduce bacteria counts in the wound, demonstrated against a wide range of bacteria.

4. Would there be an immune rejection if the cells are not HLA-typed and matched with the patient?

The cells contained in Chara products are young and primitive cells, and they do not yet possess the surface markers that would lead to an immune rejection. Stem cells from birth tissue products do not contain HLA Class II markers which would lead to an immune reaction by the recipient, and they do contain Class I markers which are important to mark these cells as human (instead of bacteria, viruses, parasites, etc.) so that no immunological attack would against these human cells.

Numerous research has been going on from around the world in over a decade, and the birth tissue-derived stem cell products are considered extremely safe.

5. If 20-30% of CharaCore are MSC's, what are the other cells?

Aside from MSC's, the other cells are mononuclear cells, including hematopoietic progenitor cells, endothelial progenitor cells, and immature immune cells, etc. Mononuclear cells contain a multitude of multipotent progenitor cells that can differentiate into blood cells, endothelial cells, hepatocytes, myocytes, cardiomyocytes, smooth muscle cells, epithelial cells, neural cells, osteoblasts, fibroblasts, etc.

In 1cc of CharaCore (8-10 million cells per cc), it would contain 1.6 to 3 million MSC's, which is at least twice the number of MSC's compared to the best-performing competitor product that is extracted from cord tissue.

6. Are these cells culture-expanded ?

None of Chara products has gone through any "expansion" process. Cell expansion is against FDA guidelines, and such expanded cell specimens can only be used for research purposes, not for clinical use.

There is research evidence that unexpanded ("native cells") are 10 times more potent, i.e. it requires 10 times as many cells to achieve the same results when the cells had been cultured and expanded.

7. As to the cells from each vial of product, are they from one donor or multiple donors?

All cells in our product (derived from cord blood, cord tissue & amniotic membrane) are from a SINGLE donor within each vial and each lot. Each vial has lot # and donor ID # that can be traced to the origin if the recipient ever desires to do so in the future.

8. What's FDA's position on these products?

At this point, the FDA is still looking into more defined ways to regulate this new area of medicine. FDA allows clinical use of umbilical cord-derived stem cell products as tissue transplantation, without going through the prolonged and expensive process of drug approval, as long as its use meets the criteria of "minimally manipulation" in preparation, and is for "homologous use."

Chara products are minimally manipulated biologic allografts, and are regulated by the U.S. Food and Drug Administration (FDA) as Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), under Section 361 of the PHS Act. When used as tissue to tissue transplantation, it is fully compliant with FDA guidelines.

9. What kind of screening is involved before birth tissue is accepted for processing?

*All tissues are sourced from **young healthy U.S.-based mothers** after **elective C-section** delivery. Donors are screened and selected based on stringent criteria (see Question #11-13 for further detailed info). Potential donating mothers are examined periodically by their ob/gyn physician throughout pregnancy, and are required to go through necessary testing.*

*Before time of birth, if a mother chooses not to store their baby's umbilical cord for private use, she is asked if she would like to donate birth tissue (placenta and umbilical cord). When their answer is yes, the mother is asked to complete an **extensive questionnaire**, which screen for infectious disease exposures, alcohol/drug/smoking or other toxic exposures, medication use, travel history, any family history of heritable and non-heritable diseases, such as cancer, autoimmune diseases, blood disorder, etc., partner's health history (baby's father), as well as any prenatal test abnormality of the baby.*

*Informed consent is obtained, and the final acceptance of the donor tissue is **determined by a licensed physician**.*

*Once the donor tissue is accepted, the donor's blood is **tested for relevant communicable diseases** in a laboratory certified under Clinical Laboratory Improvement Amendments of the 1988 (CLIA) or equivalent and registered with the FDA for donor testing. Chara's donor screening, tissue collection and processing protocols meet or exceed applicable FDA regulations and industry standards.*

A licensed physician must review the results of testing and determine that the donor has met all eligibility requirements. The physician utilizes available relevant information which may have included, but not limited to: donor interview, medical/hospital records, donor physical assessment, infectious disease test results, radiology/pathology and other records if available and pertinent. Recipient records must be maintained for the purpose of tracing tissue post-transplant per JCAHO and FDA requirements.

10. Can you explain the donor eligibility criteria to me in greater detail?

Below is Chara laboratory's donor eligibility determination process:

1) Eligibility

A donor is determined to be eligible if acceptable criteria is met for the following:

- *An Informed Consent Form (GLP-DOC-0045) is completed and signed by the Donor.*
- *Medical records do not identify areas that would cause the donor to be ineligible per the criteria identified in the FDA Guidance Document - Eligibility Determination for Donors of HCT/Ps (August 2007) or within the ineligibility criteria in this procedure.*
- *The Donor Information and Health History Form (GLP-DOC-0046) does not identify areas that would make the donor ineligible.*
- *Communicable disease testing is performed by a CLIA certified lab and includes negative results for required testing.*
- *The Physical Evaluation Form (GLP-DOC-0047) does not identify physical evidence of sexually transmitted diseases, syphilis, non-medical percutaneous drug use such as needle tracks, disseminated lymphadenopathy, unexplained oral thrush, jaundice, sepsis, large scabs, severely necrotic lesions, etc.*
- *The recovery location of the donated HCT/P was suitable as indicated on the Postnatal Birth Tissue Recovery Form (GLP-DOC-0048).*

2) Ineligibility

Any indication that a donor has responded as participating in, admission to or observing of the following, results in a ***rejection*** *of the donor's postnatal birth tissue donation.*

- *Persons who have injected drugs for a non-medical reason in the preceding 5 years, including intravenous, intramuscular or subcutaneous injections (risk factor for HIV, Hepatitis B and Hepatitis C).*
- *Persons with hemophilia or other related clotting disorders who have received human-derived clotting factor concentrates on the preceding 5 years (risk factor for HIV, Hepatitis B and Hepatitis C).*
- *A donor who received clotting factors once to treat an acute bleeding event more than 12 months ago may be eligible to donate, based on approval from the medical director.*

· *Persons who have engaged in sex in exchange for money or drugs in the preceding 5 years (risk factor for HIV, Hepatitis B and Hepatitis C).*

· *Persons who have had sex in the preceding 12 months with any person who has HIV infections, including a positive or reactive test for HIV virus, Hepatitis B infection or clinically active (symptomatic) Hepatitis C infection.*

· *Persons who have been exposed in the preceding 12 months to known or suspected HIV, HBV and/or HCV-infected blood through percutaneous inoculation (e.g., needle stick) or through contact with an open wound, non-intact skin or mucous membrane.*

· *Persons who have been in juvenile detention, lock up, jail or prison for more than 72 consecutive hours in the preceding 12 months (risk factor for HIV, Hepatitis B and Hepatitis C).*

· *Persons who have lived with (resided in the same dwelling) another person who has Hepatitis B infection or clinically active (symptomatic) Hepatitis C infection in the preceding 12 months.*

· *Persons who have undergone tattooing, ear piercing or body piercing in the preceding 12 months, in which sterile procedures were not used (e.g., contaminated instruments and/or ink were used, or shared instruments that had not been sterilized between uses were used.*

· *Persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after their 11th birthday, unless evidence from the time of illness documents that the hepatitis was identified as being caused by Hepatitis A virus, Epstein-Barr Virus (EBV) or Cytomegalovirus (CMV).*

· *Persons who have had smallpox vaccination (vaccinia virus) in the preceding 8 weeks.*

· *Persons who acquired a clinically recognizable vaccinia virus infection by contact with someone who received the smallpox vaccine (i.e., touching the vaccination area or the scab, including the covering bandages, or touching clothing, towels, or bedding that might have come into contact with an un bandaged vaccination area or scab).*

· *Persons who have had a medical diagnosis or suspicion of West Nile Virus (WNV) infection (based on symptoms and/or laboratory results, or confirmed WNV viremia).*

· *Persons who have tested positive or reactive for WNV infection using an FDA-licensed or investigational WNV NAT donor screening test in the preceding 120 days*

· *Persons who have been treated for or had syphilis within the preceding 12 months.*

· *Persons who have been diagnosed with vCJD or any other form of CJD (Creutzfeldt-Jakob disease) or persons who are at increased risk for CJD.*

· *Donors are considered to have an increased risk for CJD if they have received a non-synthetic dura mater transplant, human pituitary-derived growth hormone, or have one or more blood relatives diagnosed with CJD.*

· *Persons who have been diagnosed with dementia or any degenerative or demyelinating disease of the central nervous system or other neurological disease of unknown etiology.*

· *Blood tests with a reactive result for: HIV Type I / II, HBV, HCV, Treponema / Syphilis, HTLV.*

· *Physical evidence of sepsis, syphilis, percutaneous drug use such as needle tracks, recent tattooing, ear piercing or body piercing.*

3) Additional Review for Eligibility

Any indication that a donor has responded as participating in, admission to or observing of the following, results in an <u>additional review</u> by the Medical Director for eligibility determination. If approved, a written justification shall be provided with the eligibility determination rationale.

· *Blood tests with a reactive result for Cytomegalovirus (CMV) must include additional testing, specific to CMV IgG and CMV IgM. The results below indicate donor eligibility:*

  - *CMV IgG detected, donor is eligible*
  - *CMV IgM detected, donor is **<u>not</u>** eligible*

· *Had any one of the following cancers, either as the donor or someone within the family: Brain or other nervous system, bone or joint, kidney, thyroid, Hodgkin's lymphoma, Non-Hodgkin's lymphoma, acute or chronic myelogenous / myeloid leukemia, skin cancer.*

· *A donor who received clotting factors once to treat an acute bleeding event more than 12 months ago may be eligible to donate, based on approval from the medical director.*

· *Donors who have blood disease or disorders, either as the donor or within the family.*

· *Have a history of insulin independent diabetes, either as the donor or within the family.*

· *Have one of the following autoimmune disorders, either as the donor or someone within the family: Crohn's diseases, ulcerative colitis, lupus, multiple sclerosis, rheumatoid arthritis, sarcoidosis, polyarteris nodosa or scleroderma.*

· *Donors who have a diagnosis of delirium (e.g., delirium caused by toxic/metabolic diseases or recent head trauma) would not necessarily be considered to have a diagnosis of dementia and should be evaluated by the Medical Director.*

· *(HCT/Ps from donors with dementia confirmed by gross and microscopic examination of the brain to be caused by cerebrovascular accident or brain tumor and who are confirmed not to have evidence of TSE on microscopic examination of the brain may be acceptable based on an evaluation by the Medical Director).*

· *Persons who have had a medical diagnosis or suspicion of Zika virus infection (based on symptoms and/or laboratory results) within the last four weeks.*

· *Persons who have had a medical diagnosis or suspicion of SARS (based on symptoms and/or laboratory results) within the last 28 days.*

· *Persons who have ever been exposed to Ebola.*

· *Persons who spent three months or more cumulatively in the United Kingdom from the beginning of 1980 through the end of 1996.*

· *Persons who are current or former U.S. military members, civilian military employees, or dependents of a military member or civilian employee who resided at U.S. military bases in Northern Europe (Germany, Belgium, and the Netherlands) for 6 months or more cumulatively from 1980 through 1990, or elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more cumulatively from 1980 through 1996.*

· *Persons who spent 5 years or more cumulatively in Europe from 1980 until the present (note this criterion includes time spent in the U.K. from 1980 through 1996).*

· *Persons who received any transfusion of blood or blood components in the U.K. or France between 1980 and the present*

· *Persons or their sexual partners who were born or lived in certain countries in Africa (Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, or Nigeria) after 1977 (risk factor for HIV group O).*

· *Persons who have received a blood transfusion or any medical treatment that involved blood in an African country, after 1977 (risk factor for HIV group O).*

11. What infections have been screened?

Donated human tissue is deemed qualified for transplantation by meeting the following criteria:

1) Results from the donor pre-screening lab tests specify the donor to be free from risk factors and active infections of applicable communicable disease agents and diseases required by the FDA.

2) All tissues are obtained and processed using sterile technique. Birth tissue are obtained only through Cesarean section (thus assuring sterility)

3) Donor results from the pre-screening lab test for applicable communicable disease agents must be negative and/or non-reactive for the following:

HIV I/II Ab: Human Immunodeficiency Virus Types I & II Antibody
HIV/HCV/HBV NAT: Human Immunodeficiency/Hepatitis C/B
HBs Ag: Hepatitis B Surface Antigen
HBc Ab: Hepatitis B Core Antibody
HBx Ag: Hepatitis B viral protein
RPR/STS or Equivalent: Syphilis
HCV Ab: Hepatitis C Virus Antibody
HTLV I/II: Human T-Cell Lymphotropic Virus Antibody
CMV total Antibody
West Nile Virus NAT testing
Zika Antibody
Borrelia burgdorferi: Lyme Disease
Candida albicans
Aspergillus brasiliensis
Bacillus subtilis
Pseudomonas aeruginosa
Staphylococcus aureus
Clostridium species
E. coli

4) At the time of procurement, cultures of the tissue are taken and grown out for evaluation. Donor tissue with cultures testing positive for the following microorganisms are rejected:

- *clostridium*
- *streptococcus pyogenes (group A strep.)*
- *enterococcus*
- *fungi (mold or yeast phase)*

5) Allograft Release Testing: testing must also be negative for Endotoxin and BioBurden testing before the final product can be released for use clinically.

6) Also, screening for exposure to other viruses or parasites may have been completed. A negative/nonreactive result is not required. All results are evaluated on a case by case basis by medical director:

- *Cytomegalovirus CMV-AB (IgG & IgM)*
- *Epstein Barr Virus EBV Ab (IgG & IgM)*
- *Toxoplasma gondii Toxoplasma AB (IgG & IgM)*
- *Trypansoma cruz T.Cruzi Ab (IgG & IgM)*

12. Can you tell me more about tissue sourcing process at your laboratory?

Many laboratories who sell birth tissue-derived allograft products are venture capitalist groups, some foreign owned, who hire third party labs that purchase specimens from organ procurement organizations. These labs rely on birth materials from other states, and sometimes even from outside American borders. Donor Eligibility requirements outside of this country often times do not meet U.S. equivalent standards. When these labs ship the materials between multiple states, they have substantially longer transit times to the lab. This has been shown to reduce cellular viability and increase potential for bacterial contamination.

Chara's manufacturing laboratory has been in the cord blood banking and procurement industry for 15 years, with a spotless record. The laboratory send staff to personally recover specimens from local hospitals. Donors are pre-screened for all relevant pathogen criteria; our laboratory goes a step beyond, and even screen for high-risk lifestyles that can negatively influence cellular quality.

*Average transit time from hospital to the laboratory is **20 minutes**, and average time from C-section birth to final product is **4 hours**. The chain of custody involves less than 5 people. Additionally, our laboratory has developed proprietary technology that enables the halting of apoptosis and maximizes cellular viability post-thaw.*

In addition to viral testing above and beyond FDA standards, all products from our laboratory are quarantined for two weeks after processing until a complete aerobic bacterial

assay is completed. Only after stringent testing is completed, are our products released for patient use.

13. Has there been 3rd party testing done on your products?

Absolutely. Chara products have high viability, are remarkably rich in MSC's: about 20-30% of the cells in CharaCore are MSC's, compared to most of competitors' 1% MSC content (most birth tissue-based companies provide stem cell products derived from umbilical cord blood only).

Chara Biologics is also the first in the industry to demonstrated MSC colony formation through CFU assay -- a definitive test for MSC presence, as well as viability and health.

14. Are there any clinical trials on Chara's products?

Yes. Currently, CharaCore is the product of choice in a large nationwide 675-patient IRB study (505 intervention group and 170 control group) on osteoarthritis of all joints in extremities. Stem cell studies on this kind of large scale is still very rare.

Regenerative Care Network (RCN) who designed the study had looked at all the regenerative medicine products in the U.S., and after conducting its own independent research, and rigorous vetting process of our laboratory and products, decided that Chara's products have the highest quality and potential for therapeutic benefits. This is the only approved IRB study as far as we know in Texas (currently Texas law prohibits physicians from administering stem cell treatment without being part of an IRB study).

More studies are on the way to study the effect of CharaCore in various orthopedic, cardiovascular, pulmonary, and other systemic conditions.

15. Is it safe?

Stem cells of different sources carry different safety profiles. Using cells from one's own body avoids any concerns of tissue rejection, but carries the risks due to invasive surgical procedures. The processing of tissue to obtain stem cells typically occurs at a doctor's office, and carries its own risks of introducing infectious agents.

Birth tissue-derived stem cells have little surface markers that would make them appear "foreign" to the recipient's body, but if a product is not pure and contains more mature cells such as RBC's (red blood cells), there is more of a chance for adverse reaction due to immune incompatibility, which is why using a product that is well-processed and of high purity is important.

Birth tissues are screened before they are accepted for donation and tested before being sent to a stem cell lab. Our laboratory tests the birth tissue again before processing, and test the finished product again after the processing is completed. The risk of infectious disease transmission is at the same level as when one receives a blood transfusion or organ donation. Laboratories producing such cells are under the regulation of American Association of Tissue Banks, and they adhere to the same standards as if they are processing blood transfusion and tissue donation products.

16. What kind of stem cells are in the birth tissue product?

Mesenchymal Stem Cells (MSC's): these are multipotent stem cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells), adipocytes (fat cells), and have been shown to have the ability to trans-differentiate into many other important cells of the body, such as neurons. They are ideally suited for treating systemic autoimmune and inflammatory conditions, and play a vital role in regenerating injured tissues. They help prevent premature cell death, rescue damaged cells, stimulate local dormant stem cells, modulate the immune system; they have antimicrobial properties, and have been approved internationally (Australia, South Korea, Canada, Japan, etc.) for treating bone damage, coronary heart disease, arthritic conditions, Crohn's disease, graft vs. host disease, etc.

Hematopoietic Stem Cells (HSC's): these are immature blood-forming cells found in blood and bone marrow, and are highly suited for tissue regeneration. They have revascularization capabilities, help repair endothelial lining of blood vessels, and provide synergistic benefits in concert with the tissue-repairing function of the mesenchymal stem cells. They are able to replenish cells in the circulatory systems such as white blood cells, red blood cells, and platelets.

Other Mononuclear Cells: including a multitude of multipotent progenitor cells that can differentiate into blood cells, endothelial cells, hepatocytes, myocytes, cardiomyocytes, smooth muscle cells, epithelial cells, neural cells, osteoblasts, fibroblasts, etc.

17. What are the benefits? How long will it take before I feel something?

Numerous research studies have shown that stem cells (especially MSC's) have anti-inflammatory, anti-microbial, anti-tumorigenic, and immune-modulating properties. Depending on the conditions a person has, he/she may sense a difference within a day, or may not notice a major difference until a few weeks or even 2-3 months later. For example, pain issues may respond more quickly than neurological issues, as the healing of the nervous system tends to take much longer. Tissue repair and regeneration takes time, and different tissues repair and regenerate at different rates.

18. How often do I have to do stem cell treatment?

If the condition treated was caused by trauma, as long as re-injury does not occur, once repair is completed, no further treatment is necessary.

If the condition is chronic, underlying causes need to be addressed. In general the effects of stem cell treatment last 6 months, but when a person address his/her conditions holistically, such as optimizing nutritional intake, hormone balance, and addressing detoxification and other contributors to inflammation, the result can last 9-12 months.

19. How do stem cells help people fight aging?

Regenerate Neurons & Improve Brain Function

When we enter adult years, we lose brain cells, by 0.8% each year. By the time we are 70 years old, we only have 55% of our brain cells left. As a result of this reduced number and declined function the cells, older adults often notice memory decline, slowed and dulled cognition, insomnia, or even dementia.

In our natural state, neurons have very limited ability to regenerate, thus the trend of brain aging seems irreversible. However, stem cell research has brought hope, as stem cells can trigger local brain cells to repair and regenerate, and can also differentiate into neurons themselves. There has been significant advancements in treating Parkinson's Disease using stem cells, as well as treating stroke victims, traumatic brain injury, spinal injury, brain atrophy and Alzheimer's Dementia.

Research have found that stem cells given through IV infusion can cross blood-brain barrier, reverse degenerative changes, repair vascular ischemia and hemorrhage, modify calcified vasculature, thus restore balance and youthful state of the central nervous system. Stem cells can help regenerate new blood vessels, improve brain blood supply, thus supply adequate nutrients and oxygen and remove waste. Studies have shown that the improvement of memory and cognition in Alzheimer's dementia after stem cell treatment are stable and sustained.

Improve Metabolism

Only through metabolism, can an organism obtain nutrients and energy to conduct all necessary cellular functions. Stem cells are the source of tissue regeneration, and the quantity and quality of stem cells can directly affect our metabolic function. Research have shown that stem cells can improve our metabolism of lipoproteins, effectively lowering total cholesterol, triglyceride, LDL levels, and reduce atherosclerosis.

Stem cell treatment can significantly improve our body's ability for carbohydrate metabolism, lower blood sugar levels, improve the balance between energy intake and expenditure, thus lower excess body weight in combination with exercise.

Improve Immune Function

Our immune system is our main defense again bacteria, virus, parasites, and cancer cells. Older adults have reduced number and function of these immune cells, thus they have lowered ability to fight off infections, cancer, and other diseases. Lower immune function is another hallmark of aging.

The direct evidence that stem cells can improve immune function comes from the treatment of leukemia through transfusion of healthy stem cells into leukemic patients. Stem cells are also particularly helpful in modulating and keeping the immune system in balance, especially in the case of mesenchymal stem cells (MSC's), which have been shown as a powerful tool in treating a multitude of autoimmune disorders.
Recently, stem cells have been used in the treatment of immune deficiency diseases, AIDS, and solid tumors, through their ability to manufacture blood cells, restore immune function, and destroy invading pathogens and cancerous cells.

Reduce Inflammation

A strong inflammatory response is important to our growth and development to help safeguard us against pathogens; however, as we age, levels of inflammation seem to increase, even in the absence of acute infections or other physiological triggers. This leads to declines in organ/tissue function and structural damages.

Inflammatory response has been shown to be a prevailing response that drives tissue damage in the aging process. Extensive studies showed that increased inflammatory markers are highly correlated with disease and disability in the aging population. Many of these markers are elevated even before symptoms of diseases emerge.

As we age, our stem cells also age, and they may not be as effective as controlling excessive inflammation in our body. Stem cell treatment, especially ones using MSC's, has a strong anti-inflammatory and immunomodulatory effect, and has been shown to significantly decrease inflammatory markers. So in this sense, by calming the inflammation that's at the root of many modern chronic diseases associated with aging, we are able to help slow the aging process.

20. Will stem cells help my condition?

These are some of the conditions that stem cell treatments have been shown evidence of benefits in through research studies:

Osteoarthritis
Autoimmune Disorders (122 known, including Rheumatoid Arthritis, Lupus, Crohn's Disease, Hashimoto's Thyroiditis)
Neurological Diseases (Parkinson's, Alzheimers, Multiple Sclerosis, ALS, Stroke, Spinal Cord Injuries etc.)

Type I & Type II Diabetes
Cardiovascular Diseases
Erectile Dysfunction
Dermatological Disorders
Lung Diseases (COPD, asthma, etc.)
Liver Cirrhosis
Kidney failure
Athletic Injuries
Degenerative Disc Disease
Cancer
Premature Ovarian Failure
Autism
Migraines & Tension-Type Headache
Alcoholism
Hearing loss
Cancer
Pain Management
Wound Care, Limb Salvage
Anti-Aging (such as skin, hair, energy improvement, etc.)
Age-related frailty

21. What are the potential side effects from using birth tissue stem cell products?

Patients who receive treatment at our clinic rarely notice any side effects, and this could be the result of the high quality product that we use in our clinic.

Studies have shown very robust safety profile for clinical use of birth tissue-derived stem cells. Thea is determined to provide the very best products in the country to our patients, which is why we use products from Chara Biologics. Chara Biologics products are produced by FDA-inspected laboratories, comply with all FDA guidelines, regulated by American Association of Tissue Banks. The stem cell products from Chara Biologics have had a perfect safety record to date.

CharaCore, used in IV infusions, have been third-party tested to contain high percentage of MSC's, and is the only product on the market that has demonstrated MSC colony formation on CFU assay - the definitive test for MSC presence.

For patients using birth tissue products from other companies, about 5-10% may notice mild flu-like symptoms, such as sneezing, sniffling, watery eyes, chest tightness, shortness of breath, malaise, or low-grade fever, but typically these symptoms are transient, lasting between 1 to 3 days.

22. Can stem cells cause cancer?

There have never been any documented cases that show umbilical cord-derived stem cells to cause or promote cancer. These cells are further differentiated enough that they do not have the

potential for disorderly growth (which results in teratomas), such as what had been seen with embryonic stem cells. There has actually been evidence that stem cells of umbilical cord origin have anti-cancer properties. The potential for teratomas fuels part of the controversy for the use of embryonic stem cells, in addition to its obvious ethical implications. Stem cell therapy has been investigated as a form of treatment for cancer, with some encouraging results. Historically, stem cell transplant (in the form of bone marrow transplant) has been used as a treatment for leukemia (blood cancer) since the 1960's.

23. What are some of the misconception associated with stem cell therapy?

Many people do not know that hundreds of studies have demonstrated that stem cells are safe, and tens of thousands of patients worldwide have been infused with stem cells with no adverse reactions. The United States is a still the world leader in stem cell research despite certain bans in the Bush era.

A lot people have heard about embryonic stem cells, which is not allowed for clinical use in the US, due to its ethical concerns and safety issues (potential to cause tumors), despite its powerful potentials.

Currently cell therapy in the US is available by utilizing cells obtained from a person's own bone marrow, fat tissue or blood, as long as they are minimally manipulated. However many people do not know that minimally manipulated cells can also be obtained from birth tissue, and these cells offer the best of both worlds: compelling therapeutic potentials due to their youthfulness, excellent safety record for decades, and it is free from ethical controversies.

24. How is IV dosing determined at your clinic?

For patients interested in the wide range of benefits from IV infusion, the dosing is determined by a combination of factors, including body weight, age, and health condition. Generally, adults need at least 1cc per 60 lbs of body weight, and an additional cc would be necessary for advanced age (above age 65-70), and another cc added for someone with significant chronic illness, or with an aggressive disease process.

It is difficult to predict how each patient would respond to the treatment. After initial IV infusion, we will monitor how a patient is doing in the next 1-2 months. If a patient has only partial improvement, a booster infusion may be necessary.

25. What is the treatment process?

1. *We highly recommend to include a comprehensive evaluation of nutritional, cardiometabolic, thyroid and male/female hormone status through SpectraCell Laboratories (www.spectracell.com) prior to your infusion. This is aimed at optimizing your health, enhancing the effects of stem cell treatment, and allowing us to track your progress. The total cost for the full set of tests is about $380 for a patient with insurance coverage*

(generally any type of insurance except for MediCal or MediCare), and about $760 for cash pay patients.

2. *Please follow Pre- and Post- Treatment recommendations that will be sent to you, and adhere to a healthy diet, free from sugar, refined carbohydrates, fried and processed food. Avoid soft drinks. Drink plenty of water. Try to eat whole foods with plenty of vegetables and fruits, preferably organic.*

3. *We also recommend a detox protocol to be started prior to your infusion, which will help reduce your body's toxic load, reduce inflammation and improve its ability to properly respond to stem cell treatment. Gentle detox such as colon cleansing or infrared sauna will be helpful.*

4. *On the day of your Stem Cell treatment, especially for IV infusions, please drink plenty of water, preferably completing 6-8 glasses at least an hour prior to the procedure.*

5. *Upon arrival for your treatment, you will be asked to read about your procedure and then sign an informed consent.*

6. *Your IV infusion, joint injections and other procedures will be performed by a licensed medical professional, and will be comprised of a protocol which includes placing you on a device that helps promote microvascular circulation, and the addition of certain vitamins into your IV regimen.*

7. *We will follow up with you periodically after the infusion, and will also ask that you keep a journal to track your progress.*

8. *We will discuss your lab results with you and provide recommendations. We will be with you each step of the way to help you achieve optimal health.*

9. *Re-evaluation of your progress will occur at 1 month and 3 months, at which time we will determine whether booster infusions would be necessary. Patients are usually able to maintain their gains from the therapy for at least 6 months after the initial treatment, or even longer depending on the person's underlying health state and their effort at maintaining their health. In some cases, further infusions may not be needed. However, for general anti-aging purposes, we recommend an IV infusion at least every 6 months, although some patients prefer to do so every 3 months.*

Advice for Potential Patients:

1. Get informed on how stem cell therapy can work for you.

2. Schedule a consultation to determine your eligibility for stem cell treatment and receive comprehensive evaluation of your health

Your information will be thoroughly evaluated, and require approval that your treatment falls under a homologous functional use of stem cell therapy.

3. Upon pre-approval you will receive a treatment protocol based on your condition. And we will schedule your infusion date and location.

This will establish the dosage per IV infusion, number of treatments, and/or localized site injections.

4. Payment: Currently stem cell therapy is patient-funded. Some insurance will cover specific spinal injury treatments.

Through our research, we have seen cost of treatment as high as $30,000 or more abroad and similar pricing in major hospitals in the US. Here are some typical cost examples for your reference:

OUTSIDE USA:
South American Facility: $30,000 average cost of treatment plus transportation, for adipose and umbilical cord stem cell treatments.

INSIDE USA:
West Coast Facility: $15,000 for adipose only treatment
Major West Coast Hospital: $30,000 and up for adipose and umbilical cord stem cell treatments
Midwest Facility: $12,000- $16,000 for adipose only treatment.

THEA Pricing

You will find our pricing is very competitive compared to other treatment centers. Generally the cost depends on the dosage required. Dosage depends on a combination of factors, including body weight, age of patient, disease severity and aggressiveness of disease.

For IV infusions, the minimum dose is 2cc for adults, and 1cc for young children. Our clinic charges $4,000 for 1cc, $7,000 for 2cc, and $2,500 for each additional cc.

For specialized treatments, below is our pricing:

Face PRP Microneedling as Add-On (to IV stem cell treatment): $1,000

Face PRP Microneedling alone: $1,200

Face/Neck PRP Microneedling as Add-On (to IV stem cell treatment): $1,500

Face/Neck PRP Microneedling alone: $1,700

Hand PRP Microneedling as Add-On (to IV stem cell treatment): $750

Hand PRP Microneedling alone: $950

Facial Rejuvenation Stem Cell Microneedling Procedure: $3,500

Hair Restoration Stem Cell Procedure: 1 area $4,000, 2 areas $7,000, 3 areas $9,500

Musculoskeletal Stem Cell Injections: 1 joint $4,000, 2 joints $7,000, 3 joints $9,500

Brain Enhancement Stem Cell Intranasal Procedure: $7,500

Male Sexual Wellness Stem Cell Procedure:

Initial session - $7,500 (includes in-home use ultrasound shockwave machine)
Subsequent session - $7,000

Female Sexual Wellness Stem Cell Procedure:

Initial session - $7,500 (includes in-home use ultrasound shockwave machine)
Subsequent session - $7,000

For more on treatment approaches at THEA Center for Regenerative Medicine, please visit www.theacrm.com

Above statements have not been evaluated by the FDA, and the stem cell treatment protocols we offer have not been approved by the FDA as treatments, therapies, new drugs, or investigational drugs.