FAQ's for Physicians

1. 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***:

CharaCore, CharaFlex and CharaAmnio are all **highly rich in MSC's**. In these products, **20-30% of the total cell populations are 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.

- 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 & CharaFlex provide 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.)

- CharaAmnio is a **4th generation amniotic product**, unique in the industry in that extracted cellular components, cytokines/growth factors from the placental amniotic membrane are **suspended in rich amniotic fluid**, providing unparalleled growth factor profile.

2. What is the difference between CharaFlex, CharaCore, CharaAmnio and CharaCel?

The Foundation of CharaCore ® and CharaFlex ® is the **Umbilical Cord Tissue**. Umbilical cord tissue is a rich source of primitive cells (especially MSC's) and the Extracellular Matrix (ECM) - a complex protein system that creates the foundation of the body's tissues and organs.

CharaCore: On average 8 million cells/cc, with components from the entire umbilical cord, including umbilical cord tissue (most importantly Wharton's jelly), amniotic membrane and cord blood. It contains rich content of MSC's, some HSC's (Hematopoietic Stem Cells), and numerous growth factors & cytokines. Can be used in any form of injections (safe for IV use).

CharaFlex: On average 5 million cells/cc. Derived from umbilical cord tissue only, with significant amount of extracellular matrix, including numerous growth factors, collagen scaffold, nutrients and other crucial therapeutic factors. Extracellular matrix and collagen scaffolding are particularly helpful in joint repair. Also highly rich in MSC's. Used for tissue injections only.

CharaAmnio: On average 2 - 2.5 million cells/cc. Carefully extracted materials from the **Placental Amnion Membrane** are then suspended in **Amniotic Fluid**. This proprietary process allows for preservation of extracellular matrix and 3D collagen scaffolding to provide support and replacement for endogenous tissue. This

product has cellular content rich in MSC's, along with abundant supply of cytokines & growth factors. Used for tissue injections only.

CharaCel: On average 25 million cells/cc. Extracted from **Umbilical Cord Blood**, which gives it the advantage of higher cell count per cc and higher cell viability. It is a rich source of HSC's (Hematopoietic Stem Cells) and contain some MSC's. The serum from the blood also contains valuable cytokines and growth factors. Can be used in any form of injections (safe for IV use).

3. How do Chara injectable products help my patients?

Chara injectable products are pre-mixed flowable birth tissue matrix, formulated specifically for in-office use. These allograft products contain 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. How do I use these products?

Product Preparation

To prepare Chara products, remove from dry ice container 4-5 minutes prior to use. Thaw the vial by holding vial in hands with gentle roll against skin (it takes 3-4 minutes to thaw thoroughly). Draw product using sterile technique into syringe using 18G needle, and switch to appropriate needle for application of specific locations. Best results if product injected within 7 minutes after thawing.

Local Application Techniques

When used for local tissue injections, Chara products can be applied using tactile feel or ultrasound guidance to determine the appropriate application site. Apply utilizing multiple small injections, feathering the graft throughout the entire intended area for maximum coverage. Apply every 0.5-1cm, clockwise around the site. Inject slowly to allow the allograft to settle into the tissues. The micro-trauma from the multiple injections will help to initiate the inflammatory response.

For joint injections, use appropriate needles and ultrasound guidance if necessary.

Post-Procedure Care

Physician should determine appropriate post-procedure care. After musculoskeletal procedures, off-loading and immobilization are recommended. At physician's discretion, protected active rehabilitation with limited mobilization or anti-inflammatory agents may be prescribed.

5. What is the storage condition for these products?

Chara injectable products are cryopreserved, and are to be stored in a clean environment at -80°C temperature. Temperature can range from -65°C to -192°C until time for use.

Do not let product thaw until it is time to use. Once thawed, it cannot be re-frozen.

6. 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.

7. If 20-30% of CharaCore, CharaFlex and CharaAmnio 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 million cells per cc on average), it would contain 1.6 to 2.4 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.

8. Are these cells 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.

9. 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.

10. 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.

We will be happy to provide a copy of the FDA guidelines for your reference.

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

All tissues are sourced from live, healthy U.S.-based donors after elective C-section delivery. Donors are screened and selected based on stringent criteria. 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 they choose not to store their baby's umbilical cord for private use, they are asked if they would like to donate the birth tissue. When their answer is yes, they are asked to complete extensive questionnaires, 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. 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.

12. 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) 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
Zika antibody

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)

Allograft Release Testing: testing must also be negative for Endotoxin and BioBurden testing.

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)

13. What markers are checked to determine if stem cells are in the product?

An array of markers are checked, including CD90, CD73, HLA-DR, HLA-ABC, CD34, Cd45, glycoproteins A. Also, growth factors such as VEGF, FGF-2, IL 1-ra, SCF are tested.

14. 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 CharaFlex, CharaCore and CharaAmnio 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*.

15. What kind of tissue tracking is required?

Joint Commission standard requires that "the organization that receives tissue provide a system that fully complies with the completion and return of tissue usage information cards requested by source facilities." To comply with these requirements, a Tissue Tracking/Transplant Record (TTR) and pre-printed labels are provided with every allograft.

Physicians are to record the patient information, the transplant facility name and address, the allograft tissue information (using stickers) and comments regarding tissue use on the TTR. Physicians are to return to completed TTR to Chara Biologics, and retain a copy in the patient medical record. Even if the tissue has been discarded for any reason, a completed TTR with the allograft identification must be returned to Chara Biologics.

16. What kind of certification is needed to perform these procedures in the office?

Currently no specific certification is required to provided these cell-based therapies. Chara Biologics will be offer a one-day physician training program covering stem cell science, research evidence and clinical applications, as well as various treatment protocols.

17. Where will the products be shipped from, and how are they shipped?

It will be shipped from one of our fulfillment centers within the United States.

Products are shipped in an extended-duration shipper, specifically designed for cryopreserved product, with outer box, styrofoam box, and thermo shield. Box will be packed with dry ice to maintain a temperature of -78°C.

18. What is the cost of shipping?

$150 flat shipping & handling fee within the US. Deliveries are made Tuesdays to Fridays by 10:30am, and Saturday deliveries require an additional $75 fee, and for early deliveries (8am) Tuesday to Friday, an additional $75 fee is required.

19. How many days in advance does an order have to be placed?

Orders must to be placed by 1pm the day prior to desired delivery date. Deliveries are available between Tuesdays and Saturdays only. Saturday deliveries incur an additional fee.

We recommend that practitioners **order their products to arrive the day prior to treatment day**, to avoid possible issues with shipping delays (due to weather or other contingencies). For maximal preservation of dry ice, the box should be placed in a regular freezer upon arrival until treatment, and the freezer turned to lowest temperature setting. This way, the dry ice generally can be maintained for 3 days. Please check daily to ensure that adequate amount of dry ice remain, and add dry ice if necessary (dry ice can be purchased in stores such as Smart & Final).

20. How do I become a provider with Chara Biologics and start ordering products?

1) A provider must first fill out a Provider Verification Form, email it to us along with a copy of his/her current medical license to info@charabiologics.com. This can also be accomplished by setting up an **online account**.

2) Once an account is established, the provider can fill out the Purchase Order Form and submit to orders@charabiologics.com, or may **purchase directly online** if an online account is set up.

21. How much do Chara products cost to physicians?

Product	Volume	Unit Price
CharaFlex	1.0ml	$1,300
CharaFlex	2.0ml	$2,500
CharaCore	1.0ml	$1,500
CharaCore	2.0ml	$2,800
CharaAmnio	1.0ml	$1,200
CharaAmnio	2.0ml	$2,300
CharaCel	1.0ml	$1,600
CharaCel	2.0ml	$3,000

22. How much do physicians usually charge for procedures using such products?

In the United States, physicians on average charge between $2,000 to $5,000 for each cc of product administered.

The quantity of stem cells required and number of treatments needed will vary depending upon a person's age, weight, and the severity of a person's health conditions.

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

Cost of stem cell treatments are as high as $30,000 or more abroad, with 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.

23. How are the payments processed?

1) Convenient **ACH transfer link** will be sent to ordering physician through email once order is received and processed.
2) Physicians may also make payment via **wire transfer** or **direct bank transfer.**
3) Credit cards are accepted, but a convenience fee will be added.