



FAQ's for Physicians

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

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

- Chara products are:
 - **neonatal in origin**, obtained from a **healthy newborn baby**
 - 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
 - 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 condition.
- 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 Amniotic Products**

Amniotic products contain important cytokines/growth factors, but:

- there is significant variation among products due the different points in gestation the amniotic fluid is obtained.

- the younger and more potent amniotic fluid is collected during amniocentesis, which are usually performed when there is concern about **genetic abnormalities** or other diseases in the fetus.
- amniotic fluid contains about 200 various types of cytokines/growth factors, but it dwarfs in comparison to the **400+ cytokines/growth factors from umbilical cord tissue matrix** where Chara products are obtained.
- amniotic products contain very few live cells, so much so that the FDA prohibit these products to be called "stem cell products." Amniotic products thus **lack the many powerful benefits stem cells provide**, including the ability to home in to areas of injury/inflammation, and secrete appropriate cytokines/growth factors to target local repair.

3) When *Compared to Umbilical Cord Blood Products*

Cord blood-based products have a single FDA indication: reconstitution of the immune system after chemo-ablation of the bone marrow in leukemic patients.

it is the easiest birth tissue component to work with, as cells can be obtain via simple centrifuge cycles. However, they lack significant beneficial properties due to their **very low MSC content** (Mesenchymal Stem Cells).

Companies producing cord blood products emphasize the importance of MSC's, yet their products contain at most **1% 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.

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.

4) When **Compared to Other Umbilical Cord Tissue Products**

Very few laboratories in the U.S. have the knowledge and skill to produce stem cell products from umbilical cord tissue, due to the technical challenges of separating cells from the tissue matrix they are embedded in.

- Umbilical cord tissue are known for being highly rich in MSC's, and Chara products contain **20-40% MSC's**, validated by 3rd party testing.
- 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 a laboratory with a **perfect safety record**, even after 20,000 doses have been administered.
- All donors are U.S.-based, and selection criteria is the most stringent in the industry.
- Chara products provide the **highest cell concentration & viability** compared to other cord tissue-based products in the U.S.
- Chara products provide **more complete cell types, abundant cytokines/ growth factors**, due to its **delicate extraction process** which allows for more therapeutic agents to be preserved.

Our flagship product CharaCore is unique in the industry in that it is processed from the **cord tissue, cord blood and amniotic membrane**, harnessing the regenerative potential of all 3 birth tissue compartments.

And 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.

2. What is the difference between CharaCore™ and CharaFlex™?

CharaCore™: Higher cell count, with components from umbilical cord tissue (both Wharton's jelly and perivascular region), amniotic membrane and cord blood. This product contains rich content of MSC's, HSC's (Hematopoietic Stem Cells), and numerous growth factors & therapeutic elements. Can be used in any form of injections (safe for IV use). Offered in 1cc & 2cc vials.

CharaFlex™: On average 5-8 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. Used for tissue injections only. Offered in 1cc & 2cc vials for local injections.

3. Can you explain the injectable products to me in more detail?

The Foundation of Chara products is the umbilical cord tissue. **Umbilical Cord Tissue** is a rich source of progenitor cells and the ExtraCellular Matrix (ECM) - a complex protein system that creates the foundation of the body's tissues and organs.

Chara injectable products are pre-mixed flowable birth tissue matrix, formulated specifically for in-office use. This fluid tissue combination contains collagens, growth factors, and other key biologic components.

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,[8] 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.

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.

Indication

CharaCore™ and CharaFlex™ are intended to replace or supplement damaged or inadequate integumental tissue.

Storage

Chara injectable products are cryopreserved, and can be kept at -60°C for storage up to 6 months, or -81°C for long term storage. Chara injectable products have a 5 year shelf life.

Tissue Safety

All tissues are sourced from live, healthy U.S.-based donors after C-section delivery. Donors are screened and selected based on a stringent criteria, and the final disposition of the donor is determined by a licensed physician. Serologic testing and tissue culture swabs are performed for each donor. Donor screening, tissue collection and processing protocols meet or exceed applicable FDA regulations and industry standards.

4. How do I use these products?

Product Preparation

To prepare CharaCore™ or CharaFlex™ products, remove from dry ice container 5-10 min prior to use. Thaw the vial by holding vial in hands with gentle roll against skin (it takes 4-5 minutes to thaw thoroughly). Draw product into syringe using 18G

or 20G needle using sterile technique, 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 injection, 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.

Post-Procedure Care

Physician should determine appropriate post-procedure care. Typically, off-loading and immobilization are recommended. At physician's discretion, protected active rehabilitation with limited or no immobilization or anti-inflammatories may be prescribed.

5. 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.

6. If 20-40% of Chara stem cell products 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 3.2 million MSC's, which is at least twice the number of MSC's compared to the best-performing competitor that extracts cells from cord tissue.

7. What are the growth factors contained in Chara products?

The list below are some of the growth factors contained in Chara products. Individual growth factor proteins tend to occur as members of larger families of structurally and evolutionarily-related proteins. There are many families, and some of which are listed below:

- Adrenomedullin (AM)
- Angiopoietin (Ang)
- Autocrine motility factor
- Bone morphogenetic proteins (BMPs)
- Ciliary neurotrophic factor family
 - Ciliary neurotrophic factor (CNTF)
 - Leukemia inhibitory factor (LIF)
- Colony-stimulating factors
 - Macrophage colony-stimulating factor (m-CSF)
 - Granulocyte colony-stimulating factor (G-CSF)
 - Granulocyte macrophage colony-stimulating factor (GM-CSF)
- Epidermal growth factor (EGF)
- Ephrins
- Erythropoietin (EPO)
- Fibroblast growth factor (FGF)
- GDNF family of ligands
- Growth differentiation factor-9 (GDF9)
- Hepatocyte growth factor (HGF)
- Insulin
- Insulin-like growth factors
- Interleukins
 - IL-1- Cofactor for IL-3 and IL-6. Activates T cells.
 - IL-2 – T-cell growth factor. Stimulates IL-1 synthesis. Activates B-cells and NK cells.
 - IL-3 – Stimulates production of all non-lymphoid cells.
 - IL-4 – Growth factor for activated B cells, resting T cells, and mast cells.

- IL-5 – Induces differentiation of activated B cells and eosinophils.
- IL-6 – Stimulates Ig synthesis. Growth factor for plasma cells.
- IL-7 – Growth factor for pre-B cells.
- Keratinocyte growth factor (KGF)
- Migration-stimulating factor (MSF)
- Macrophage-stimulating protein (MSP), also known as hepatocyte growth factor-like protein (HGFLP)
- Myostatin (GDF-8)
- Neuregulins
- Neurotrophins
 - Brain-derived neurotrophic factor (BDNF)
 - Nerve growth factor (NGF)
 - Neurotrophin-3 (NT-3)
 - Neurotrophin-4 (NT-4)
- Placental growth factor (PGF)
- Platelet-derived growth factor (PDGF)
- Renalase (RNLS) – Anti-apoptotic survival factor
- T-cell growth factor (TCGF)
- Thrombopoietin (TPO)
- Transforming growth factors
 - Transforming growth factor alpha (TGF- α)
 - Transforming growth factor beta (TGF- β)
- Tumor necrosis factor-alpha (TNF- α)
- Vascular endothelial growth factor (VEGF)
- Wnt Signaling Pathway

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. 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.

10. 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.

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

Chara products are obtained from donors through the most stringent selection criteria. Donating mothers have been followed by their ob/gyn, and are required to go through testing. Before time of birth, they are asked if they would like to have the baby's umbilical cord stored. 90% of the mother choose not to. At that point they are asked if they would like to donate the birth tissue. If they say yes, they are required to fill out extensive questionnaires (89 questions), 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, cancer, autoimmune diseases, blood disorder, etc., as well as any prenatal test abnormality of the baby.

Donated birth tissue goes through infectious disease testing before it is accepted by the laboratory. Upon arrival of the birth tissue at the laboratory, it is screened again for infectious diseases such as Hepatitis, syphilis and HIV. In addition, prior to being allowed to be used clinically, the finished products go through further testing, to ensure quality and sterility. All Chara products have their own tissue ID number, and can be traced back to the original donor if such need ever arises in the future.

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 and are negative and/or non-reactive for the following:

HIV I/II Ab: Human Immunodeficiency Virus Types 1/2 and O Antibody

HIV/HCV/HBV NAT: Human Immunodeficiency/Hepatitis C/B

HBc Ab: Hepatitis B Core Antibody

HBx Ag: Hepatitis B viral protein

RPR/STS or Equivalent: Syphilis

HCV Ab: Hepatitis C Virus

HTLV I/II: Human T-Cell Lymphotropic Virus

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 20-40% of the cells in CharaFlex and 20-30% of the cells in CharaCore are MSC's,

compared to most of our competitors' 1% MSC content in their products. 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. Chara products are also extremely rich in growth factors (see list of growth factors in Q #7).

15. How much do these products cost to physicians?

| <i>Product</i> | <i>Volume</i> | <i>Unit Price</i> |
|----------------|---------------|-------------------|
| CharaFlex™ | 1cc | \$1,300 |
| CharaFlex™ | 2cc | \$2,500 |
| CharaCore™ | 1cc | \$1,500 |
| CharaCore™ | 2cc | \$2,800 |

16. 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. There are some clinics that charge even higher rates.

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.

17. 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.

18. What about malpractice coverage for these procedures?

Providers can obtain coverage through their existing malpractice carriers, although some carriers do not cover stem cell treatment, and some offer a rider policy at around \$4,000 per year.

Chara has partnered with a stem cell training & marketing program which provides the only stand-alone stem cell malpractice insurance policy in the country, at \$2,500 per year, or at a monthly payment. To qualify for this policy, a provider is required to go through their training program, and the policy only covers approved products. At this point, only products from two laboratories are approved, one of which is the laboratory that produces Chara products. If you are interested, please contact us at info@charabiologics.com.

19. 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.

20. Where will the cells be shipped from?

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

21. How are the cells shipped?

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.

22. 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.

23. 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).

24. How are the payments processed?

- 1) Preferred method of payment is through **wire transfer** or **direct bank transfer**. Payments should be sent to Chara Biologics account at Bank of America.
- 2) Credit card payments are also accepted (with a maximum amount of \$14,000 per transaction)