

*Adipose
Derived
Stem Cell
Therapy*

Understanding Injuries

- There are two main ways of repairing injuries
 - White Blood Cells
 - Form scar tissue
 - Stem Cells
 - Regenerate the original tissue that was initially injured
- When we are young, we recover quickly because stem cells are widely available in our bodies
- As we age, our stores of stem cells decrease, white blood cells are more prevalent and injuries are typically healed with scar tissue



white blood cells

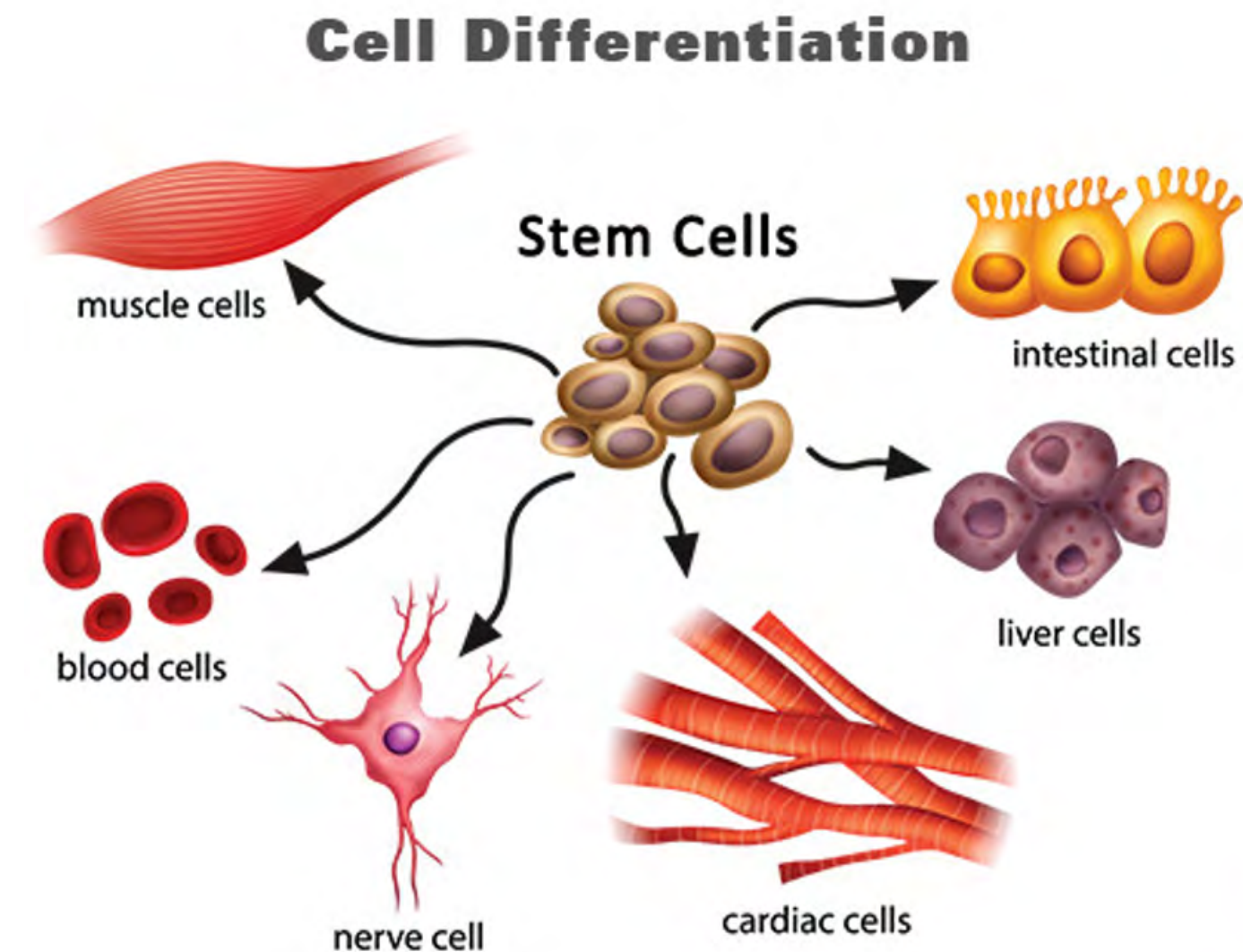


stem cells

Healing Injuries with stem cells result in significantly improved functional outcomes

Stem Cells – The Key to Injury Repair

- Stem cells have the ability to differentiate into functional tissues
- Stem cells are not just harvested from embryos
- Stem cells exist throughout our bodies
 - Found in all tissues: blood, fat, bone marrow, skin, liver, heart, brain...
- We can easily harvest blood, fat, or bone marrow in order to isolate the stem cells and use them for regenerative therapies
 - Helps physicians increase the number of stem cells bio-available in order to heal injuries with like tissue as opposed to scar tissue





International Journal of Stem Cell Research & Therapy

ORIGINAL ARTICLE

Prospective Study of Autologous Adipose Derived Stromal Vascular Fraction Containing Stem Cells for the Treatment of Knee Osteoarthritis

*Mark Berman, MD**, *Elliot Lander, MD*, *Thomas Grogan*,
Jonathan Braslow, MD, *Shawntae Dowell* and *Sean Ber*

Knee

Results: 2,586 patients were treated. Statistically significant improvement was seen at 1 and 2 years - meaning less pain and greater ease of mobility. There was no difference between male or female outcomes (82% overall improvement). All BMI levels showed improvements though higher BMIs had less improvement. There was no difference in outcomes between SVF alone or with PRP added to SVF. Improvement was the same regardless of payment or receiving free care. There were very few adverse events and those that did occur were largely very minor or easily treatable.



Back

ORIGINAL ARTICLE

Prospective Safety and Efficacy Study for the Use of Adipose Derived Cellular Therapy in Degenerative Lumbar Spine Disorders

Khoshal Latifzai MD¹, Mark Berman MD², Sean Berman MS², Elliot Lander MD² and Vassily T Eliopoulos MD^{1}*

Results: With a single SVF intervention significant pain improvement was documented out to 2 years from the time of intervention (79% of respondents reported significant pain improvement at 24 months). Adverse events were minimal and in line with or better than traditional minimally invasive therapies. No significant morbidity or mortality was identified.

Adipose Derived Stem Cells



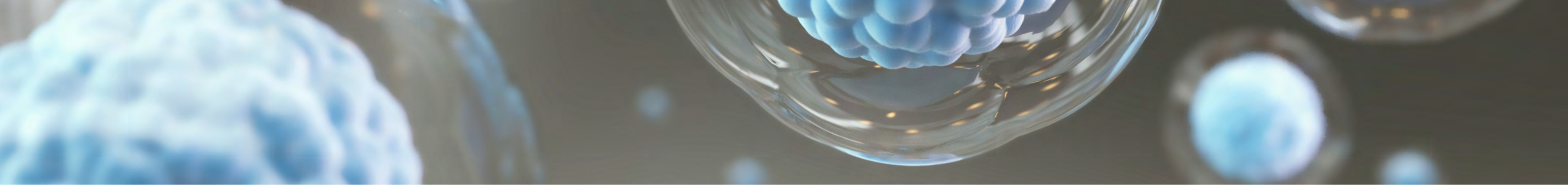
500-2500 times more stem cells can be harvested from your fat than your bone marrow (Fraser 2006, Casteilla 2011)

- **Autologous** – cells harvested from the patient are returned to the same patient
 - Simple procedure performed under local anesthesia
 - Requires a 50cc lipo-aspirate, which takes 15 minutes
 - Cells can be isolated and returned to the patient surgically in under 2 hours
- **Allogeneic stem cells** such as umbilical cord stem cells contain foreign DNA, but are increasing in popularity as they can be sold in a bottle off a shelf and require no surgery
 - **Unfortunately, there is no way to validate complete sterility for these cells**
 - Cannot screen for all viruses or prions (which are believed to cause neurological diseases like Alzheimer's/Dementia)
 - Risk of Graft Versus Host Disease with Allogeneic stem cells
 - Can initially bypass the immune system, but once they differentiate, present foreign antibodies which the host immune system can then attack years after the initial transplantation (Jacobsohn 2007)

Stromal Vascular Fraction (SVF)

- Isolated from Adipose (fat) Tissue
- SVF contains:
 - **Adipose derived stem cells**
 - **Hematopoietic stem cells**
 - **Pericytes**
 - **Pre-adipocytes**
- Isolated through an automated sterile surgical procedure
- Uses GMP collagenase enzyme produced by Roche to break down collagen matrix binding the stem cells to the fat





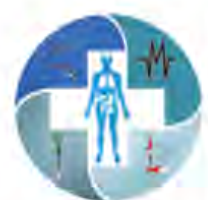
Why Stromal Vascular Fraction?

- **Autologous** – your own cells, DNA, and will not be rejected
 - SAFE
- **High Quantity**
 - 500-2000x more than those in bone marrow
- **High Quality**
 - High viability with CSN Time Machine vs mechanical isolation techniques = more cells to do more work
 - Very young cell type.
 - All cells are different ages. Adipose tissue is largely dormant and very robust
- **Point of Care**
 - Get your cells back and the healing process started within 2 hours

Results

Reported Complaint	Number	Percentage of Total
Total Operations Performed	549	100%
No Complaints Reported	527	95.99%
Pain During Surgery	7	1.28%
Deployment Site Inflammation	5	0.91%
Unspecified Complaint	5	0.91%
Harvest Site Infection	5	0.91%

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ORIGINAL ARTICLE

Prospective Safety and Efficacy Study for the Use of Adipose Derived Cellular Therapy in Degenerative Lumbar Spine Disorders

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78 pt's with 50% attrition at follow up

Mean age 35.8

Good short term (up to 6 months) pain relief

76.8% develop return of pain

29% require repeat steroid injections

48.7% go on to require surgical intervention

Human Adipose-Derived Stem Cells Exhibit Enhanced Proliferative Capacity and Retain Multipotency Longer than Donor-Matched Bone Marrow Mesenchymal Stem Cells during Expansion In Vitro

3. Results

3.1. Effect of In Vitro Expansion on CD Profile, Morphology, Population Doubling Number, and Telomere Length. The CD profile of MSCs and ASCs was comparable at ELSC (Figure 1(a)), with an average of >95% of both cells expressing the positive markers CD73, CD90, and CD105. The both cells demonstrated low levels of the negative marker panel (CD14, CD20, CD34, and CD45). CD marker profile did culture demonstrating stability of CD profile throughout their lifespan (Figure 1(b)).

Morphologically, both MSCs and ASCs displayed a characteristic spindle-shaped fibroblastic appearance during early lifespan in culture. By late lifespan, the majority of both MSCs and ASCs displayed a large, flattened polygonal morphology and ragged appearance, with the presence of stress fibres within the cytoplasm (Figure 2(a)), indicative of senescence.

Assessment of cumulative population doublings (CPD) over time in culture demonstrated similar rates of expansion between MSCs and ASCs at ELSC. However, assessment of CPD at MLSC and LLSC demonstrated greater PD number achieved by ASCs (MLSC: 16.5 ± 2.1 CPD; LLSC: 20.3 ± 2.3 CPD) compared with MSCs (MLSC: 14.7 ± 1.3 CPD; LLSC: 16.9 ± 1.2 CPD). In addition, the MLSC and LLSC timepoints

for ASCs (MLSC: 54.6 ± 5.9 days; LLSC: 80.8 ± 7.7 days) were, on average, reached within a lower number of days in culture compared to MSCs (MLSC: 64.6 ± 8.5 days; LLSC: 95.8 ± 14.5 days) (Figure 2(b)).

Telomere length was measured on genomic DNA extracted from MSCs and ASCs at ELSC, MLSC, and LLSC (Figure 2(c)). Telomere length was significantly longer in ASCs compared to MSCs at every lifespan point. While MSCs did not show a significant decrease in telomere length with time in culture, ASCs demonstrated a significant decrease in mean telomere length between ELSC and LLSC and MLSC and LLSC.

difference in the amount of GAG formation in MSCs and ASCs, and no significant difference in GAG levels were observed between cell types (Figure 4(b)). Histological staining at ELSC showed greater deposition of proteoglycan and collagen within MSCs compared to ASCs, with proteoglycan distribution throughout the pellet and collagen deposition largely located at the periphery of the cell pellet (Figure 4(c)). Extracellular matrix deposition within ASCs at ELSC appeared more randomly distributed, with collagen deposition often mirroring the deposition of proteoglycan. Histological staining for proteoglycan and collagen was less intense in MSCs at LLSC compared to ELSC, while ASCs

A blue-tinted microscopic image showing various cells and structures, including a large, textured cell in the center and several smaller, round cells scattered around it.

How is SVF Used?

- Deployment protocols vary based on the condition and injury
- IRB approved deployment protocols:
 - Intraarticular, Intravenous, Intrathecal, Intradiscal, Facet Injection, Intracerebral-ventricular
- Limitless Health & Wellness works under IRB (institutional review board) approved protocols for:
 - Orthopedics: Knee, Hip, Shoulder, Back, Joints
 - Neurology: Parkinson's, Alzheimer's, Multiple Sclerosis, Dementia, ALS
 - Urology: Erectile Dysfunction, Peyronie's, Interstitial Cystitis, Incontinence
 - Ophthalmology: Dry Eye, Macular Degeneration, Optic Neuritis
 - Cardiac/Pulmonary: Asthma, Congestive Heart Failure, Post Myocardial Infarction
 - Autoimmune: Lupus, Myasthenia Gravis, Rheumatoid Arthritis, Crohn's Disease

Sample of Peer to Date Reviewed Publications

ISSN: 2469-870X

International Journal of Stem Cell Research & Therapy

Original Article

Prospective Study of Autologous Adipose Derived Stromal Vascular Fraction Containing Stem Cells for the Treatment of Knee Osteoarthritis

Mark Berman, MD¹, Elliot Lander, MD, Thomas Grogan, MD, Walter O'Brien, MD, Jonathan Braslow, MD, Shawntae Dowell and Sean Berman, MS

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Abstract: The management of osteoarthritis of the knee has the spectrum of care from a variety of conservative treatments often culminating in total joint arthroplasty. We initiated a large prospective study to evaluate whether autologous adipose derived stromal vascular fraction (ADSVF) in stem cell therapy is a safe and effective option.

Methods: A patient funded prospective study of 2,500 patients from a network of physicians participated in an IRB approved study using autologous stromal vascular fraction (SVF) (CellSolve) to treat knee osteoarthritis. All patients were treated with a standardized surgical protocol to harvest adipose, isolate and deploy autologous SVF. Data were collected on patient demographics, clinical outcomes, and patient satisfaction.

Introduction: Multiple peer-reviewed publications exist showing that adipose derived stromal vascular fraction contains adult mesenchymal stem cells that may improve the condition of inflammatory knee conditions [1-5].

Animal studies show double-blind examples of significant improvements in using adipose derived stem cells for degeneration and injuries [6].

Multiple studies suggest that allogeneic stem cells may be efficacious and safe [7-11]. While an off-the-shelf stem cell product might be ideal, there are still

RESEARCH Open Access

The ratio of ADSCs to HSC-progenitors in adipose tissue derived SVF may provide the key to predict the outcome of stem-cell therapy

Mohamed Elmaghrabi¹, Antonio Sanchez-Gonzalez¹, Yuhua Min¹, Robert Loh¹, Deborah Dragomir¹, Doung Nguyen¹, Elliot Lander¹, Mark Berman¹, Boris Minov¹ and Andre A. Sanyal^{1,2*}

Abstract: Adipose tissue-derived stromal vascular fraction (ADSVF) represents an attractive source of adult stem cells and progenitors including adipogenic, hematopoietic and mesenchymal stem cells. In this study, we explored the relationship between the ratio of adipogenic to hematopoietic stem cells in ADSVF and the clinical outcome of stem cell therapy in patients with degenerative, inflammatory, autoimmune diseases, and advanced age-related degeneration.

Results: This analysis showed that highly enriched SVF from very heterogeneous and highly adipogenic adipose tissue (ADSVF) with a high ratio of adipogenic to hematopoietic stem cells (ADSCs/HSCs) was associated with improved clinical outcomes in patients with degenerative, inflammatory, autoimmune diseases, and advanced age-related degeneration. The ratio of ADSCs to HSCs in ADSVF was a significant predictor of clinical outcome in patients with degenerative, inflammatory, autoimmune diseases, and advanced age-related degeneration. The ratio of ADSCs to HSCs in ADSVF was a significant predictor of clinical outcome in patients with degenerative, inflammatory, autoimmune diseases, and advanced age-related degeneration.

HSOA Journal of Stem Cells Research, Development and Therapy

Journal of Stem Cell Research & Therapy

Autologous Stromal Vascular Fraction: A New Era of Personal Cell Therapy

Elliot B. Lander, MD and Mark H. Berman

Cell Surgical Network, University of Southern California, USA

Abstract: The emerging use of stem cell therapy (SCT) and its application in the treatment of degenerative diseases and autoimmune diseases is a rapidly growing field. This article discusses the history of SCT and its application in the treatment of degenerative diseases and autoimmune diseases.

Autologous Stromal Vascular Fraction Containing Stem Cells Combined with Low Intensity Shock Wave for the Treatment of Human Erectile Dysfunction

Elliot B. Lander¹ and Mark H. Berman

Cell Surgical Network, University of Southern California, USA

Abstract: The study seeks to determine whether the addition of autologous adipose-derived stem cells (ADSCs) may safely synergize with the clinical effects of Low Intensity Shock Wave Therapy (LIST) to improve Erectile Dysfunction (ED) in a small series of men.

Therapeutic Advances in Urology

Original Research

Stromal Vascular Fraction Combined with Shock Wave for the Treatment of Peyronie's Disease

Elliot B. Lander, MD, Mark H. Berman, MD, Jackie R. See, MD

Background: This pilot study was used to evaluate safety and subjective outcomes in a small series of Peyronie's disease patients using a combination of autologous stromal vascular fraction (SVF) and penile shock wave treatment. SVF can be processed and deployed into Peyronie's plaques, enabling the surgeons to procure and mobilize significant numbers of both adult mesenchymal stem cells and autologous progenitor cells from the adipose collagen matrix after collagen digestion. Penile shock wave therapy stimulates targeted tissue and may increase stem cells found in the SVF and promote healing and fibrosis mitigation.

Personal cell therapy for interstitial cystitis with autologous stromal vascular fraction stem cells

Elliot B. Lander, MD, Mark H. Berman and Jackie R. See

Background: The objective of this study was to evaluate whether autologous stem-cell-based therapy may mitigate the symptoms of interstitial cystitis.

Journal of Translational Medicine

RESEARCH Open Access

Delivery of oncolytic vaccinia virus by matched allogeneic stem cells overcomes critical innate and adaptive immune barriers

Devin D. Dragomir¹, Antonio F. Sanchez-Gonzalez¹, Yuhua Min¹, Doung Nguyen¹, Mohamed Elmaghrabi¹, Robert Loh¹, Mark Berman¹, Boris Minov¹ and Andre A. Sanyal^{1,2*}

Abstract: Personalized medicine has identified a key role for the immune system in cancer progression. The ability to deliver and activate immune cells in the tumor microenvironment is a key challenge in cancer immunotherapy. We have developed a novel approach to deliver oncolytic vaccinia virus (VACV) to the tumor microenvironment using matched allogeneic stem cells (MSCs) as a delivery vehicle.

Safety of stromal vascular fraction cells applications in chronic pain

Elliot B. Lander, MD¹, Mark H. Berman, MD, Jackie R. See, MD

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Abstract: Autologous stromal vascular fraction (SVF) can be enzymatically released from liposuction aspirates under local anesthesia. SVF is known to have regenerative, anti-inflammatory, pain-relieving, and immune-modulatory properties. Our translational research group has been studying the safety and efficacy of SVF. Our research group has been studying the safety and efficacy of SVF in patients with chronic pain.

Journal of the American Society of Plastic Surgeons

Original Article

A Prospective Safety Study of Autologous Adipose-Derived Stromal Vascular Fraction Using a Specialized Surgical Processing System

Mark Berman, MD^{1,2} and Elliot Lander, MD²

Abstract: Autologous adipose-derived stromal vascular fraction (SVF) has been proposed as a remedy for a number of inflammatory, autoimmune, and degenerative conditions. This procedure had mainly been evaluated in veterinary medicine and outside the United States when this study was initiated. This study looks at adverse events to evaluate safety as its primary objective and secondarily follows efficacy of SVF as deployed through intra-articular injections and intravenous infusions for a variety of orthopedic and non-orthopedic conditions. We hypothesized that autologous SVF deployment using a specialized surgical processing system (the CSN Time Machine system, trademark name for the MedKhan Liposol/Maxim system; MedKhan, Los Angeles, California) was safe (i.e., minimally acceptable adverse events) and that clinical efficacy could be demonstrated.



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