Biologic Injections and Treatments

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THE UNIVERSITY OF KANSAS HEALTH SYSTEM

Disclosures

- No financial disclosures
- I am not a PhD in cell biology or molecular biology

Overview

- Brief historical recap of biologics
- Ongoing excitement and broad uses
- Basic sciences of biologics
- PRP, Stem Cells, etc.
- Regulations and limitations
- Utilizing Ultrasound
- Ethical Concerns

Historical Context

- 1950s… trauma surgeon, Dr. George Hackett, and other pioneers began working with “local irritants” as a non-surgical approach to joint hypermobility --- coined the procedure “prolotherapy”
- Hackett targeted “weak backs [spinal ligaments]” and progressed to other joints
- 1980s -- Liu et al injected rabbit MCLs with "sclerosing agents" and showed significant increase in collagen fibrils and increased stabilization
- PRP first developed by hematologists to treat thrombocytopenia in 1970s
- Maxillofacial surgeons began using PRP in the 1980s.
- Continued expansion of through early 2000s, and then…

George Hackett M.D.

G.A. Hemwall M.D.

Minneapolis

MINNEAPOLIS, MINN.,

MINNEAPOLIS TRIBUNE

It Hurts Here Dr. G. A. Hemwall, Chicago (left), got a Tuesday from Dr. George S. Hackett, Canto can Academy of Physical Medicine and Rehabilitation ended two the Leamington hotel, and the American Congress of Physical M tation got ready for three days of meetings starting today. Hac calls “an irritating solution” into weak backs to strengthen the puts it, “stimulate production of new bone and fibrous tissue ce weld of ligament to bone.” The method is not generally accepte ed good results over 20 years.

2009 Super Bowl

The New York Times

A Promising Treatment for Athletes, in Blood

Share full article 18

By Alan Schwarz
Feb. 16, 2009

Two of the Pittsburgh Steelers' biggest stars, Hines Ward and Troy Polamalu, used their own blood in an innovative injury treatment before winning the Super Bowl. At least one major league pitcher, about 20 professional soccer players and perhaps hundreds of recreational athletes have also undergone the procedure, commonly called platelet-rich plasma therapy.

Experts in sports medicine say that if the technique's early promise is fulfilled, it could eventually improve the treatment of stubborn injuries like tennis elbow and knee tendinitis for athletes of all types.

Why are we excited?

- Human body has a built-in repair system
  - stem cells, progenitor cells, signaling cells, etc.
- Science is proving that we can harness this healing cascade
- Safe – no known systemic adverse effects
- Customizable – can manipulate preparation techniques to optimize results

Broad Uses

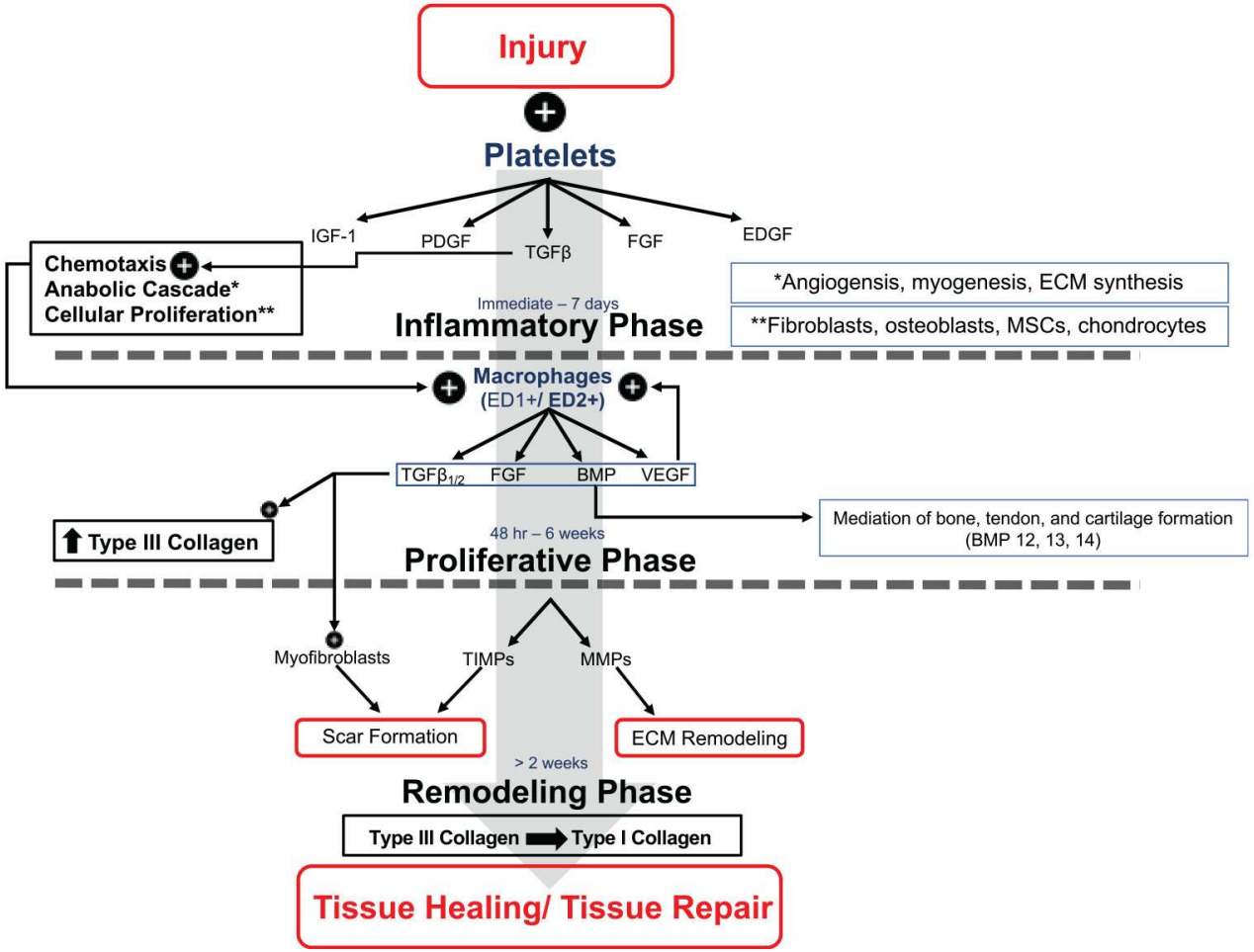
- Cardiac surgery
- Pediatric surgery
- Gynecology
- Urology
- Plastic surgery
- Dermatology
- Ophthalmology
- Orthopedics

But are there too many cooks in the kitchen?

- Advanced PRF (A-PRF)
- Autologous conditioned plasma (ACP)
- Autologous growth factors (AGF)
- Autologous platelet gel (APG)
- Clinical PRP (C-PRP)
- Fibrin-plasma rich in growth factors (FPRGF)
- Leukocyte-poor PRP (LP-PRP)
- Leukocyte-rich PRP (LR-PRP)
- Platelet-derived factor concentrate (PFC)
- Pure PRP (P-PRP)
- Platelet fibrin sealant (PFS)
- Platelet-leukocyte gel (PLG)
- Platelet lysate (PL)
- Activate platelet releasate (aPR)
- PRF
- PRF Matrix
- Preparation rich in growth factors
- Albumen gel PRFM (Al-PRF)
- Injectable PRF (i-PRF)
- Injectable leukocyte-PRF (iL-PRF)

Basic Sciences of Autologous Biologics

- Cellular therapies derived from patient's own tissue
  - Platelet rich plasma (PRP), Bone Marrow Concentrate (BMAC), Adipose Derived Stem Cells (ADSCs)
- *Potential* to augment healing for multiple musculoskeletal conditions
- Concentrate endogenous growth factors in tissues with limited intrinsic healing capacity


Injury
Platelets
IGF-1
PDGF
TGFβ
FGF
EDGF
Chemotaxis
Anabolic Cascade*
Cellular Proliferation**
*Angiogensis, myogenesis, ECM synthesis
**Fibroblasts, osteoblasts, MSCs, chondrocytes
Immediate – 7 days
Inflammatory Phase
Macrophages
(ED1+/ ED2+)
TGFβ1/2
FGF
BMP
VEGF
Type III Collagen
Mediation of bone, tendon, and cartilage formation
(BMP 12, 13, 14)
48 hr – 6 weeks
Proliferative Phase
Myofibroblasts
TIMPs
MMPs
Scar Formation
ECM Remodeling
> 2 weeks
Remodeling Phase
Type III Collagen
Type I Collagen
Tissue Healing/ Tissue Repair

PRP

Stem Cells

- Bone Marrow Concentrate
- Adipose Derived Stem Cells

Amniotic-Based Materials

Exosomes

Biological Cell Scaffolds

What is PRP?

- Processed liquid fraction of harvested fresh peripheral blood with a platelet concentration above baseline value (more later)
- Complex composition of multi-cellular components
  - Over 300 distinct cytokines and growth factors
- Components
  - Alpha granules → accelerate healing, reduce inflammation, and stimulate tissue regeneration
  - Dense granule constituents → local immune modifiers
  - Angiogenic factors →new blood vessel formation

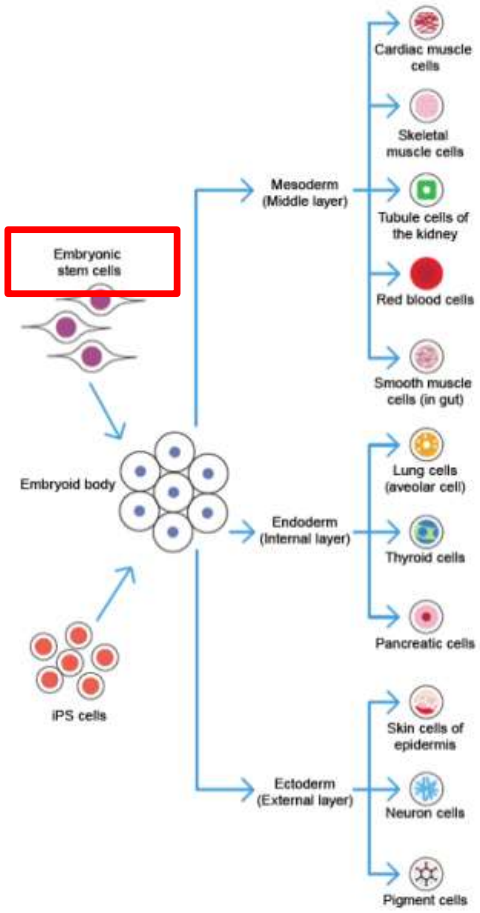
What are Stem Cells?

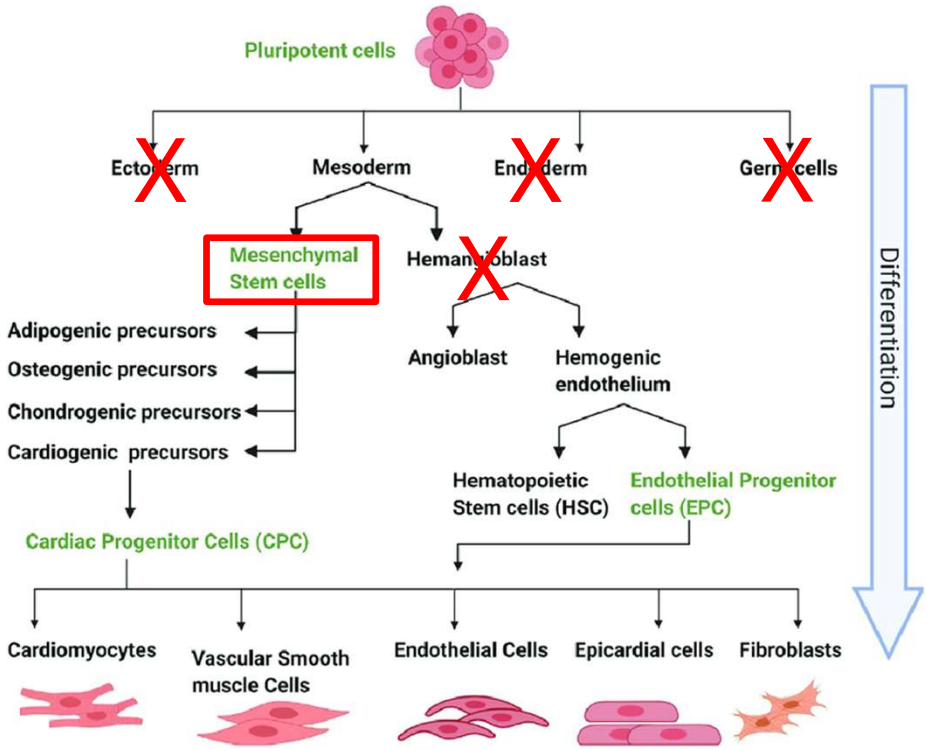
Embryonic

- Pluripotent
- Early-stage embryos (blastocyst, 4-7 days old)
- ability for self-renewal; proliferate indefinitely
- can become all three germ layers
- True "regeneration"

Adult Stem Cell

- “multipotent”
- Differentiated; "mature"
- Bone marrow, skin, adipose, etc.
- Low chance of immune rejection or tumor formation
- Limited/no ethical concerns


Embryonic stem cells
Embryoid body
iPS cells
Mesoderm (Middle layer)
Endoderm (Internal layer)
Ectoderm (External layer)
Cardiac muscle cells
Skeletal muscle cells
Tubule cells of the kidney
Red blood cells
Smooth muscle cells (in gut)
Lung cells (aveolar cell)
Thyroid cells
Pancreatic cells
Skin cells of epidermis
Neuron cells
Pigment cells


Pluripotent cells
Ectoderm
Mesoderm
Endoderm
Germ cells
Mesenchymal Stem cells
Hemangioblast
Adipogenic precursors
Osteogenic precursors
Chondrogenic precursors
Cardiogenic precursors
Angioblast
Hemogenic endothelium
Hematopoietic Stem cells (HSC)
Endothelial Progenitor cells (EPC)
Cardiac Progenitor Cells (CPC)
Cardiomyocytes
Vascular Smooth muscle Cells
Endothelial Cells
Epicardial cells
Fibroblasts
Differentiation

Bone Marrow Aspirate Concentrate

- Common source of mesenchymal stem cells
  - Easily accessed (typically iliac crest), low(er) cost
  - +/- painful harvest, safe
- Considered “minimal cellular manipulation” by FDA
- Similar equipment needed to PRP
- Cassano et al compared PRP with BMAC
  - BMAC had 11.8x leukocytes, 19.4x neutrophils, and 2.5x platelets
  - “medicinal drugstore for immunomodulation and anabolic stimulation of the host microenvironment”
- How do we optimize outcomes?
- Is there synergy with PRP?

Adipose-derived stem cells

- Micro-fragmented adipose (MFAT) vs stromal vascular fraction (SVF)
  - MFAT – mechanical
  - SVF – enzymatic
- +/- painful harvest
- More MSCs than BMAC?
- Regulatory challenges given “manipulation” – no culturing or altering
- Encouraging preliminary studies as a future non-surgical treatment option
- Systematic review by Hohmann et al (2025) looked at micro-fragmented adipose tissue versus other orthobiologics for treating symptomatic knee arthritis and found it “as effective” and showed improved pain scores and functional outcomes

September 27, 2024

In *United States v. California Stem Cell Treatment Center, Inc.*[1], the FDA brought a lawsuit against doctors who create and administer a stem cell mixture called stromal vascular fraction (SVF), alleging violations of the Food, Drug, and Cosmetic Act (FDCA). The district court ruled in favor of the doctors, but the Ninth Circuit Court of Appeals court reversed that decision.

SVF as a "Drug

The Ninth Circuit Court of Appeals held that SVF constitutes a "drug" under the FDCA based on the plain text of the statute. SVF is administered to treat diseases and affect body structures, fitting the definition of a drug. The court rejected arguments that this interpretation improperly intrudes on medical practice or raises major questions about FDA authority.

Same Surgical Procedure Exception

The court rejected the doctors' argument that their same-day SVF treatment is exempt from FDA regulation under the "same surgical procedure" exception. This exception applies when an establishment removes and implants the same HCT/Ps (human cells, tissues, or cellular/tissue-based products) during one surgical procedure. The court held that for the SVF procedure, the

Conclusion

The appeals court reversed the district court's judgment in favor of the doctors and remanded the case for further proceedings. The court's decision means the FDA can regulate SVF treatments as drugs under the FDCA, requiring premarket approval to demonstrate safety and efficacy.

judgment without unfair surprise.

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[1] No. 22-56014 D.C. No.5:18-cv-01005-JGB-KK (2024)

Amniotic-Based Materials

- Some potential in complex tissue regeneration; possible evidence of some anti-microbial properties, which makes them appealing.
- Typically obtained from donors who undergo an uncomplicated cesarean section
  - Screened, sterilized, and processed → can be costly and complicated to rely on donors
- Paucity of studies in human trials with MSK applications (small case series, or non-randomized trials); some promising animal studies
- Panero et al were **unable** to identify presence of mesenchymal stem cells in several of the commercially available products that are marketed as “stem cell therapy”

Exosomes

- Extracellular vesicles (EVs) contain the “cargo” of parent cell and are involved in paracrine effects that impact local tissue environment
- Fundamental in the role of intercellular communication and homeostasis
- Can promote cartilage regeneration, decrease inflammation/pain in arthritis, improve collagen organization in tendinopathy
- Need guidelines on nomenclature and characterization
- No FDA approved exosome/EV therapies, despite aggressive marketing

Biological Cell Scaffolds

- Utilized to fill defects and provide stable microenvironment for new tissue to develop.
- Can be ‘customized’ to carry specific growth factors to promote desired tissue growth; work to mimic extracellular matrix
- HA, fibrin, collagen, etc.
- Bone regeneration, cartilage repair, tendon/ligament regeneration, wound healing, etc.
- Solo treatment? Adjunct PRP or BMAC?

Orthopedics Applications

1) Chronic tendinopathy
    - PF, Achilles, Rotator Cuff. etc
2) Acute ligamentous injuries
    - i.e. MCL injury or Achilles injury
3) Muscle injuries
    - Decrease in return to play timeline, but at what cost?
4) Intraoperative augmentation
    - Rotator Cuff, meniscal repair, ACL repair/reconstruction, bone healing, etc.
5)Osteoarthritis
    - Knee OA, Hip OA, glenohumeral OA, etc.

- Trunz et al looked at hamstring injuries in 55 athletes in a 2022 study. Athletes with grade 2 hamstring strains treated with a combination of hematoma aspiration and PRP injection had a significantly shorter return-to-play and a lower recurrence rate compared with athletes receiving conservative treatment.

- 2020 study by Centeno et al looked at partial and full thickness supraspinatus tears and sowed “significant differences” in pain and function outcomes in the PRP + BMAC group compared to exercise therapy alone.

Regenerative Rehabilitation

- Educate the patient as to why physical therapy is a pivotal part of the regenerative/orthobiologic landscape
- PT helps to **stimulate** and **accelerate** the healing process by applying controlled movement and stress to the treated area
  - Encourages proper motion and the re-establishment of normal function
  - Optimal loading is tissue and adaptation specific
- Will progress through rehab based on expected healing cascade
  - i.e. inflammatory phase, proliferative phase, and remodeling phase

*For me, not a consideration, but a **requirement**.*

Limitations of Orthobiologics

- LACK OF CONSENSUS
- Centrifuge performance variations
  - Speed, acceleration/deceleration
- Cellular yields
  - Platelet concentration
  - Non-platelet cellular constituents
  - Amount of whole blood
- Accuracy of delivery
- Finances → cost limitations, insurance coverage, funds for research

What we need to figure out…

- Recent analysis reviewed 105 studies on PRP processing for musculoskeletal conditions (105 studies) --- only 11.5% of studies reported on all necessary variables of PRP processing required to reproduce the protocol
  - Ideal platelet concentration
  - Injectate dose
  - Blood harvest
  - Do we include local anesthetic?
  - Does needle size matter for blood draw?
  - Do you buffer the PRP?
  - Pre/post procedure NSAIDS?
  - Injection series vs single dose?
  - Added biological scaffold?

And that's just for PRP!

My Goals with PRP Dosing

- Baseline platelet count typically ranges from 150,000 to 350,000 platelet/µl (mean ~2.5×10^5 platelet/µl).
- Goal is concentration > 10 million platelets (10.0×10^5 platelet/µl)
  - Improved pain killing effects, better outcomes in vivo/vitro, reduction in visual analog pain scores, etc.
- Centrifuge settings adjusted from patient to patient based on blood draw amount, patient age, estimated baseline platelet count, and goal final injectate amount
- Limit red blood cells
- Leukocyte count dependent on patient specifics and where/what I'm injecting

Do we have *anything* figured out?

PLoS One. 2016 Jun 3;11(6):e0156137. doi: 10.1371/journal.pone.0156137. eCollection 2016.

Leukocyte-Rich Platelet-Rich Plasma Injections Do Not Up-Modulate Intra-Articular Pro-Inflammatory Cytokines in the Osteoarthritic Knee

Erminia Mariani [1,2], Valentina Canella [1], Luca Cattini [1], Elizaveta Kon [3], Maurilio Marcacci [3], Berardo Di Matteo [3], Lia Pulsatelli [1], Giuseppe Filardo [3]

Affiliations + expand

PMID: 27258008 PMCID: PMC4892682 DOI: 10.1371/journal.pone.0156137

Abstract

Introduction: The presence of leukocytes in platelet concentrates is deemed to cause deleterious effects when injected intra articularly. The aim of this study is to analyse both local and systemic effects induced by leukocyte-rich Platelet-rich Plasma (PRP) injections through a proteomic characterization of serial synovial fluid and blood samples obtained from subjects treated for knee OA. Secondary aim was to compare the effects on knee homeostasis and systemic response with those obtained with visco-supplementation.

Conclusions: In contrast with the evidence reported by "in vitro" studies, where a cellular pro-inflammatory response appears to be induced by the presence of leukocytes, these results suggest that the presence leukocyte-rich PRP doesn't induce a relevant in vivo up regulation of pro-inflammatory mediators.

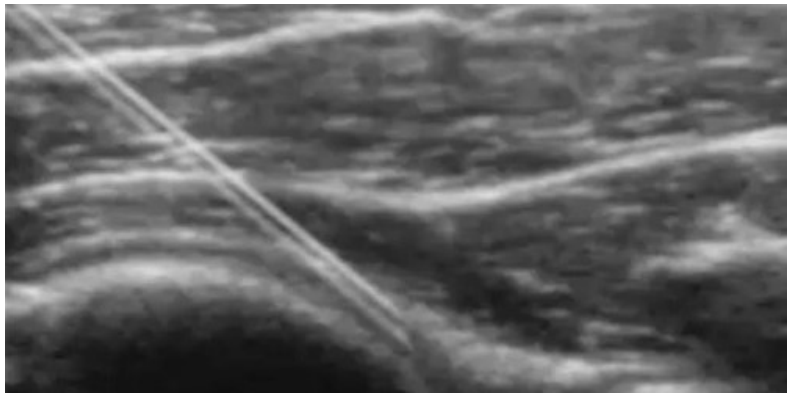
treatment whereas anti-inflammatory ones were nearly undetectable. L-PRP administration did not modulate significant changes of cytokine concentrations either in synovial fluid or plasma, whatever the time points analyzed. No different trend was observed between L-PRP and HA administration in terms of pro- and anti-inflammatory cytokines, as well as growth factors.

Conclusions: In contrast with the evidence reported by "in vitro" studies, where a cellular pro-inflammatory response appears to be induced by the presence of leukocytes, these results suggest that the presence leukocyte-rich PRP doesn't induce a relevant in vivo up regulation of pro-inflammatory mediators.

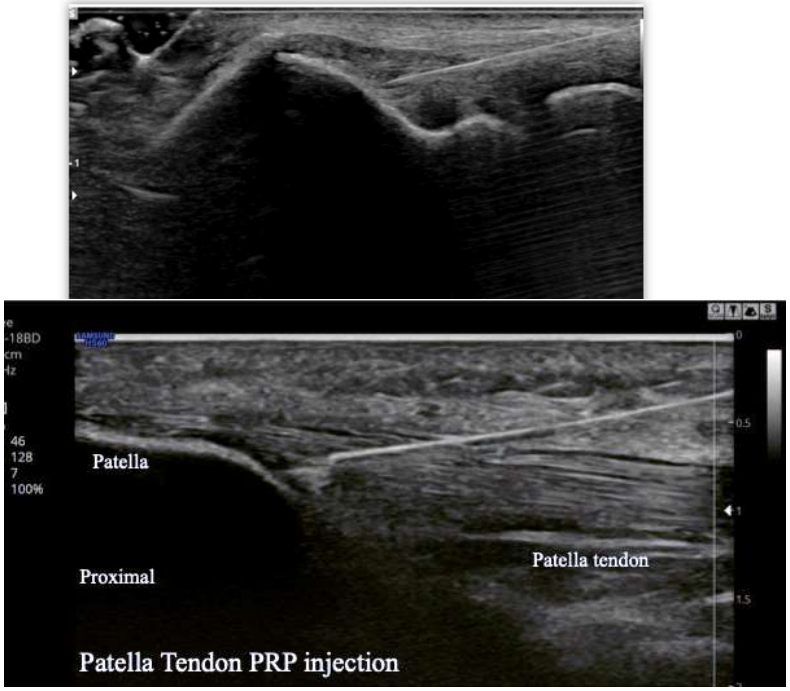
‘Minimally Manipulated’

- Understand what is legal in the United States
  - “minimally manipulated” – FDA regulations within ‘Human cells, tissues, and cellular based products (HCT/P) through the Public Health Services (PHS) Act.
- Anything beyond ‘minimally manipulated’ is not approved and are off-label if marketed/distributed.
- Culture expansion is illegal in the united states
- ”medical tourism”

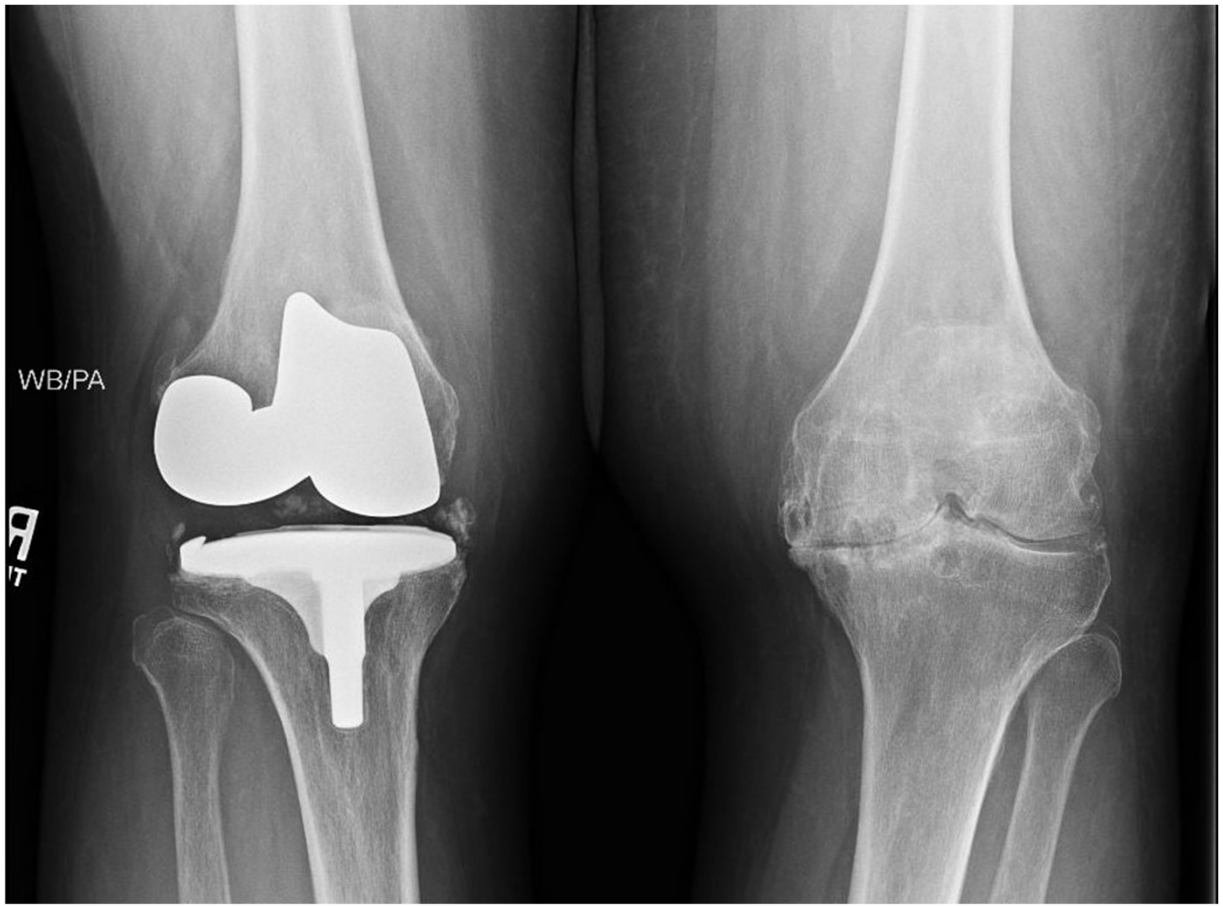
Use of Ultrasound



- “More accurate”
- “Improved pain management scores”
- “superior benefit”
- “Higher accuracy”



My final point…


WB/PA

Roll over image to zoom in

Roll over image to zoom in

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Use for	Face
Scent	No Scent
Special Ingredients	Hyaluronic Acid

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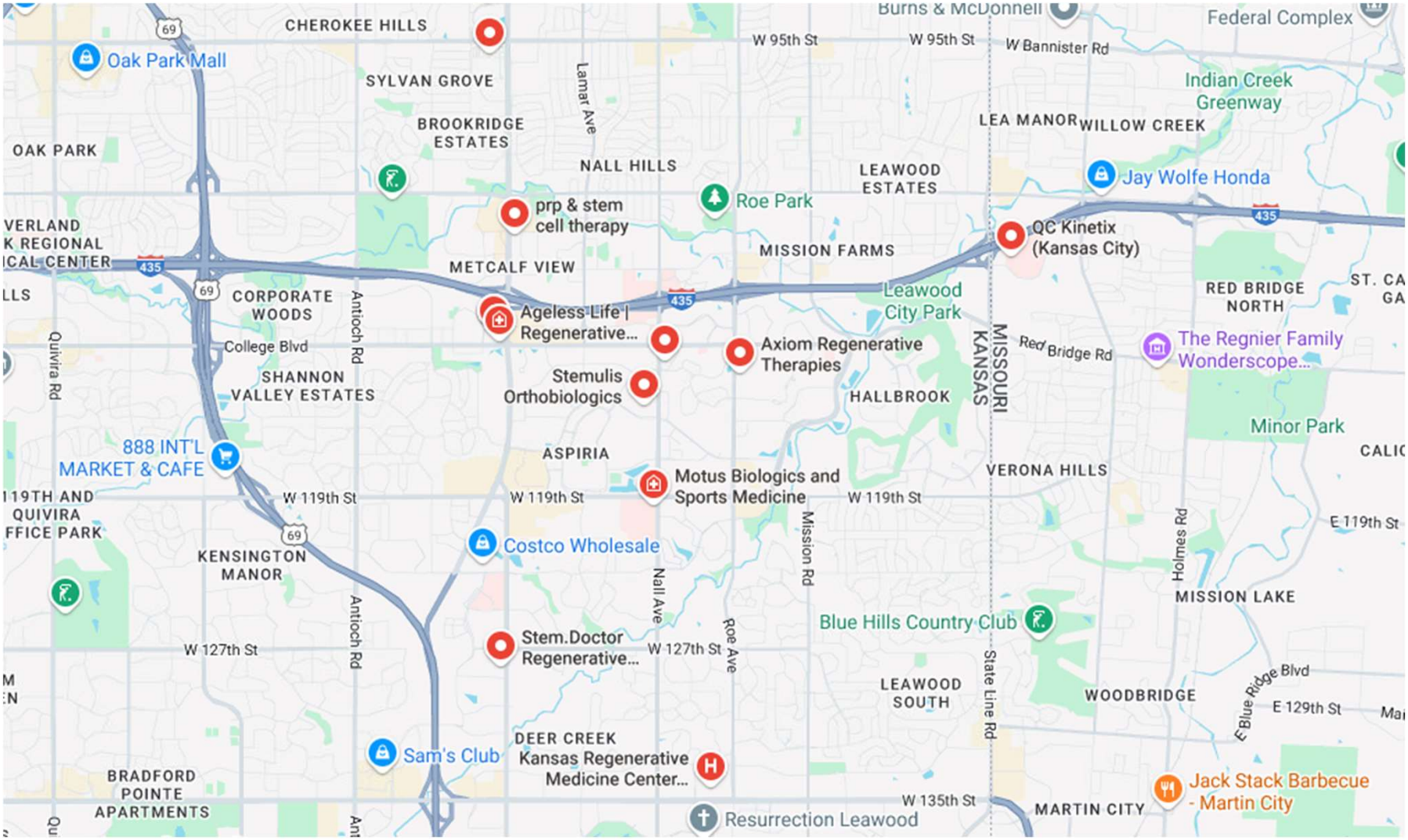
Unit Count	16.9 Fluid Ounces
Item Form	Liquid
Item Weight	2.4 Pounds

See more

About this item


Burns & McDonnell
Federal Complex
CHEROKEE HILLS
Oak Park Mall
W 95th St
W 95th St
W Bannister Rd
Indian Creek Greenway
SYLVAN GROVE
BROOKRIDGE ESTATES
Lamar Ave
LEA MANOR
WILLOW CREEK
OAK PARK
NALL HILLS
LEAWOOD ESTATES
Jay Wolfe Honda
Roe Park
prp & stem cell therapy
QC Kinetix (Kansas City)
MISSION FARMS
METCALF VIEW
CORPORATE WOODS
Antioch Rd
Ageless Life | Regenerative...
Leawood City Park
RED BRIDGE NORTH
College Blvd
Axiom Regenerative Therapies
Red Bridge Rd
The Regnier Family Wonderscope...
Quivira Rd
SHANNON VALLEY ESTATES
Stemulis Orthobiologics
HALLBROOK
MISSOURI
KANSAS
Minor Park
888 INT'L MARKET & CAFE
ASPIRIA
Motus Biologics and Sports Medicine
VERONA HILLS
W 119th St
W 119th St
W 119th St
E 119th St
KENSINGTON MANOR
Costco Wholesale
Mission Rd
Holmes Rd
MISSION LAKE
Nall Ave
Roe Ave
Blue Hills Country Club
W 127th St
W 127th St
Stem.Doctor Regenerative...
LEAWOOD SOUTH
State Line Rd
WOODBRIDGE
E Blue Ridge Blvd
E 129th St
DEER CREEK
Sam's Club
Kansas Regenerative Medicine Center...
BRADFORD POINTE APARTMENTS
W 135th St
MARTIN CITY
Jack Stack Barbecue - Martin City
Resurrection Leawood

Are we moving too fast?

- Marketing may be preceding science
- Is the marketing ethical?
- In vivo versus in vitro versus clinical applications
- “Regenerative medicine”
- **WHERE ARE THE STUDIES??**

Recap

- The basic science makes sense and *should* be effective in modulating inflammation, pain, and promoting regeneration
- There are broad applications of various orthobiologics
- Including ‘regenerative rehab’ is imperative
- Ultrasound offers a no-harm approach to improving precision and accuracy
- Careful with wording and injectate labeling → “stem cells”

Open Access Review

Mesenchymal Stem Cells for Regenerative Medicine

by Yu Han [1,2,†], Xuezhou Li [1,2,†], Yanbo Zhang [3,*], Yuping Han [4,*], Fei Chang [1,*] and Jianxun Ding [2]

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Research | Open access | Published: 07 June 2013

Platelet-rich plasma preparation for regenerative medicine: optimization and quantification of cytokines and growth factors

Paola Romina Amable, Rosana Bizon Vieira Carias, Marcus Vinicius Telles Teixeira, Ítalo da Cruz Pacheco, Ronaldo José Farias Corrêa do Amaral, José Mauro Granjeiro & Radovan Borojevic

Stem Cell Research & Therapy **4**, Article number: 67 (2013) | Cite this article

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Thank you

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