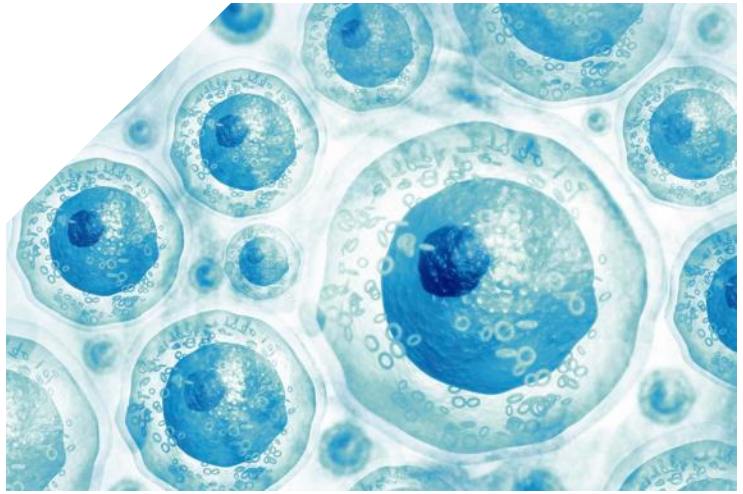
Bioactive Injection Therapies for Knees and Shoulders



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…..going beyond “stem cell” therapy

Phil Davidson, MD

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Bioactive injections in Orthopedics

- Integrated Modern Orthopedic Care
- Noninvasive Treatments
- Injection Therapies
- Surgery
- NO PRECONCEIVED BIAS
- Individualized Treatment Plan

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Personalized, Accurate, Holistic Diagnosis

….first things first

- Makes no sense to lead encounter with bias/chosen treatment…..
- Therefore… treatment is systematically, scientifically and carefully implemented for each unique individual
- Not advocating for any particular treatment
- Patient Advocate with WIDE array of options

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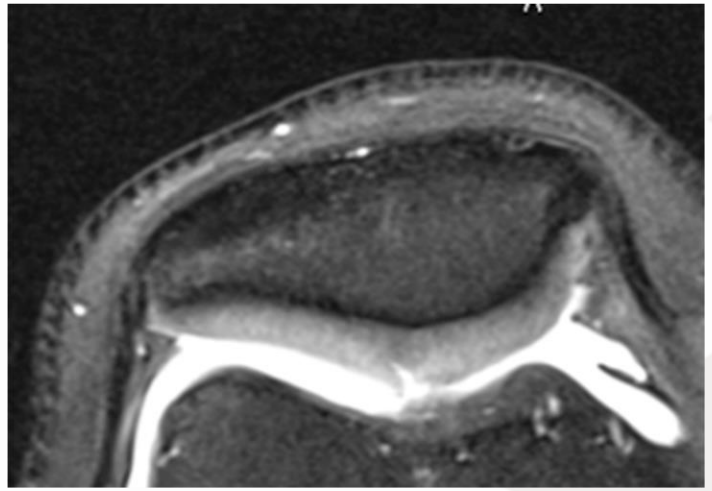
Personalized Diagnostics

- Understand Patient Goals
- Specific Anatomic Diagnosis
- Imaging Studies
- Identify Comorbidities



Non-Invasive Management of Arthritis

- NSAIDS: Oral Anti-inflammatories
- Dietary supplements and modification
- Physical Therapy
- Weight loss
- Bracing

Injection Therapies for Damaged Tendons and Joints

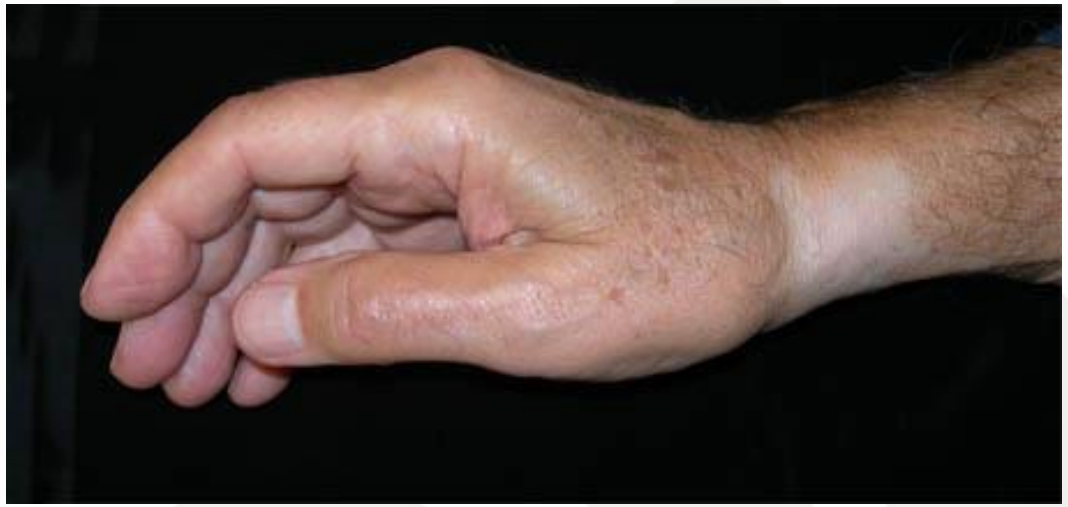
- Corticosteroids “cortisone”
- Viscosupplementation (Hyaluronic Acid)
- PRP – Leukoctye Poor (for joints)
- PRP – Leukocyte Rich (for soft tissue)
- Alpha-2 Macroglobulin (A2M) Therapy
- Autologous Stem Cells
- Amniotic Tissue Graft- Allogeneic “Stem Cells”
- Exosome Therapy

Corticosteroid “cortisone”

- Can be helpful, frequently used
  - Rapidly reduce pain due to inflammation
  - Last for several weeks to months
  - Joints, Spine Radiculopathy, Bursitis, Tendonitis, Neural Inflammation (CTS)
  - New, 12 week sustained steroid

Corticosteroid Negative/Side Effects

- Atrophy
- Depigmentation
- Hyperglycemia
- Infection
- Post injection flare
- Tissue structure weakening, tendon ruptures



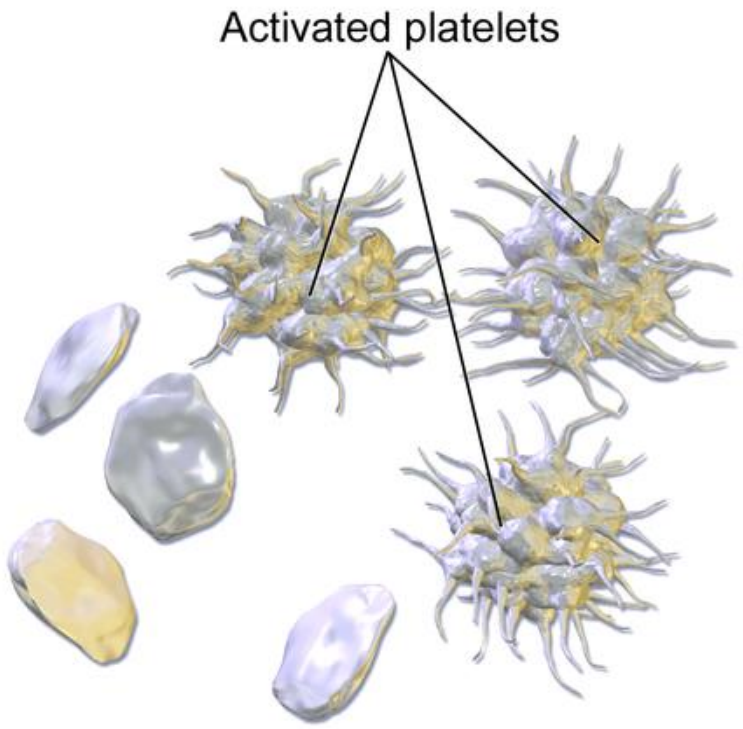
Viscosupplementation – Hyaluronic Acid

- Brands: Synvisc, Orthovisc, Supatz, Euflexa…
- Potential to address aching pain - 6 months
- No reparative capacity
- Covered by some insurances
- Works well in some patients, not others

Biologics to treat Osteoarthritis

- Biologic treatment is interactive
- KEY ELEMENTS ALL REQUIRED:
  - Growth factors, cells, scaffold
  - Mechanically favorable environment
- A “Nutrient Rich Soup” includes;
  - Cells (Platelets, MSCs)
  - Growth factors (from platelets, plasma, amniotic, exosomes)
  - Scaffolds
- Potential sources of this “Soup”:
  - Bone Marrow Aspirate, Adipose, PRP, Amniotic Fluid, Exosomes

PRP – What is it?

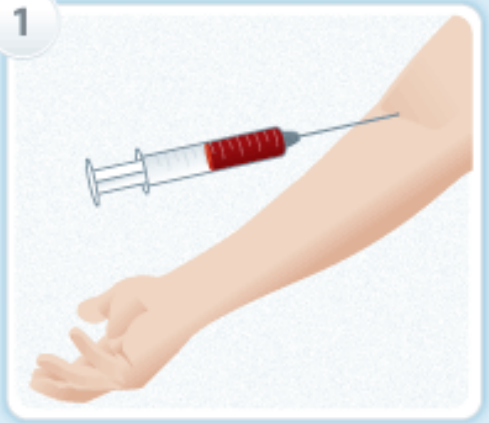


- A concentration of one's own platelets
- Platelets are the body's cells that conduct healing
- They make Growth Factors (active agent, proteins)
- Can be processed in a variety of ways
- Blood is taken from vein
- Centrifuged and Filtered

PRP Therapy

PROCESS OF **PRP THERAPY**

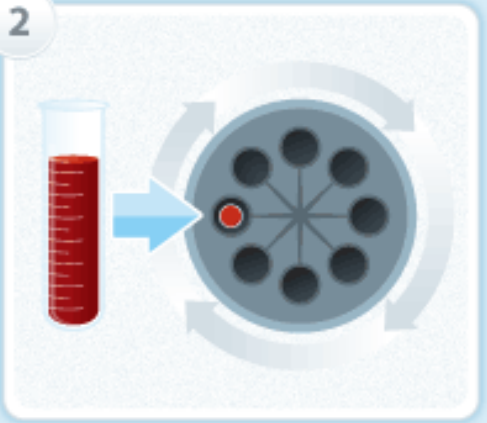
1



Collect blood

30-60ml of blood is drawn from the patient's arm.

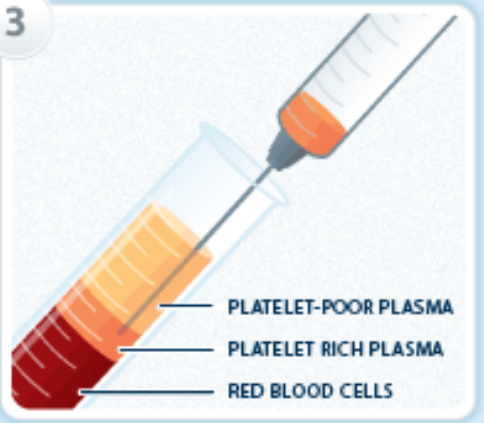
2



Separate the platelets

The blood is then placed in a centrifuge. The centrifuge spins and separates the platelets from the rest of the blood components.

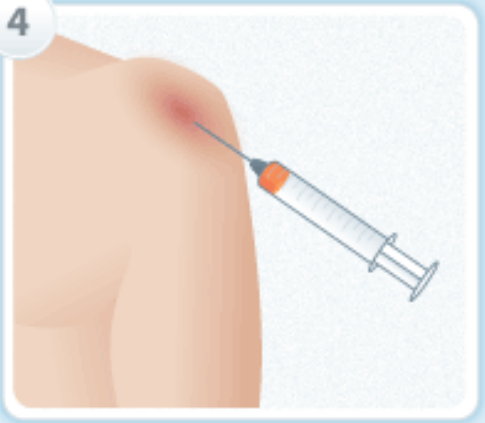
3



Extract platelet-rich plasma

Extract 3-6ml of platelet-rich plasma.

4



Inject injured area with PRP

Using the concentrated platelets, we increase the growth factors up to eight times, which promotes temporary relief and stops inflammation.

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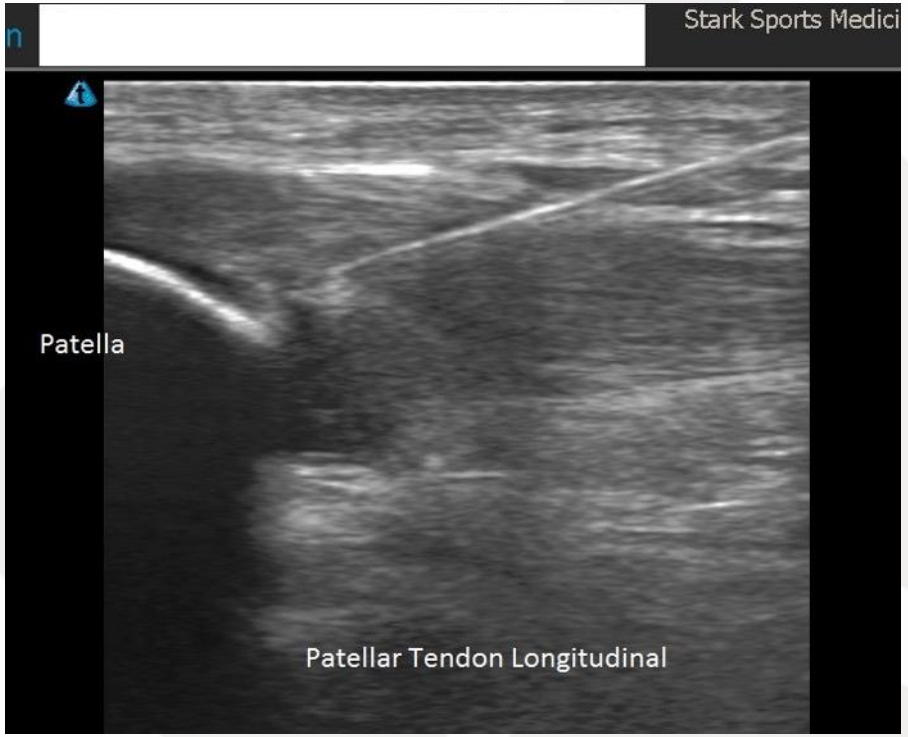
PRP in Cartilage/Joint Repair

- Promotes Cartilage Growth and Healing:
  - Chondrocytes and MSCs exposed to PRP show increased cell proliferation and cartilage extra-cellular matrix synthesis of PG and Type II collagen
- Promotes Better Joint Health
  - Synoviocytes cultured in PRP produce more HA
    - Better lubrication and chondroprotection
- Decreases Pain of Arthritis
  - Better pain scale outcomes with PRP injections versus HA injections for management of knee OA
- Leukocyte POOR PRP superior for use in joint

PRP to Treat Damaged Tendons

Ultrasound used for precise localization



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PRP to Treat Damaged Tendons

- PRP shown to be **SUPERIOR** to corticosteroids for healing
- Leukocyte RICH PRP used for tendons
- Tendons Treated in Knee, Shoulder, and other areas

PRP Combined with HA

- Combined treatment used to sustain and improve joint health
- PRP - Leukocyte Poor AND HA
- Can be administered regularly to promote long-term joint health and pain relief

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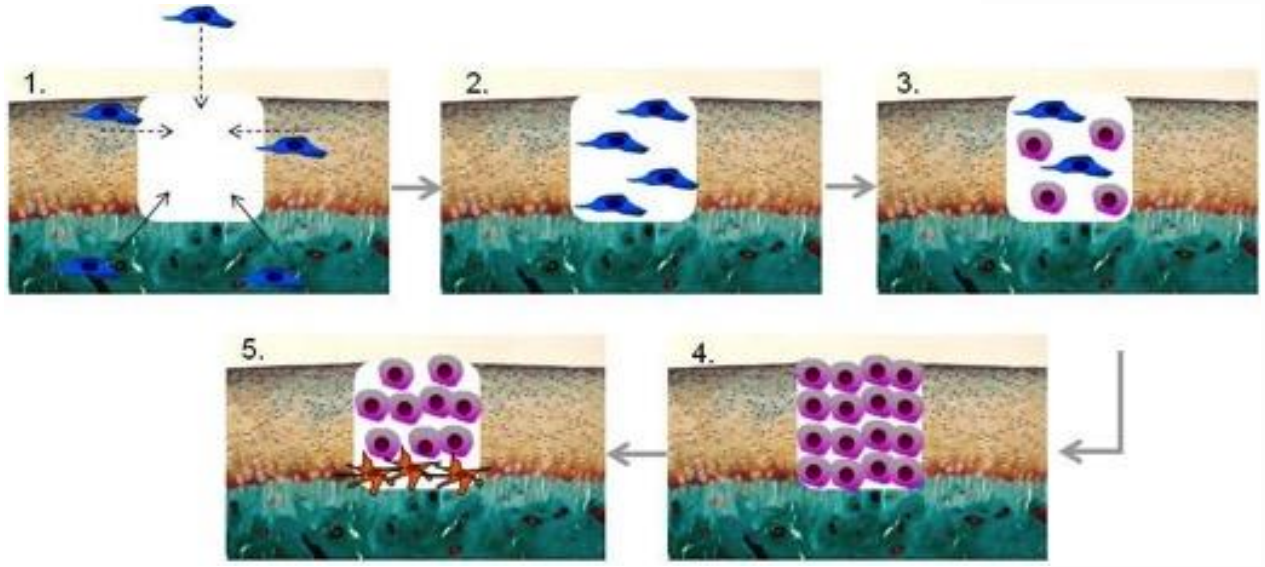
Alpha-2 Macroglobulin “A2M”

Natural Joint Protector

- A2M protects the joint
  - A2M is a large molecule that can protect the joint from arthritis by inhibiting/binding the “breakdown” enzymes (proteases) of arthritis
  - The body naturally has A2M, in small quantities
- Process called APIC-A2M can make a 6x concentration from your blood for joint injection
- FAC testing of joint fluid determines if you are a candidate

Stem Cells

Reparative Promise in Worn Joints, Damaged Tendons and Ligaments



- Anti-inflammatory and Pain relief effect
- Meniscal Regeneration
- Restore Cartilage
- Accelerate Tendon and Ligament Healing

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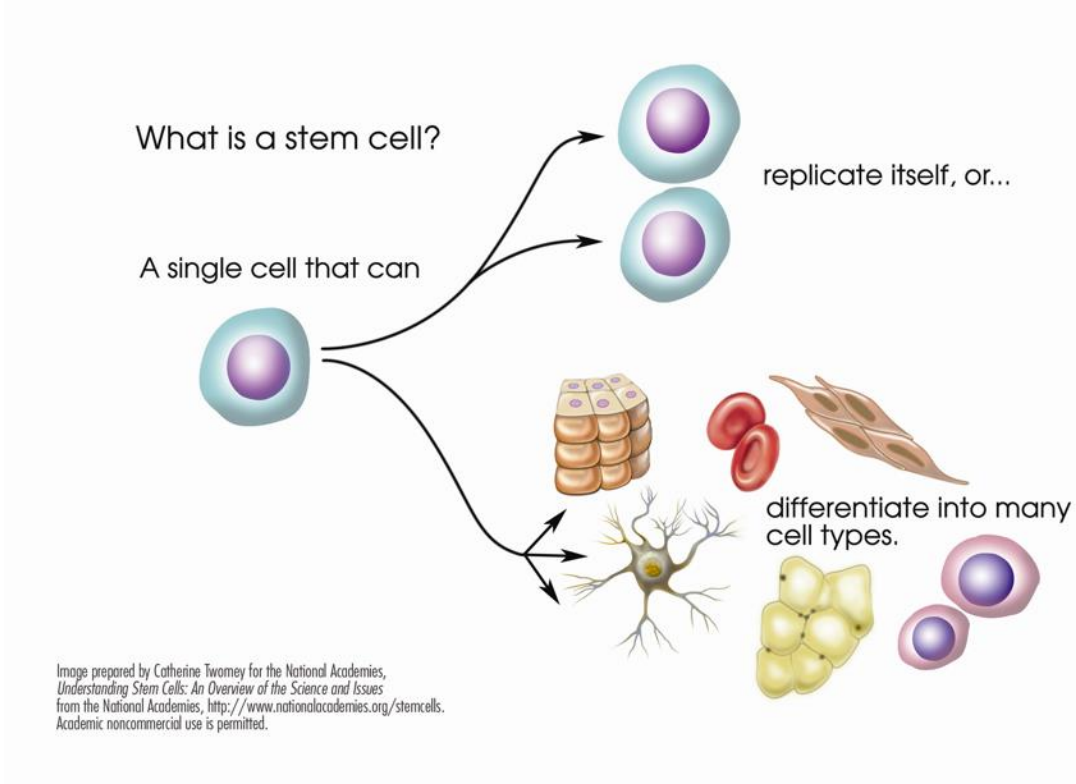
Source of stem cells?

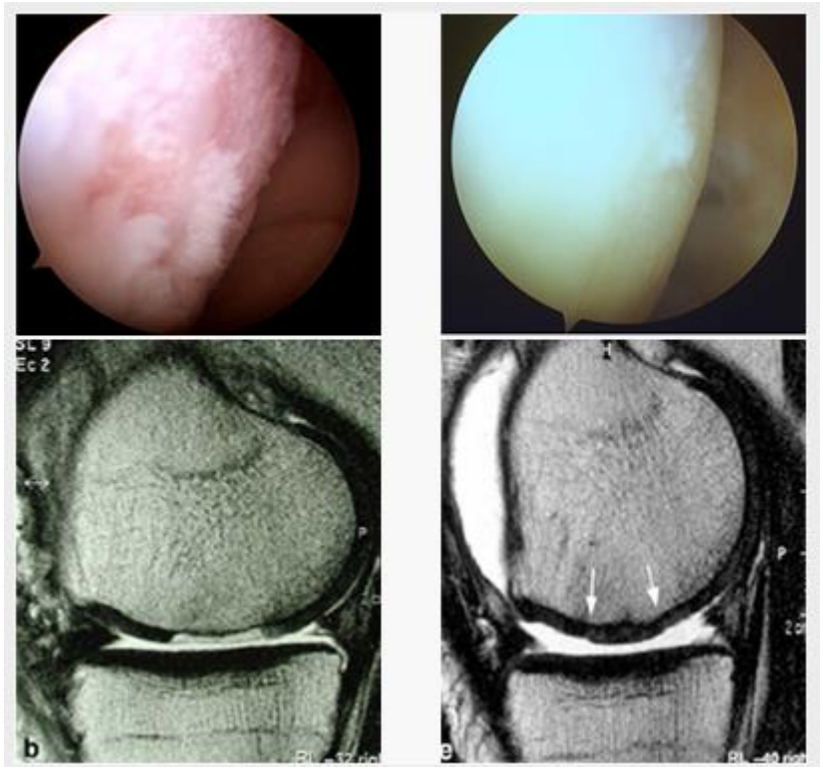


- Autogenous
  - Bone Marrow
  - Adipose
  - Whole Blood
- US: no expansion
- Allograft
  - Amniotic Tissues
  - Wharton's Jelly
  - CFUs

MSC - stem or “signaling” cells

- “Mesenchymal Signaling Cells"
- MSC’s are undifferentiated cells
  - Capacity for prolonged self-renewal
  - Ability to differentiate into specialized cell types
  - By definition they are NOT immunogenic
  - They signal and communicate with surroundings
- Have shown enhanced cartilage, tendon and meniscus healing
- These results have increased patient awareness and demand

MSCs in Orthopedics

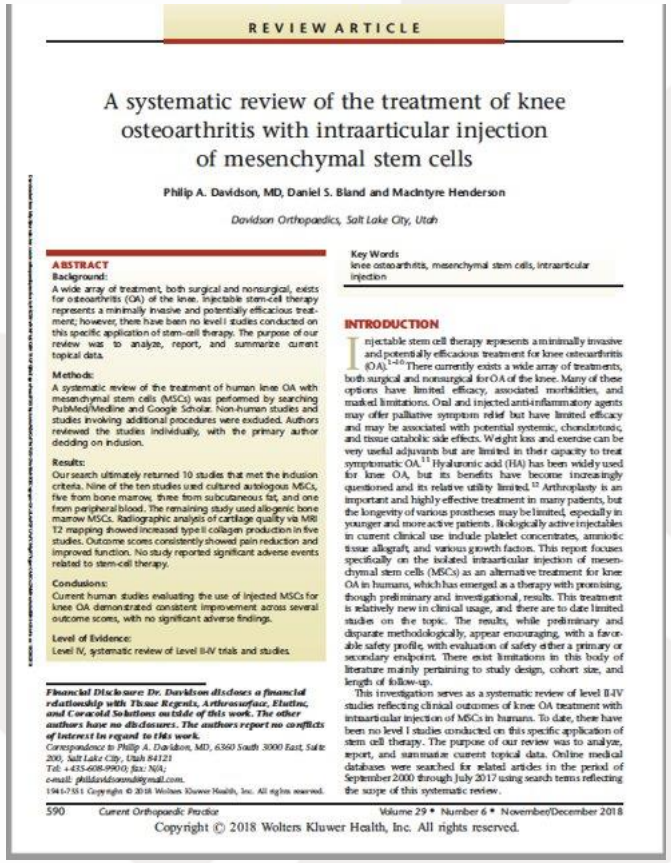


- Regeneration technology rather than replacement
- Harness your own body's ability to heal
- Not taking drugs
- You are using your own cells to heal your tissues
- Stem cells and their byproducts have the potential to reverse the trend of degeneration, not just hide it

A Systematic Review of the Treatment of Knee Osteoarthritis with intraarticular injection of mesenchymal stem cells.

Davidson, P., Bland, D., Henderson, M, Current Ortho Practice, Vol 29, No 6, 590-596.

- 10 studies
- Knee injection of MSCs for arthritis
- Safe, no complications from treatment
- Consistent improvement in clinical outcomes



REVIEW ARTICLE

A systematic review of the treatment of knee osteoarthritis with intraarticular injection of mesenchymal stem cells

Philip A. Davidson, MD, Daniel S. Bland and MacIntyre Henderson

Davidson Orthopaedics, Salt Lake City, Utah

ABSTRACT

Background:
A wide array of treatment, both surgical and nonsurgical, exists for osteoarthritis (OA) of the knee. Injectable stem-cell therapy represents a minimally invasive and potentially efficacious treatment; however, there have been no level I studies conducted on this specific application of stem-cell therapy. The purpose of our review was to analyze, report, and summarize current topical data.

Methods:
A systematic review of the treatment of human knee OA with mesenchymal stem cells (MSCs) was performed by searching PubMed/Medline and Google Scholar. Non-human studies and studies involving additional procedures were excluded. Authors reviewed the studies individually, with the primary author deciding on inclusion.

Results:
Our search ultimately returned 10 studies that met the inclusion criteria. Nine of the ten studies used cultured autologous MSCs, five from bone marrow, three from subcutaneous fat, and one from peripheral blood. The remaining study used allogenic bone marrow MSCs. Radiographic analysis of cartilage quality via MRI T2 mapping showed increased type II collagen production in five studies. Outcome scores consistently showed pain reduction and improved function. No study reported significant adverse events related to stem-cell therapy.

Conclusions:
Current human studies evaluating the use of injected MSCs for knee OA demonstrated consistent improvement across several outcome scores, with no significant adverse findings.

Level of Evidence:
Level IV, systematic review of Level II-IV trials and studies.

Key Words
knee osteoarthritis, mesenchymal stem cells, intraarticular injection

INTRODUCTION

Injectable stem cell therapy represents a minimally invasive and potentially efficacious treatment for knee osteoarthritis (OA).[1-10] There currently exists a wide array of treatments, both surgical and nonsurgical for OA of the knee. Many of these options have limited efficacy, associated morbidities, and marked limitations. Oral and injected anti-inflammatory agents may offer palliative symptom relief but have limited efficacy and may be associated with potential systemic, chondrotoxic, and tissue catabolic side effects. Weight loss and exercise can be very useful adjuvants but are limited in their capacity to treat symptomatic OA.[11] Hyaluronic acid (HA) has been widely used for knee OA, but its benefits have become increasingly questioned and its relative utility limited.[12] Arthroplasty is an important and highly effective treatment in many patients, but the longevity of various prostheses may be limited, especially in younger and more active patients. Biologically active injectables in current clinical use include platelet concentrates, amniotic tissue allograft, and various growth factors. This report focuses specifically on the isolated intraarticular injection of mesenchymal stem cells (MSCs) as an alternative treatment for knee OA in humans, which has emerged as a therapy with promising, though preliminary and investigational, results. This treatment is relatively new in clinical usage, and there are to date limited studies on the topic. The results, while preliminary and disparate methodologically, appear encouraging, with a favorable safety profile, with evaluation of safety either a primary or secondary endpoint. There exist limitations in this body of literature mainly pertaining to study design, cohort size, and length of follow-up.

This investigation serves as a systematic review of level II-IV studies reflecting clinical outcomes of knee OA treatment with intraarticular injection of MSCs in humans. To date, there have been no level I studies conducted on this specific application of stem cell therapy. The purpose of our review was to analyze, report, and summarize current topical data. Online medical databases were searched for related articles in the period of September 2000 through July 2017 using search terms reflecting the scope of this systematic review.

***Financial Disclosure:** Dr. Davidson discloses a financial relationship with Tissue Regenix, Arthrosurface, Elutinc, and Coracoid Solutions outside of this work. The other authors have no disclosures. The authors report no conflicts of interest in regard to this work.*

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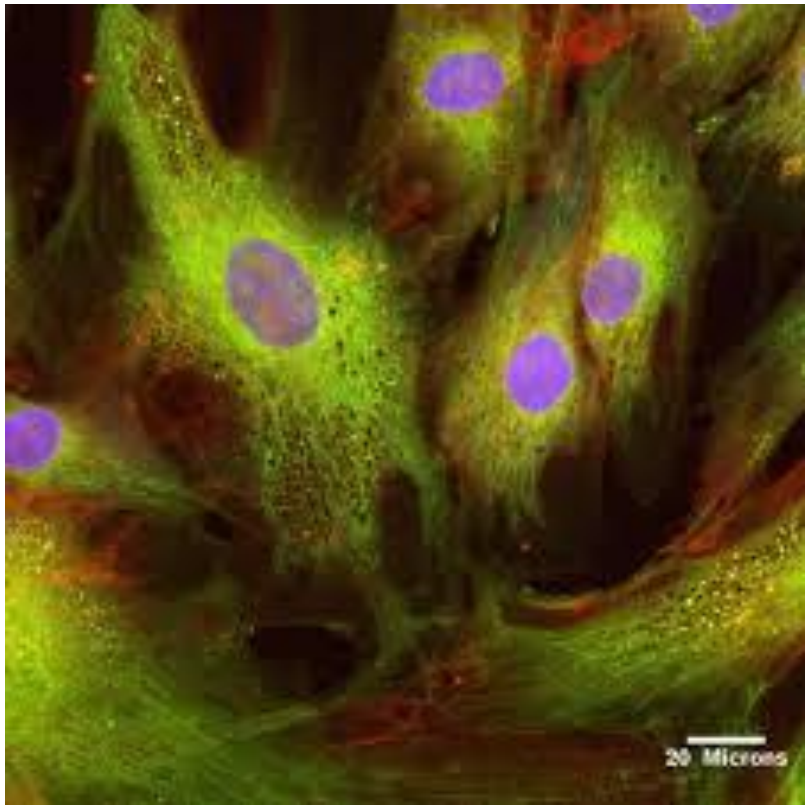
MSCs in Orthopedics



- MSCs can potentially recreate tissue
  - Tendon, cartilage, ligaments, muscle
- Modify the environment to enhance healing
- Patients feel better:
  - Anti-inflammatory effect
  - Pain Relief
- May potentially improve Osteoarthritis
- We don't know the ideal type or number of stem cells in specific indications

MSCs Reparative Promise in Knees

- Current MSC treatments for OA include BMA derived autogenous stem cells that are immediately injected into the knee
- Andrews Institute believes it controls swelling and inflammation and eases pain in knee OA
- Results in a pilot study of 31 NFL players, at 10 months, showed efficacy
- Reported decreased pain up to 45%
- Knee scores improved by 50% from baseline at 6 months

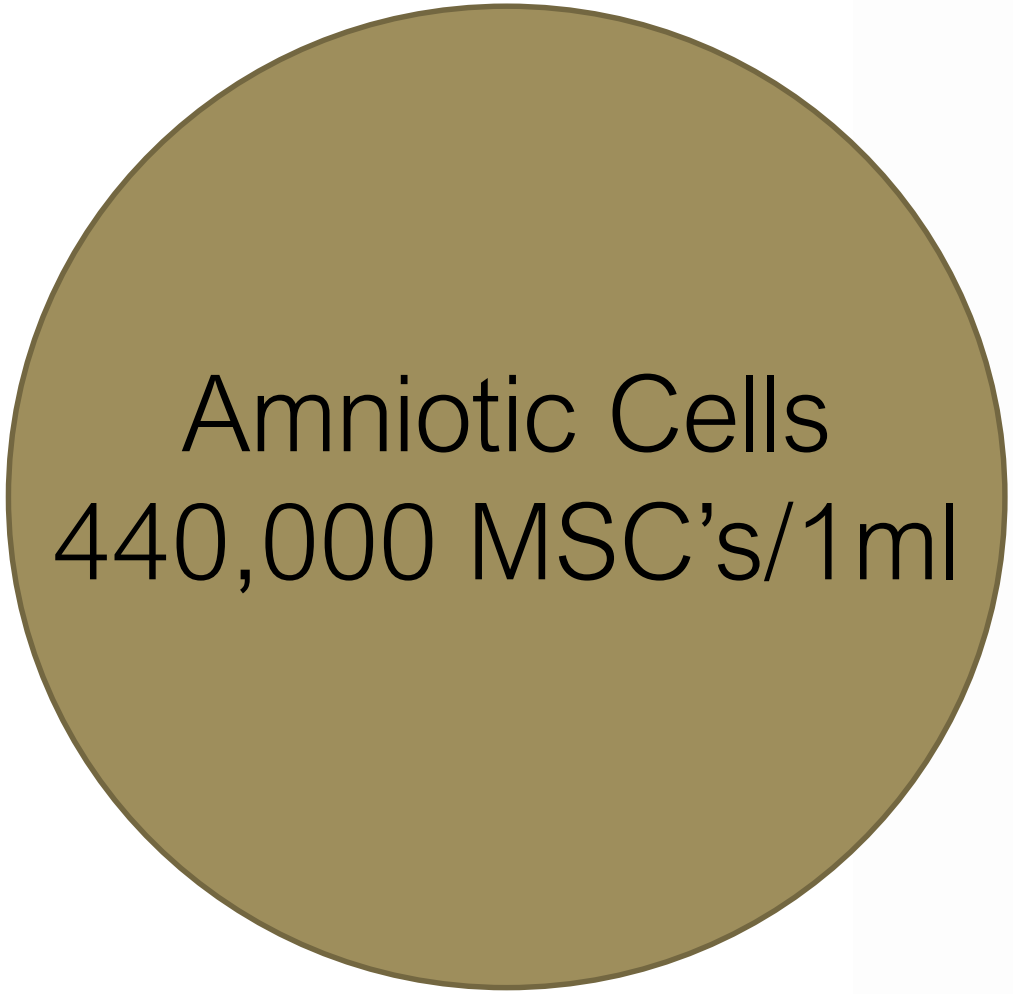
Amniotic and Placental Tissues

- So why use Allograft Tissue and Cells ???
- Growth factors, scaffolding, and MSCs in LARGE quantities
  - First used in 1910
  - Preservation techniques in 1940
  - Has been proven in ophthalmology, burns, plastic surgery, foot and ankle, diabetic ulcers
  - Amniotic fluid stem cells have a delayed/more robust differentiation compared to bone marrow derived MSC in recent studies

Allograft Bioactive “Stem Cell” Therapy

- 900,000 cells/mL
- 44% MSCs; remainder-kerintinocytes, fibroblasts, epidermal cells
- Collagen Types III, IV, V, VII
- Amino acid precursors – taurine, glutamine
- Growth factors: Epidermal growth factor, TGF alpha & beta-1, Insulin-like growth factor 1, Granulocyte colony stimulating factor

Amniotic Allograft vs BMA: MSC Volume Comparison



Bone Marrow Aspirate
1,600 MSC's/1ml

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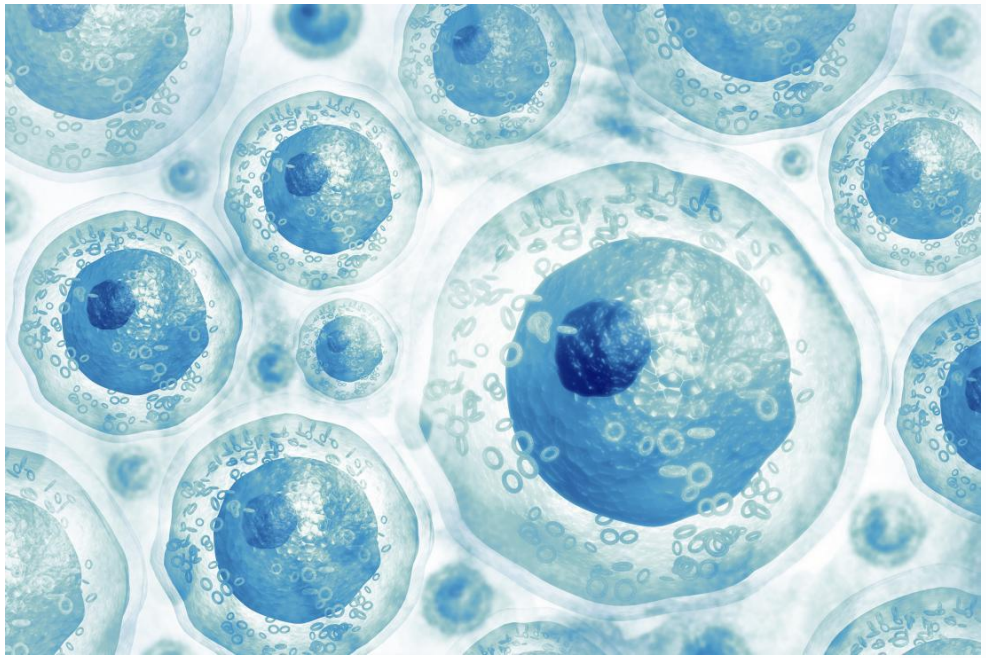
Jing Li et al: Chin J Cancer Res 23(1): 43-48, 2011

Stem Cell numbers decrease rapidly as we age



- MSCs in bone marrow
  - 1/4000 as newborn
  - 1/400,000 as 50 year old

Exosomes

- Exosomes are produced by MSCs and are lipid containers of mRNA material
- These are an important way that Stem Cells communicate with their environment
- They may be a critical active component in promoting healing locally where released
- These can be made from healthy stem cells in large quantities and are available for clinical use in US

Discussing bioactive injection therapy

- Attractive option for many patients
- Can successfully treat arthritis or tendon damage in many cases
- Each case needs to be individually evaluated
- Recommendations must be comprehensive and holistic
  - Surgery, Therapy and Bracing may all be included in plan
- Orthobiologic treatment includes the 3 key elements: cells, growth factors and scaffolding
- I explain that senescent MSCs may have limited use
- It is not a magic bullet but it does have great promise
- I explain that it can by relatively expensive and presently is not covered by insurance

My experience with bioactive therapies over 15+ years

- Hundreds of patients thus far
- Best indications for knee: “medium arthritis”
- Best indications for shoulder: partial or small rotator cuff tears
- Response to treatment is typically early: 4-8 weeks
- Presence of inflammation/effusion seems to enhance the response
- Ultrasound or needle probe guidance
- BMI & level of OA (KL grade) are theoretically negative predictors

Best indications for knee treatment

- For “medium grade” arthritic change
- As adjuvant for cartilage restoration surgery
- In conjunction with selective bracing

Best indications for shoulder treatment

- Partial or small rotator cuff tears
- Arthritic shoulder joint

PEARLS

- No anti-inflammatories
  - (1 week before & 4 weeks after)
  - Includes NSAID, Aspirin, Vit E, Fish Oil
- Increased tissue vascularity improves cellular incorporation
- Carriers: PRP, Lidocaine 1% preservative free
- Full activity (restrictions only if warranted by diagnosis)
- Limit ice afterward for 1 week

Summary – Thank You

- Bioactive injections can be used to treat traumatic, inflammatory and degenerative knee and shoulder conditions
- Protocols for administration and ongoing support are actively being modified
- Early observations very encouraging
- More data being collected

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