Regenerative Medicine: Platelet Rich Plasma and Stem Cell

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Objectives

- Definite platelet rich plasma (PRP) and stem cell
- Explain how PRP and stem cell are harvested
- Understand the biological model of PRP and stem cell
- Review indications for use of PRP and stem cell
- Expectations from the injections
- Develop idea of how they are used for the spine and other joints

Platelet Rich Plasma (PRP)

- Many athletes have use PRP therapy
  - Rafael Nadal
  - Tiger Woods
  - Hines Ward
  - Kobe Bryant
  - Brandon Roy

Or non-athletes…..

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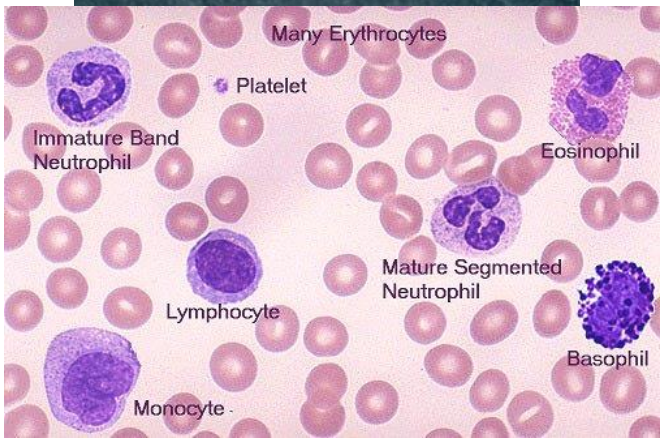
www.foxsportsnorth.com/07/03/12/Platelet-rich-plasma-therapy-big-with-at/landing_timerbvolves.html

What is PRP?

- PRP is a therapy that utilizes a patient's own blood to stimulate a healing response within a damaged tissue or joint

- Growth factors in the platelets recruit and produce cells necessary for healing



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Arnoczky et al. Operative Techniques in Sports Medicine. 2011;19(3):142-148

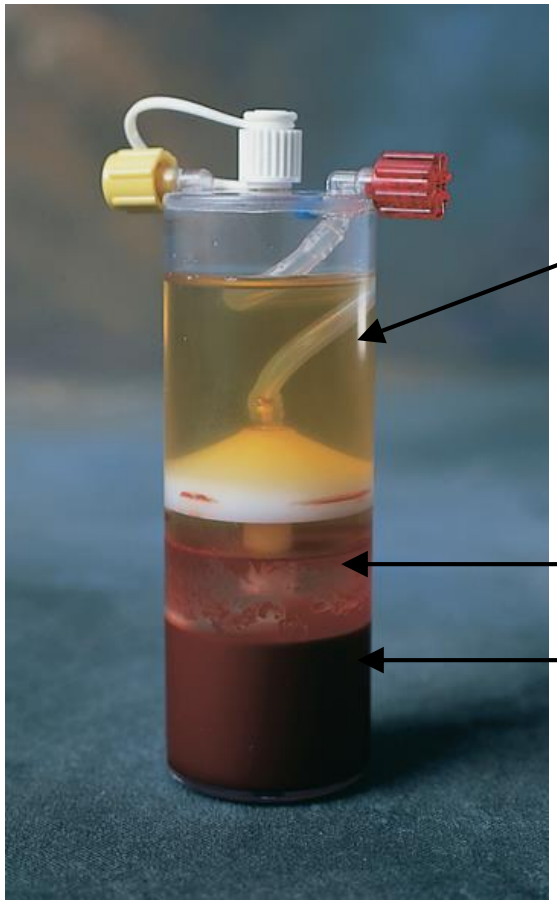
Harvest PRP

- **PRP Retrieval**
  - Withdraw 30 cc of peripheral blood
  - Place blood in GPS canister
  - Centrifuge for 15 minutes at 3200 RPMs

Biomet.com

PRP Retrieval

- Remove PPP
- This process concentrates platelets and white blood cells in what is called “buffy coat” that is extracted and delivered to the injured area



Platelet Poor Plasma

(PPP)

Platelet Rich Plasma

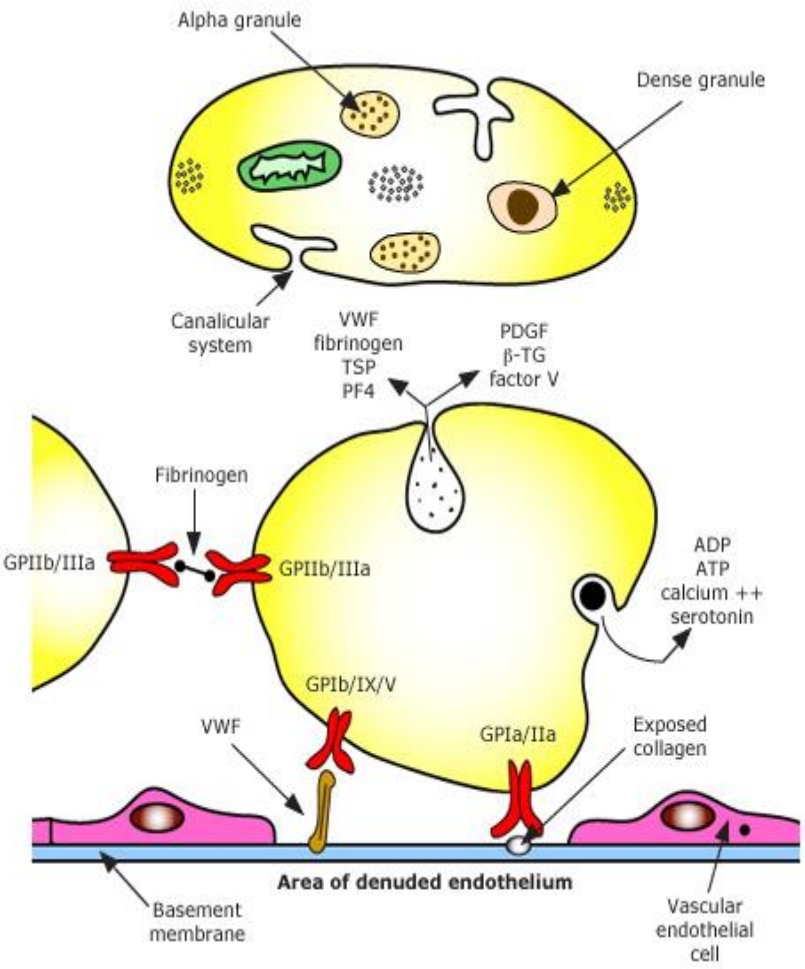
(PRP)

Packed Red Blood Cells

Biomet.com

What's so special about Platelets?

- Platelets contain granules that store large numbers of "*growth factors*"
- Alpha granules released (activated) when platelets aggregate and adhere to a site of injury or inflammation
- It is the activation of platelets and release of the various growth factors that makes them special and is the key to enhancing tissue repair and healing!



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Kon E, et al. Knee Surg Sports Traumatol Arthrosc. 2011;19:516-27

Growth Factors

Factor	Principal Source	Primary Activity	Comments
PDGF	platelets, endothelial cells, placenta	promotes proliferation of connective tissue, glial and smooth muscle cells	two different protein chains form 3 distinct dimer forms; AA, AB and BB
EGF	submaxillary gland, Brunners gland	promotes proliferation of mesenchymal, glial and epithelial cells	
TGF-a	common in transformed cells	may be important for normal wound healing	related to EGF
FGF	wide range of cells; protein is associated with the ECM	promotes proliferation of many cells; inhibits some stem cells; induces mesoderm to form in early embryos	at least 19 family members, 4 distinct receptors
NGF		promotes neurite outgrowth and neural cell survival	several related proteins first identified as proto-oncogenes; trkA (trackA), trkB, trkC
Erythropoietin	kidney	promotes proliferation and differentiation of erythrocytes	
TGF-b	activated TH_1 cells (T-helper) and natural killer (NK) cells	anti-inflammatory (suppresses cytokine production and class II MHC expression), promotes wound healing, inhibits macrophage and lymphocyte proliferation	at least 100 different family members, including BMPs
IGF-I	primarily liver	promotes proliferation of many cell types	related to IGF-II and proinsulin, also called Somatomedin C
IGF-II	variety of cells	promotes proliferation of many cell types primarily of fetal origin	related to IGF-I and proinsulin

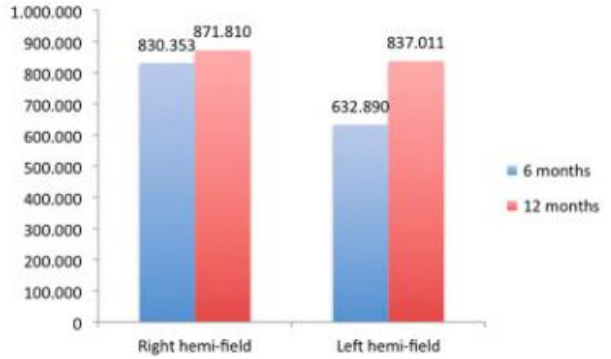
Kon E, et al. Knee Surg Sports Traumatol Arthrosc. 2011;19:516-27

Growth Factors

- PDGF
  - Immediate (within 5 minutes)
    - Second messenger stimulation
    - Inflammatory response
  - Early (30min to 4 hours)
    - M-RNA stimulation, protein synthesis
    - Chemotaxis (draws cells to the area)
  - Late (4-24 hours)
    - Fibroblast mitosis

- TGF-Beta
  - Actually inhibits cell growth
  - More of a modulator of cell growth, differentiation
    - Very important in wound repair

Posterolateral Arthrodesis in Lumbar Spine Surgery Using Autologous Platelet-Rich Plasma and Cancellous Bone Substitute: An Osteoinductive and Osteoconductive Effect



- 20 patients undergoing lumbar surgery
  - 15 lumbar stenosis and 5 lumbar body fractures
  - 8 males and 12 females with mean age 70 yrs
- Each operation included:
  - Cancellous bone substitute soaked with autologous PRP was implanted on the right hemifield
  - Cancellous bone substitute soaked with saline solution on the left hemifield.
- Main effect of value of density after 6 months was significant ($F(1,19)$ 5.522, $p < 0.05$)
  - Right hemifield after 6 months was significantly different from the value of the density on the left hemifield (mean 1⁄4 830.353 [SD 61.8] for the right hemifield versus mean 1⁄4 632.890 [SD 59.5] for the left hemifield)

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Tarantino, R. *et al. Glob. Spine J. 4:137–142, 2014*

Influence of platelet-rich plasma on the anterior fusion in spinal injuries: a qualitative and quantitative analysis using computer tomography

- 15 pts undergoing anterior fusion using cages of thoracic and lumbar spine (vs 20 control)
  - Posterior stabilization and/or anterior implants as well as bone graft combined with PRP (or no PRP)
  - Mean age 39.8 years (range 18–64)
  - 7 patients were female, 13 male
  - 13 type A, 5 type B and 2 type C fractures.
  - Follow-ups took place 12.5 months post-op
- Results
  - No or minimal fusion
    - 20% vs 30%, PRP and control

	PRP group	Control group	Significance
Number of patients	12	14	
Mean density (HU)			
Total	235.9	209.9	No
Fraction > 100 HU	639.7	514.2	Yes ($p < 0.05$)
Fraction > 500 HU	930.7	846.0	No
Volume fractions (%)			
Fraction > 100 HU	56.48	56.60	No
Fraction > 500 HU	29.33	23.57	No

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Archives of orthopaedic and trauma surgery. 2010;130(7): 909-914

Intervertebral Disc and PRP

- Wang SZ, Rui YF, Tan Q, Wang C: Enhancing intervertebral disc repair and regeneration through biology: platelet-rich plasma as an alternative strategy. Arthritis Res Ther 2013; 15:220.

- Nagae M., et al. 2007 Intervertebral disc regeneration using platelet-rich plasma and biodegradable gelatin hydrogel microspheres. Tissue Eng. 13;147–157.

Osteoarthritis and PRP

- Hip OA
  - Only randomized controlled trial of PRP in hip osteoarthritis
    - 100 patients were allocated at random to PRP or high-molecular-weight hyaluronic acid.
    - Significant improvements in pain (VAS score) and function (Harris score) were documented in both groups after 1 month then after 3 and 6 months
    - The improvements were less marked after 12 months but remained statistically significant compared to baseline. No differences were found between the two groups in any of the disease severity subgroups (Kellgren II to IV)
    - Post-injection pain was twice as common with PRP as with hyaluronic acid ($P < 0.05$).

- Knee OA
  - Only randomized trial reported to date compared PRP to hyaluronic acid, and no studies have used a placebo as the comparator
  - Most of the randomized trials in patients with knee osteoarthritis support a slightly better symptomatic effect compared to hyaluronic acid, at least in patients with early disease and within the limited study follow-ups (usually 6 months).
  - However, the designs of these trials were not always well suited to the demonstration of non-inferiority, and caution is in order given the well-demonstrated strong placebo effect of intraarticular injections in osteoarthritis.

Ornetti P, et al. Does platelet-rich plasma have a role in the treatment of osteoarthritis? Joint Bone Spine (2015), http://dx.doi.org/10.1016/j.jbspin.2015.05.002

Limitations in the use of PRP

- Efficacy
  - Lack of clinical data
    - Number of studies being done
    - Indications are being developed
- Uniformity of prep
  - PRP classification
- Insurance recognition
  - CMS tracking code
- $$$$$$$ - Evidence based?
  - Shady clinics

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Candidates for PRP Therapy

Qualification	Candidate	Not a Candidate
Failed previous treatment	✔	
Will not allow blood removal or injection into their body		✔
Inability to take oral anti-inflammatory drugs due to allergy	✔	
On blood thinners		✔
Symptoms persistent enough to consider surgery or repeat treatment	✔	
Unable to be off of aspirin or anti-inflammatory drugs before or after the procedure		✔
Allergic to lidocaine or numbing agents		✔

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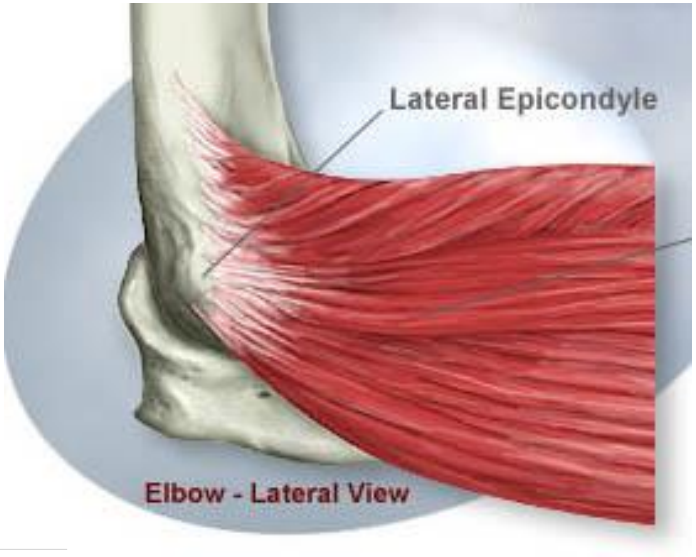
PRP Injection

- Inject 2-3 cc of PRP into the ECRB--Peppering technique
- Effective concentration
  - 1 million/uL, 3-5x platelet level baseline
- Expression of growth factor receptors decrease with age



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De Mos et al. Am J sports Med 36:1171-1178, 2008

Post injection Management

- Rest (sling/crutches) for a few days to a week
- NO NSAID'S
- PT (HEP or Rx)
- Slow stretching program
- Low weight and hi repetition pain free isotonic PRE's
- No high loading activities until criteria met
  - No rest pain
  - Minimal tenderness
  - Full motion
  - Normal strength

Are all PRP treatments the same?

No!

- Platelet level base is different in every patient
- Many different types and use of PRP (liquid or gel forms)
- Treatments with red or white blood cells, thrombin or calcium chloride
- Intra-individual variability
- Inter-individual variability

Lopez-Vidriero E, et al. Arthroscopy. 2010;26(2):269-78

PRP versus Stem Cells

PRP acts to provide a favorable environment to recruit progenitor cells and stimulate healing of musculoskeletal tissues, stem cell therapy offers the possibility of directly injecting progenitor cells to the area of damage.

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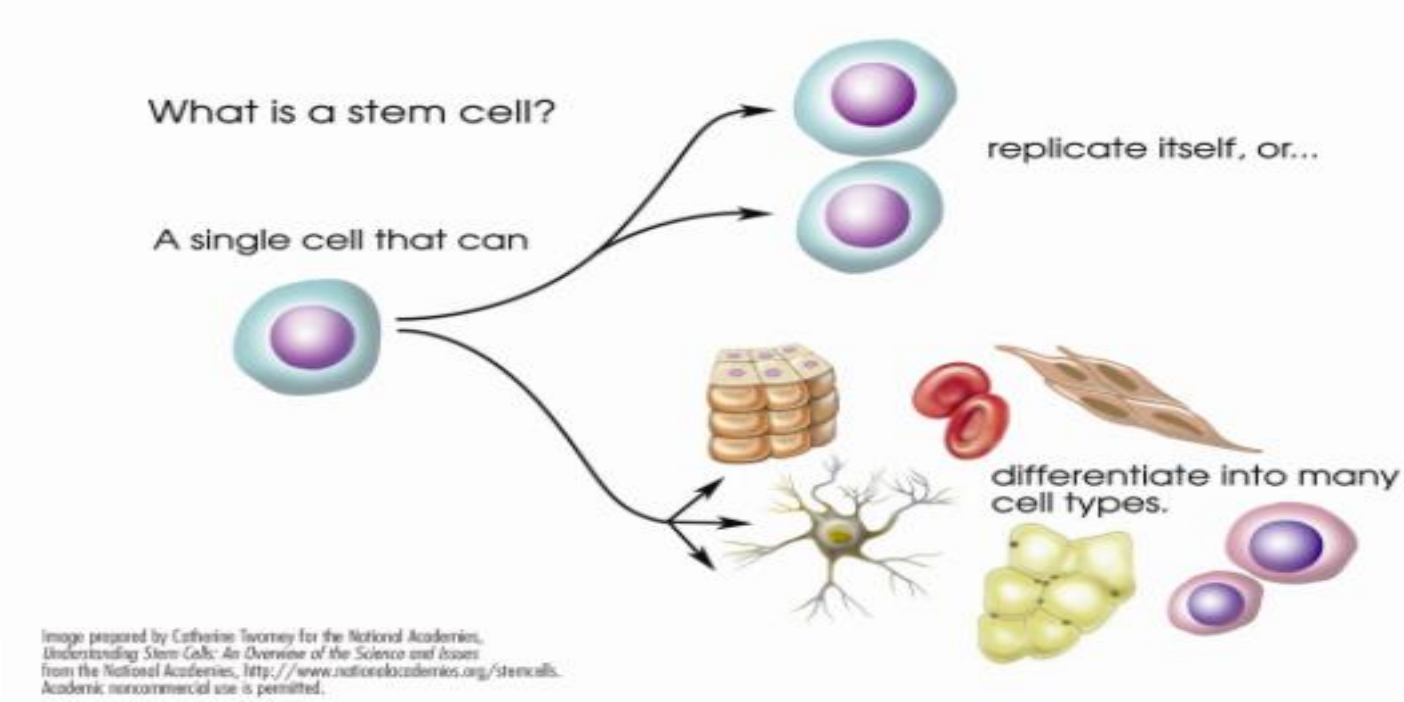
Mautner K, et al. PM&R. 2015;7.4: S33-S40.

Stem Cell

- Many athletes have use stem cell therapy
  - Peyton Manning
  - Chris Johnson
  - And rumors of……..

What are Stem Cells?

Is a undifferentiated cell found among differentiated cell in a tissue organ



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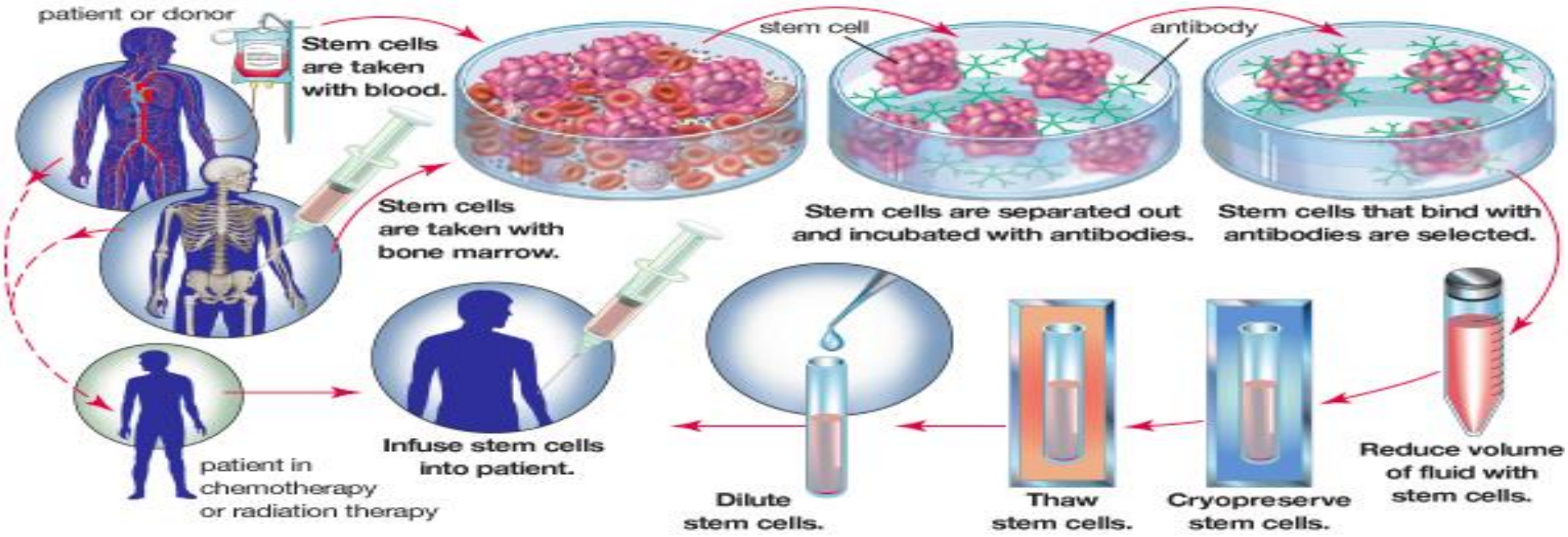
Nas-sites.org

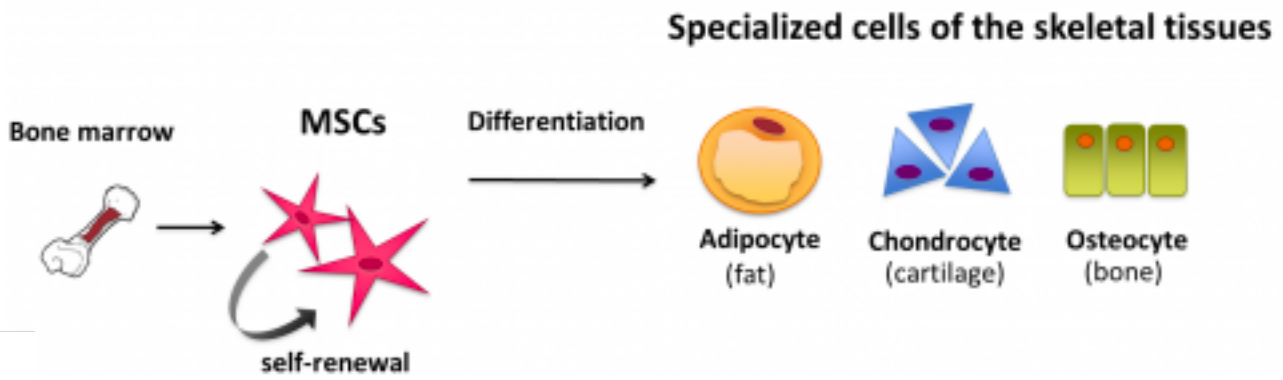
Harvest Stem Cells

- Adult stem cells
  - Harvest from bone marrow
    - Two types:
      - Hematopoietic (blood forming cells)
      - Mesenchymal stem cell



Stem Cell

- Adult mesenchymal stem cells (MSCs):
  - Isolated easily from multiple sources, most notably bone marrow (BM-MSCs) or adipose tissue (AD-MSCs), divide rapidly, and are capable of differentiating into cells of the mesenchymal lineage



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Wei X, et al. Acta Pharmacologica Sinica. 2013; 34(6): 747-754.

Outcomes of spinal fusion following autologous stem cell transplantation

- Case series of 3 patients with successful spinal fusion after previous myeloablative chemotherapy followed by autologous HSCT
  - Average surgery time after HSCT: 4.5 years
  - Only 1 of 3 on maintenance chemotherapy

Patient no.	Age (years)	Sex	Reason for HSCT	Preoperative symptoms	Time between HSCT and surgery (months)	Surgery	Radiographic follow-up (months)	Fusion	Complications
1	35	F	Hodgkin's disease	Back pain and radiculopathy	42	L5–S1 PLIF, carbon–fiber interbody cage and local bone autograft	41	Yes	None
2	49	M	Primary amyloidosis	Kyphosis, low thoracic back pain, T11 burst Fx	39	T11 corpectomy, local bone autograft, and BMP	28	Yes	T11 cage subsidence, post-operative ileus
3	55	F	Multiple myeloma	Right hip and leg pain, L3–4 synovial cyst	80	L2–4 PLIF, iliac crest bone graft	43	Yes	Lumbar epidural hematoma, re-operation

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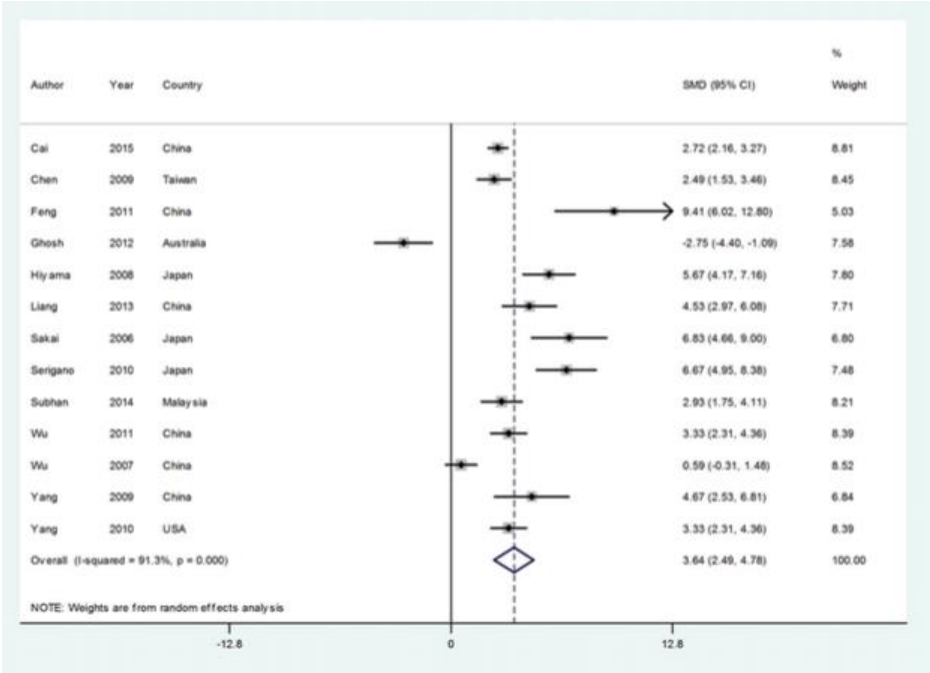
Shaikh KA, et al. Journal of Clinical Neuroscience. *2013; 20(1): 62-65*

Efficacy of intervertebral disc regeneration with stem cells- A systematic review and meta-analysis of animal controlled trials

- Inclusion
  - Stem cell transplantation on disc regeneration
  - Animal studies
  - 22 studies included
  - Pool mice



Outcomes	Number of studies	SMD	95% CI	p value	I^2	Heterogeneity p value
Disc height Index	13	3.64	2.49, 4.78	<0.001	91.3%	<0.001
MRI T2 signal	14	2.28	1.48, 3.08	<0.001	88.5%	<0.001
Histologic disc degenerative grade	11	−2.97	−3.97, −1.97	<0.001	80.1%	<0.001
Type II collagen expression	9	3.68	1.66, 5.70	<0.001	95.8%	<0.001

Note: SMD, standardized mean difference; 95% CI, 95% confidence interval.

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Wang Z, et al. *Gene 2015; 564(1):1-8*

Exploring the Application of Stem Cells

- The current evidence shows that stem cells can have a positive effect on tendon healing. This is most likely because stem cells have regeneration potential, producing tissue that is similar to the preinjury state but the results can be variable

"The use of adjuncts such as molecular signaling, mechanical stimulation, and augmentation devices can potentially enhance stem cell therapy"

Ahmad Z et al. Arthroscopy. 2012; 28(7):1018-1029

Limitations of Stem Cell Therapy

- Long term side effects of the therapy are still unknown
- Embryonic cells are used then the disadvantage is that the cells will not be from the same human body and there are chances of rejection
- Infections
- Not FDA approved
- Costly
  - Non-FDA approved injections in the USA ($10,000)
  - Other countries injections ($20,000-$100,000)