AOASM 2026

Orthobiologics: Science, Current Status, and Future Directions

Adam M. Pourcho, D.O.

ELITE SPORTS PERFORMANCE MEDICINE
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Disclosures

- AMSSM Bridge to LR34 research grant Award winner
- Barbara Stephanus foundation donation for regenerative medicine research award winner.
- FDA approved investigation on Autologous concentrated serum: DBPCT for knee OA – starting 2026

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Dr. Adam Pourcho, DO, ATC

- Michigan State University- BS Kinesiology
- Athletic trainer certified
- Detroit Lions Athletic Trainer
- Michigan State University- College of Osteopathic Medicine
- Wayne State University- Physical Medicine and Rehabilitation Residency
  - Chief Resident
- Wayne state university team physician (2011-2013)
- Head team physician Seattle Storm 2016- 2020
- **Board certified Physical Medicine and Rehabilitation**
- **Board certified (Mayo Clinic) sports Medicine fellowship**
- **Certified Musculoskeletal Ultrasound**
- Faculty and professor Swedish Sports medicine fellowship
- **Owner of Elite Sports Performance Medicine (Seattle, Kirkland)**
- Instructor AIUM, AMSSM, TOBI, AOASM, and AAPMR musculoskeletal ultrasound courses

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Special Thanks

Jacob Sellon, MD

Jay Smith, MD

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Over Arching Concept

We are embarked as pioneers upon a new science and industry in which our problems are so new and unusual that it behooves anyone to dismiss any novel idea with the statement that ‘it can’t be done!’
- William Boeing

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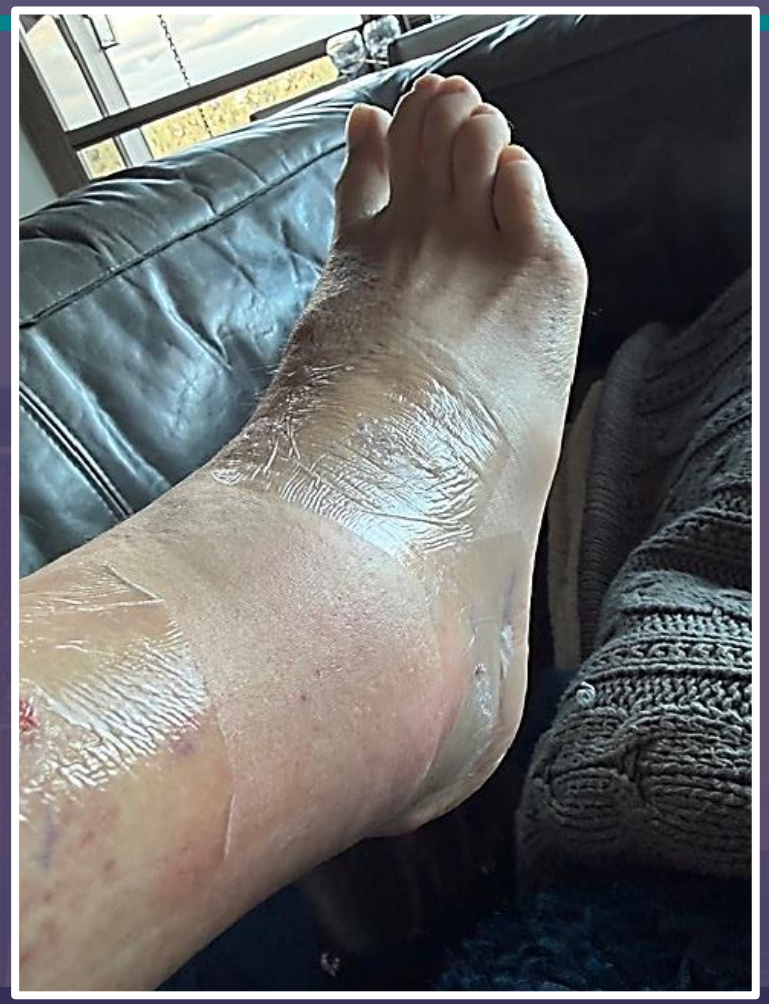
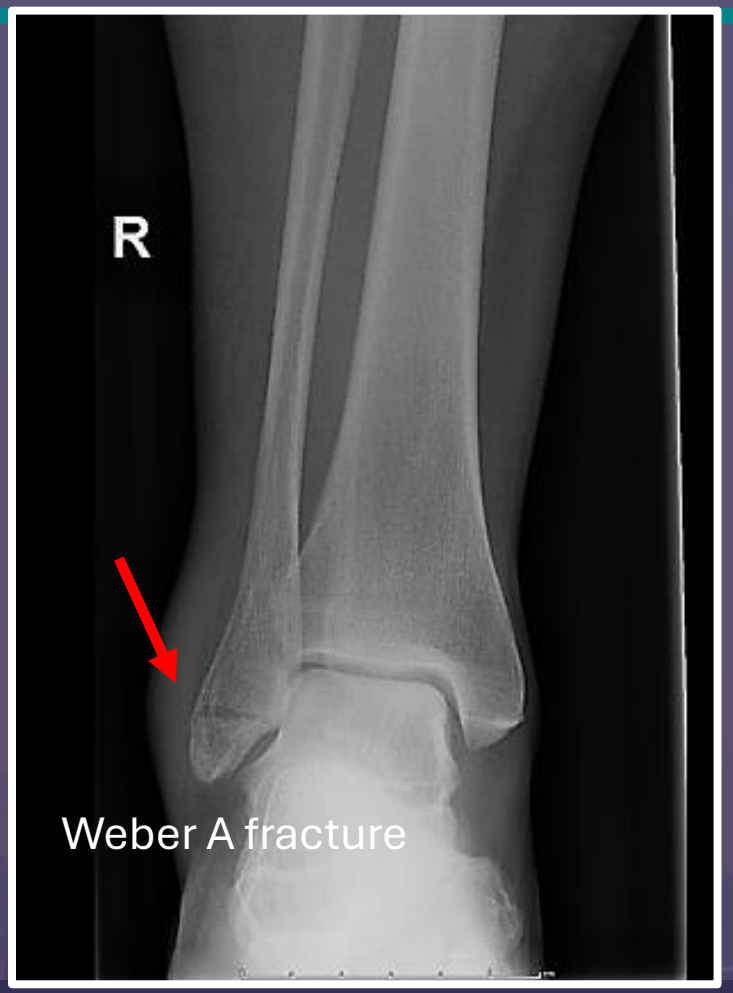
46-year-old physician walks off a curb





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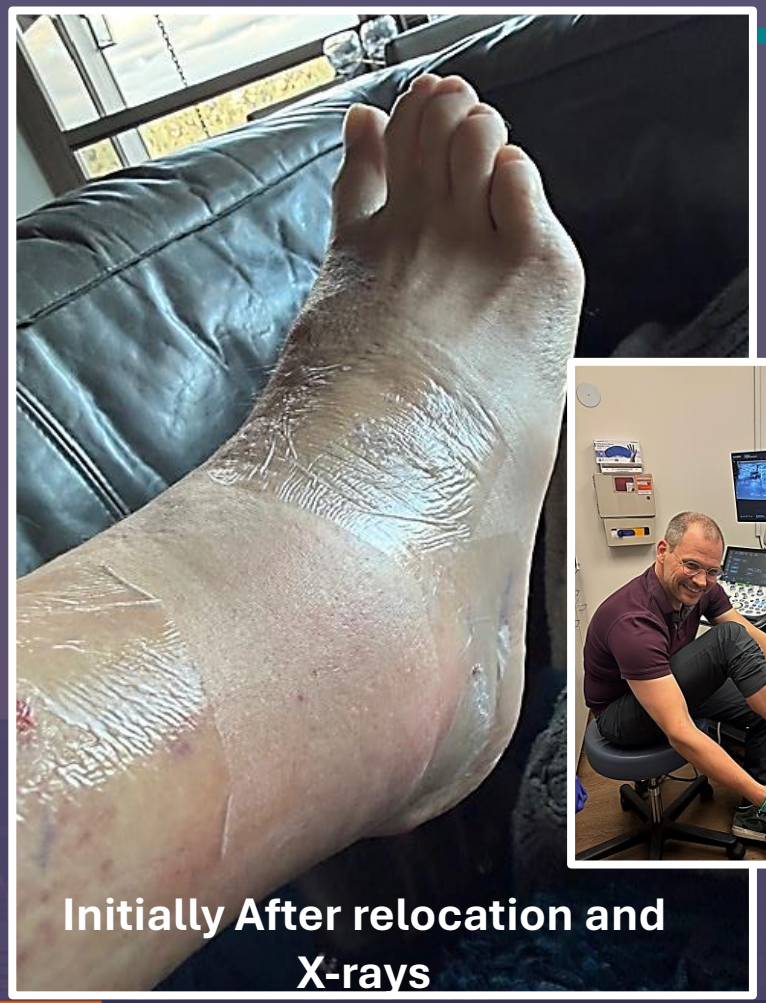
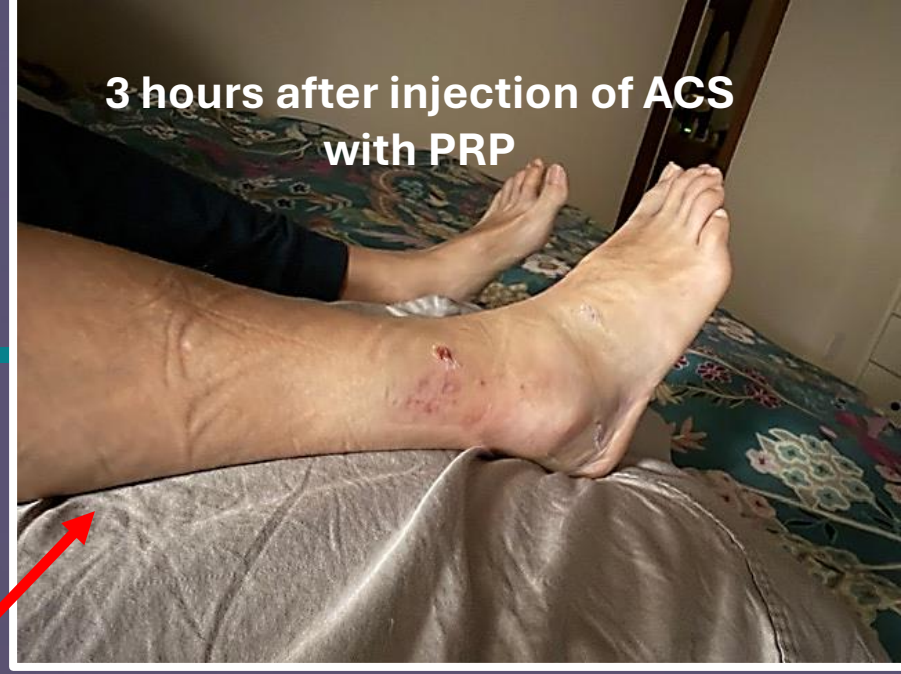
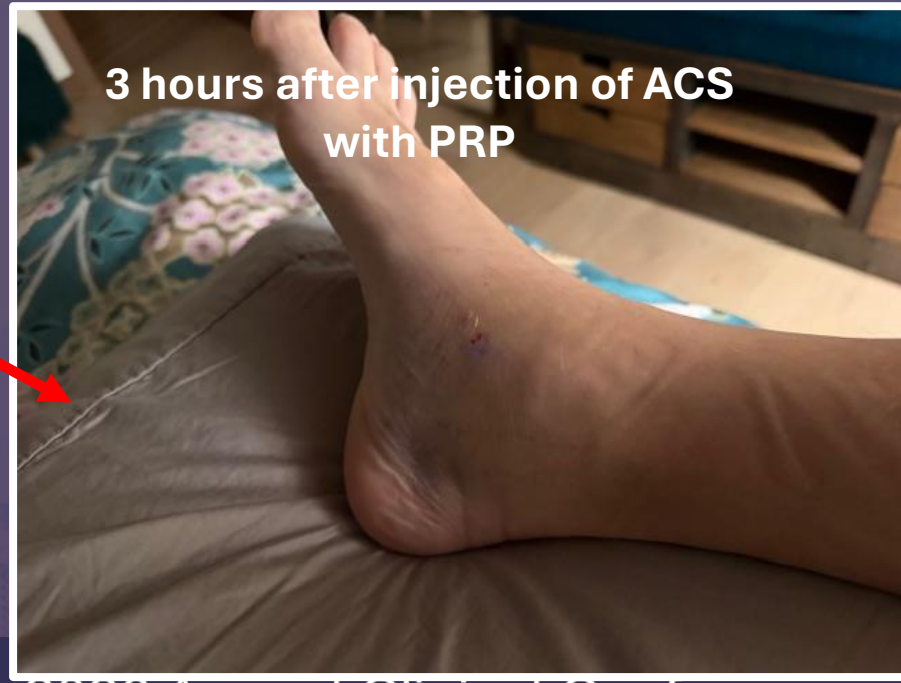
After joining the idiot men's club as the new club president...



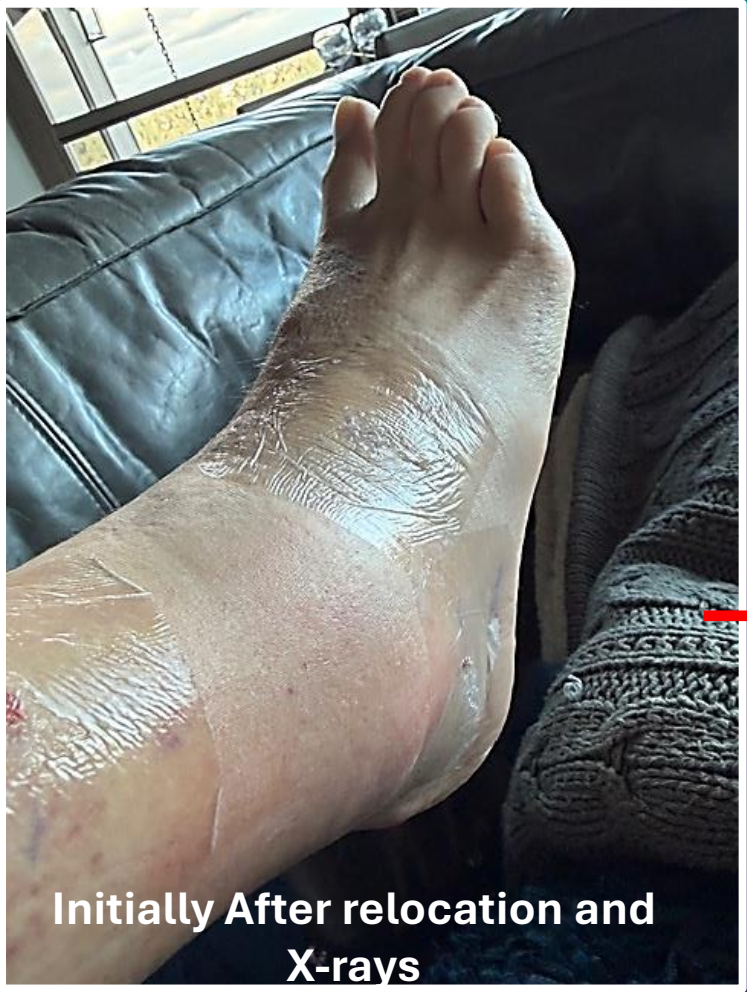
Initially After relocation and X-rays

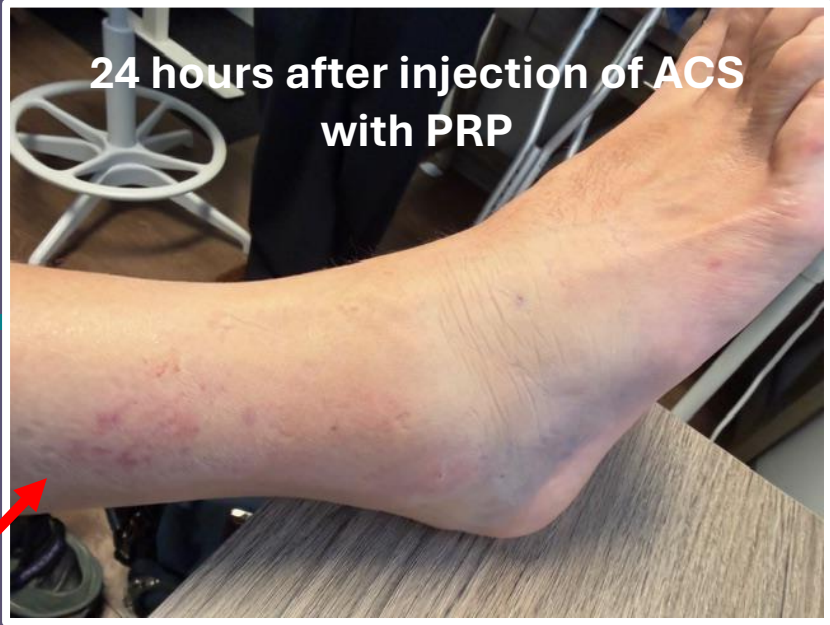
Injected 12 hours after injury





24 hours after injection





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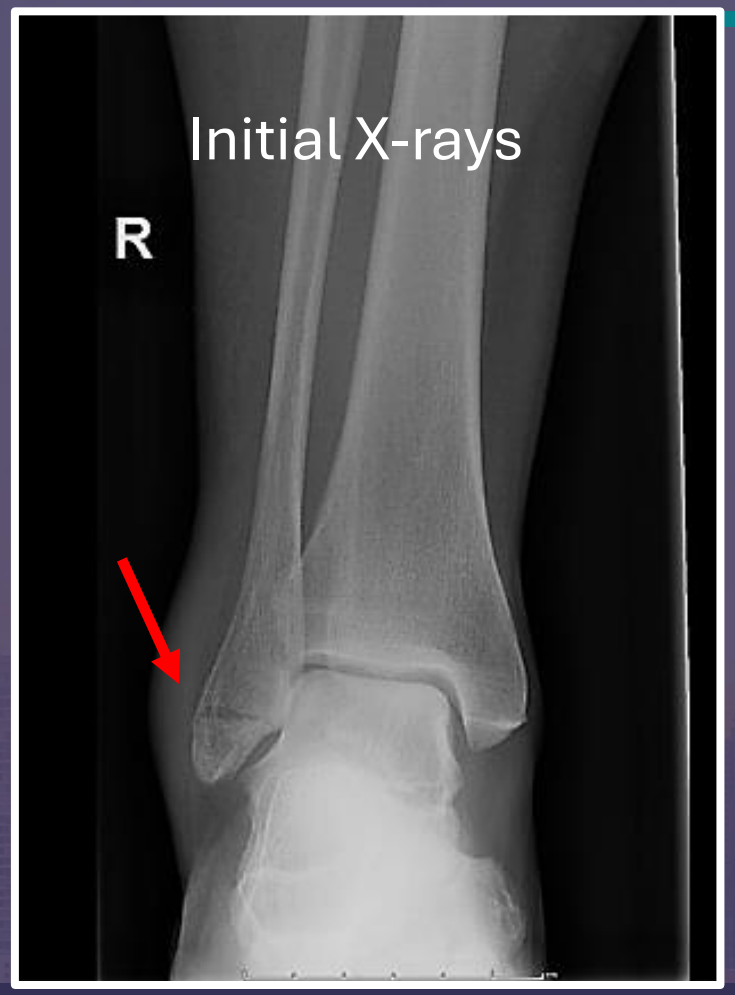

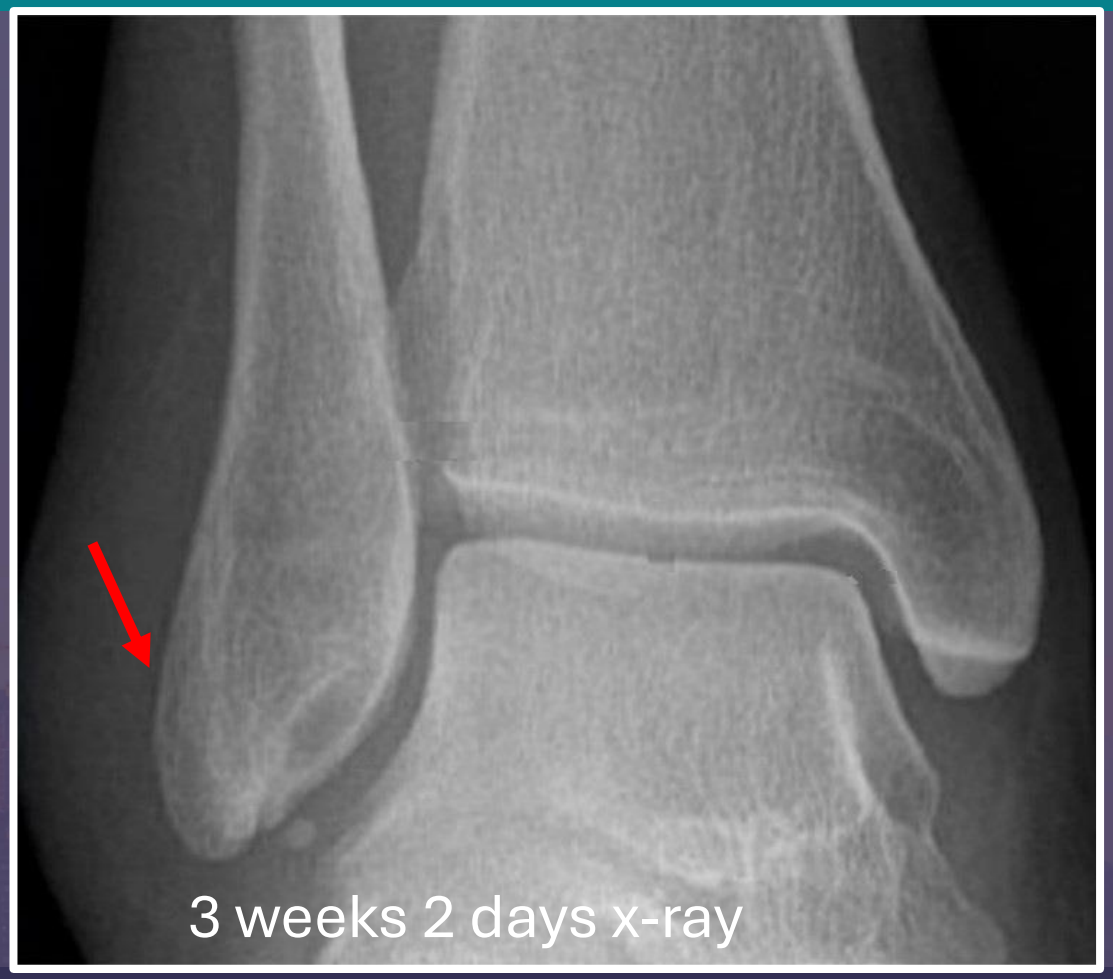

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4 weeks after initially injury and injection

2026 beer league hockey champion!

VISITOR SCORING

	Nº	PER	CLO…	G	ASST
	1	1ST	09:35	16	91
	2	1ST	00:19	91	8 / 16
	3	2ND	13:38	16	-
	4	2ND	05:39	91	16

Y	OFFENCE	MIN	OFF	START	ON
	Tripping	2	12:39		
	Interference	2	05:16		

VISITOR PLAYER ROSTER

POS	#	PLAYER	
D/F	86	MICHELLE BRADFORD	
D/F	97	DEREK ERDMANN	
F	16	ALEX FEDEROV	
D	72	TOM HARDY	
D/F	7	CASEY LACROIX	
F	9	SARA LACROIX	
D/F	43	ANDREW MAJORS	
D	54	LIV MONGILLO	
G	27	DAVID PFEIFER	AFFILIATE
F	91	ADAM POURCHO	
F	8	DAVID WIGHTMAN	

VISITOR TEAM OFFICIALS

MANA…	CHRIS BENTIVEN…	
MANA…	MICHELLE BRADF…	
MANA…	CASEY LACROIX	
MANA…	ANDREW MAJORS	
MANA…	ANDREW MAJORS	

VISITOR GOALKEEPING

	SAVES				
#	1st	2nd	3rd	OT	TOTAL
27	8	18	20	-	46
33	-	-	-	-	0
TOTAL	8	18	20	-	46

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Outline

- What is regenerative medicine?
- What is platelet-rich plasma (PRP)?
- What are “Stem cells”?
- What is Alpha-2 Macroglobulin?
- What is Autologous concentrated serum?
- Patient Selection
- Future Directions

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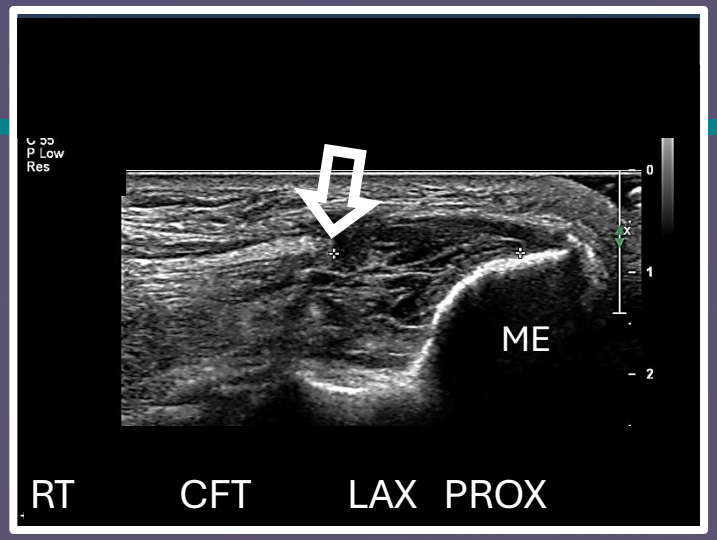
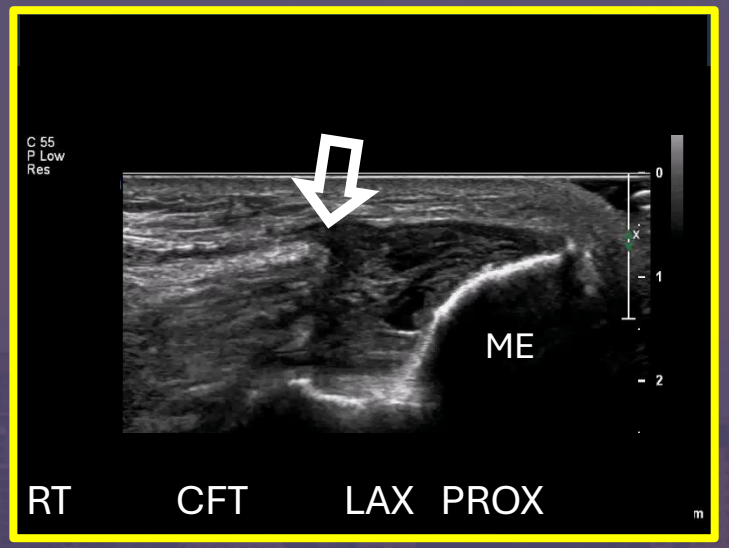
Let's Talk about Steroids/ Cortisone Injections

- ***We have known since 1977*** that steroids are ***genotoxic*** ,tenotoxic, chondrotoxic **(1980's),** increase risk of infection, cause osteoporosis, temporarily raise blood sugar, ***increase risk of tendon rupture*****,** and lower immune response.
- Furthermore, there have been multiple studies now showing that tendinopathy is ***NON-INFLAMMATORY.***
- Therefore, treating tendinopathies and arthritis with anti-inflammatories is counter-intuitive and given what we know about steroids.
- ***The risks probably outweighs the benefits of injection for most patients.***





Halpern AA, et al. 1977; Rees JD, et al. 2014; McAlindon TE, et al. 2017; Kompel AJ, et al. 2019

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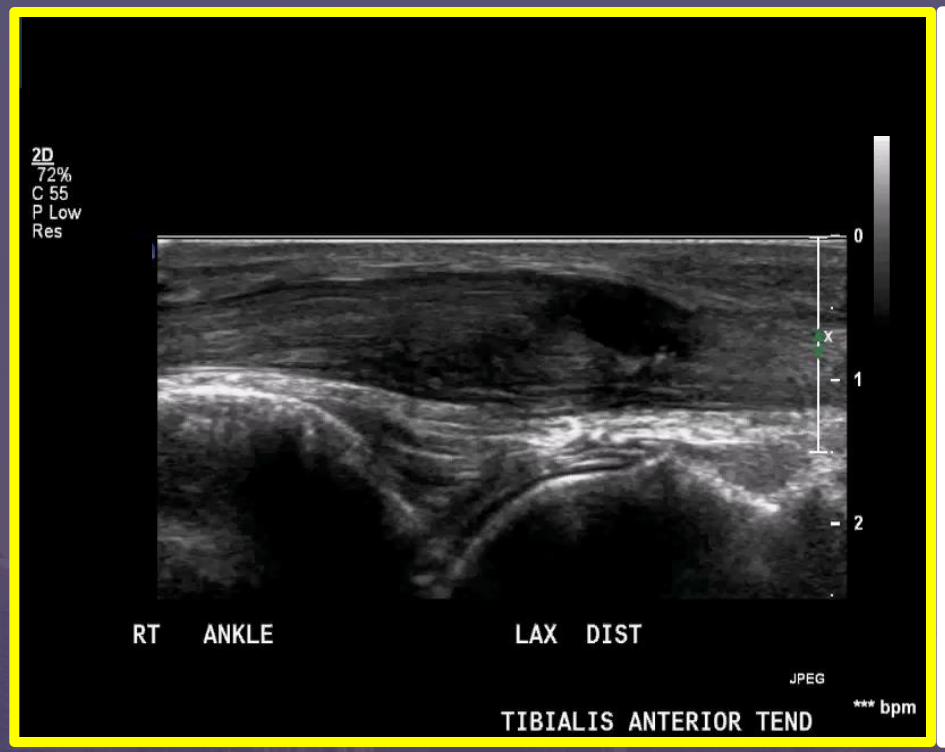
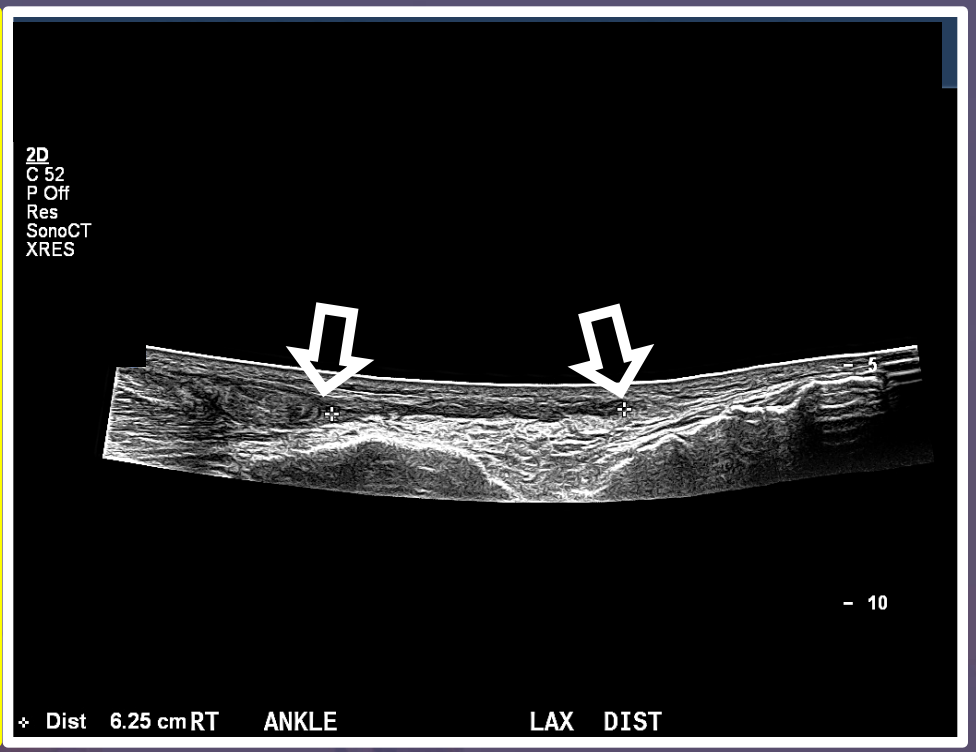
Tibialis Anterior Rupture S/P CSI





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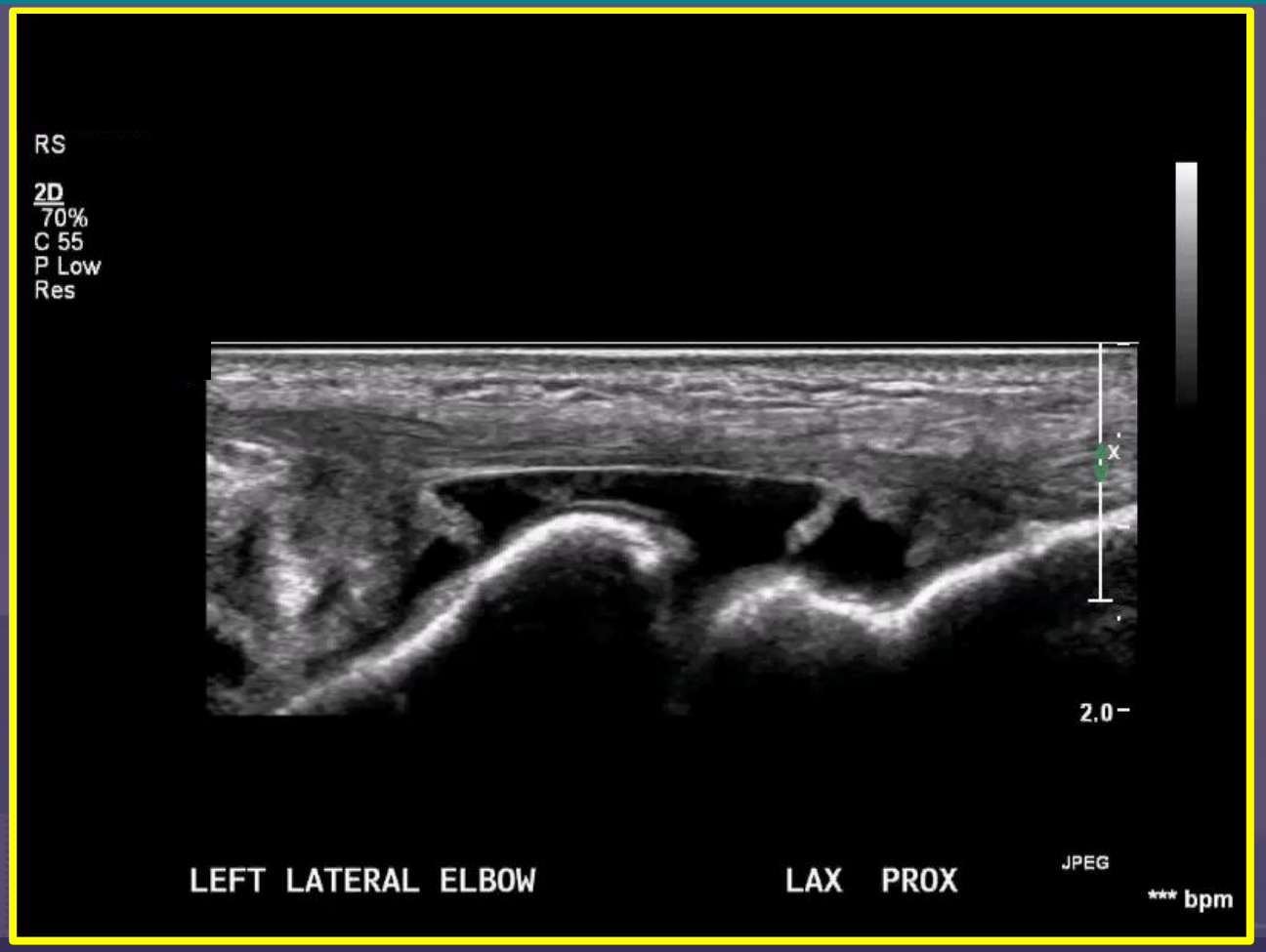
CET rupture following PG steroids



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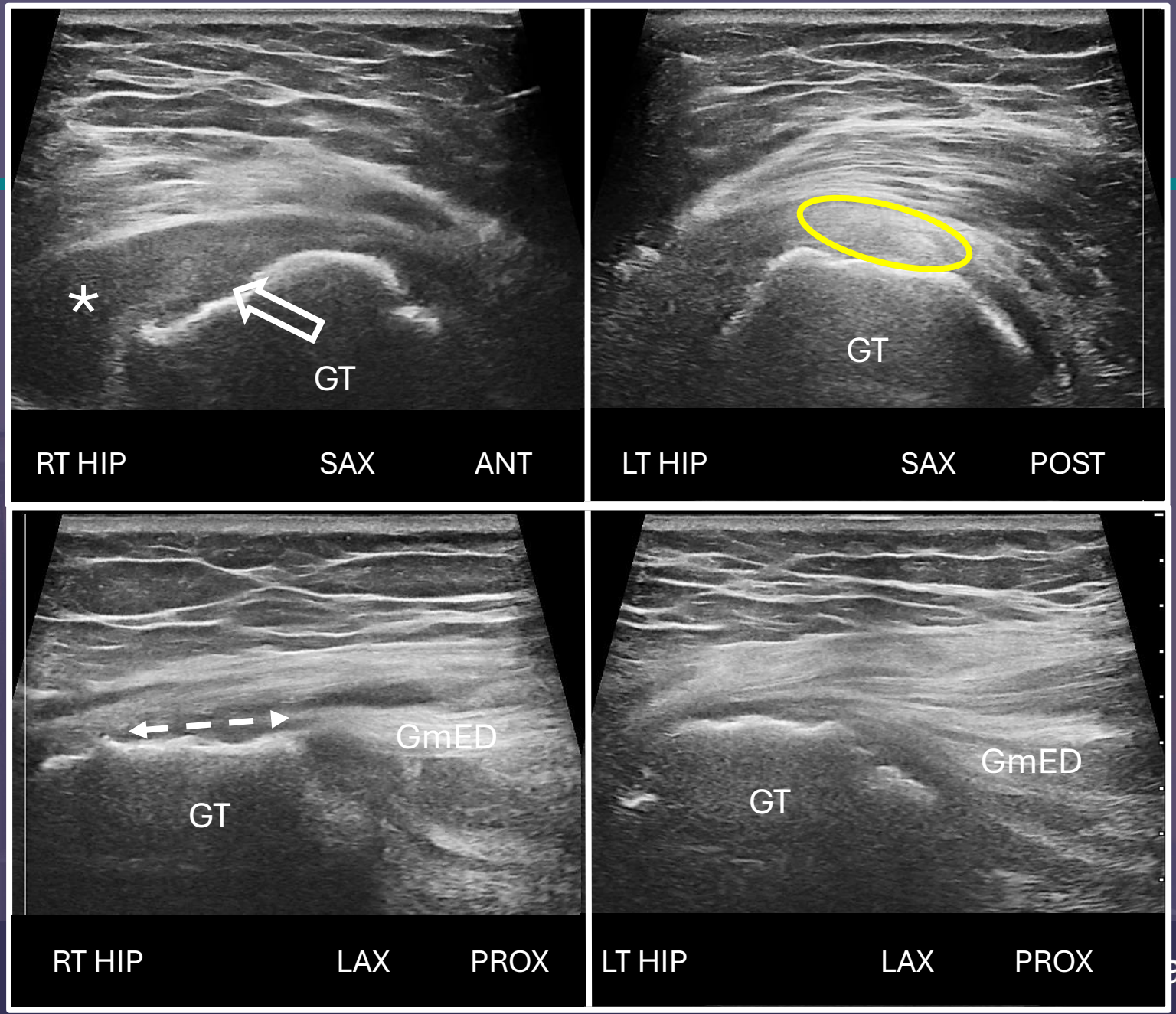
Gluteus medius medius complete rupture following PG CCS X4



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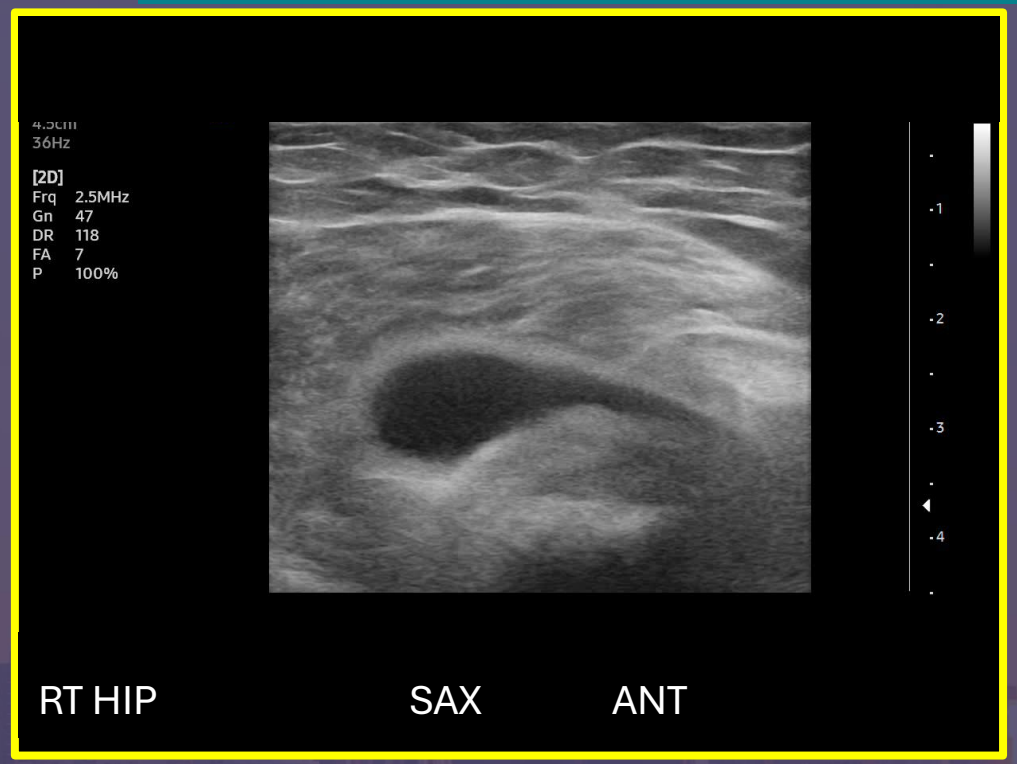
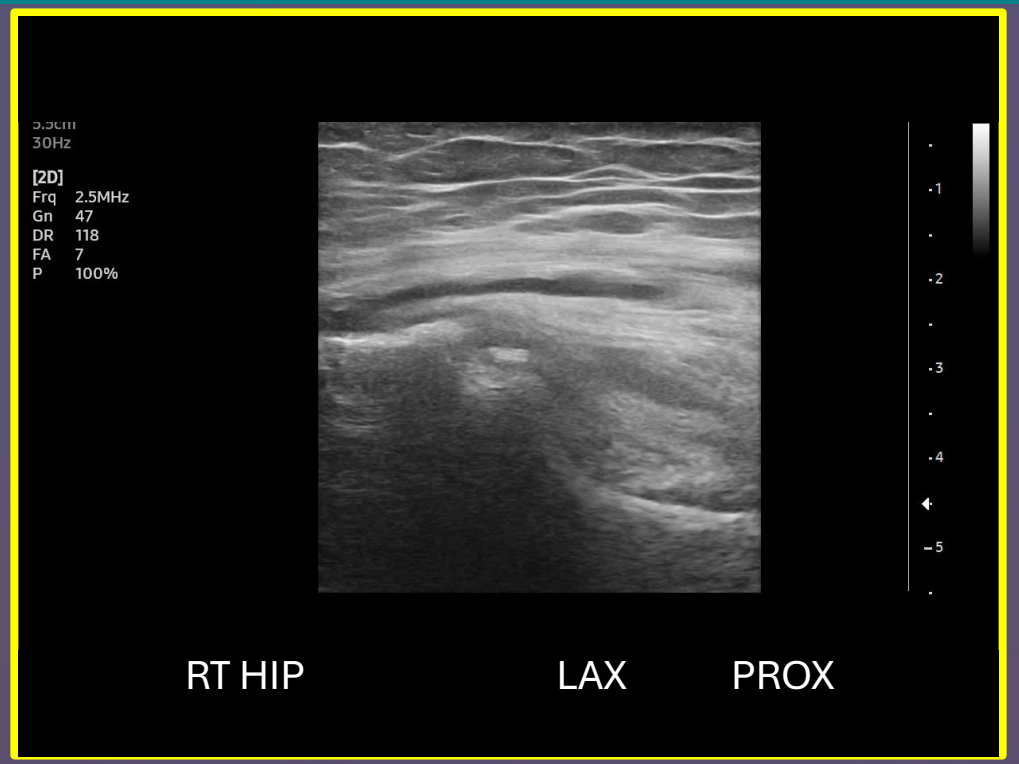
Gluteus minimus complete rupture following PG CCS





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Radiology

ORIGINAL RESEARCH • SPECIAL REPORT

Intra-articular Corticosteroid Injections in the Hip and Knee: Perhaps Not as Safe as We Thought?

Andrew J. Kompel, MD • Frank W. Roemer, MD • Akira M. Murakami, MD • Luis E. Diaz, MD • Michel D. Crema, MD • Ali Guermazi, MD, PhD

- Four main adverse joint findings have been structurally observed in patients after IACS injections:
  1. accelerated OA progression,
  2. subchondral insufficiency fracture,
  3. Complications of osteonecrosis, and
  4. rapid joint destruction, including bone loss.

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RESEARCH

Common elective orthopaedic procedures and their clinical effectiveness: umbrella review of level 1 evidence

Ashley W Blom,[1,2] Richard L Donovan,[2] Andrew D Beswick,[2] Michael R Whitehouse,[1,2] Setor K Kunutsor[1,2]

- Ten of the most common elective orthopaedic procedures—arthroscopic anterior cruciate ligament reconstruction, arthroscopic meniscal repair of the knee, arthroscopic partial meniscectomy of the knee, arthroscopic rotator cuff repair, arthroscopic subacromial decompression, carpal tunnel decompression, lumbar spine decompression, lumbar spine fusion, total hip replacement, and total knee replacement—were studied
- Randomized controlled trial evidence supports the superiority of carpal tunnel decompression and total knee replacement over non-operative care.
- No randomized controlled trials specifically compared total hip replacement or meniscal repair with nonoperative care.
- ***Trial evidence for the other six procedures showed no benefit over non-operative care.***

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What happens if we blunt acute inflammation?

We may increase the risks of chronic pain

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

PAIN

Acute inflammatory response via neutrophil activation protects against the development of chronic pain

Marc Parisien[1]†, Lucas V. Lima[2]†, Concetta Dagostino[3]†, Nehme El-Hachem[1], Gillian L. Drury[1], Audrey V. Grant[1], Jonathan Huising[4], Vivek Verma[1], Carolina B. Meloto[1], Jaqueline R. Silva[5], Gabrielle G. S. Dutra[2], Teodora Markova[2], Hong Dang[6], Philippe A. Tessier[7], Gary D. Slade[8], Andrea G. Nackley[9], Nader Ghasemlou[5], Jeffrey S. Mogil[2]*, Massimo Allegri[10,11]*, Luda Diatchenko[1]*

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What about postoperative pain?

BJA

British Journal of Anaesthesia, 131 (1): 93–103 (2023)

doi: 10.1016/j.bja.2023.03.031
Advance Access Publication Date: 23 May 2023
Pain

Dexamethasone and persistent wound pain: a prespecified analysis of the randomised Perioperative Administration of Dexamethasone and Infection (PADDI) trial

Tomás B. Corcoran[1,2,3,*], Catherine Martin[3], Edmond O'Loughlin[2,4], Kwok Ho[1,2,4,5], Matthew Chan[6], Andrew Forbes[3], Kate Leslie[3,7,8] and Paul Myles[3,9]

- 8,400 patients randomized to dexamethasone vs placebo
- Dexamethasone group:
  - Lower post-operative pain
  - Relative risk of 1.2 for ***persistent pain in Dex group.***
  - ***Higher incidence of pain at 6 months (8mg Dex)***

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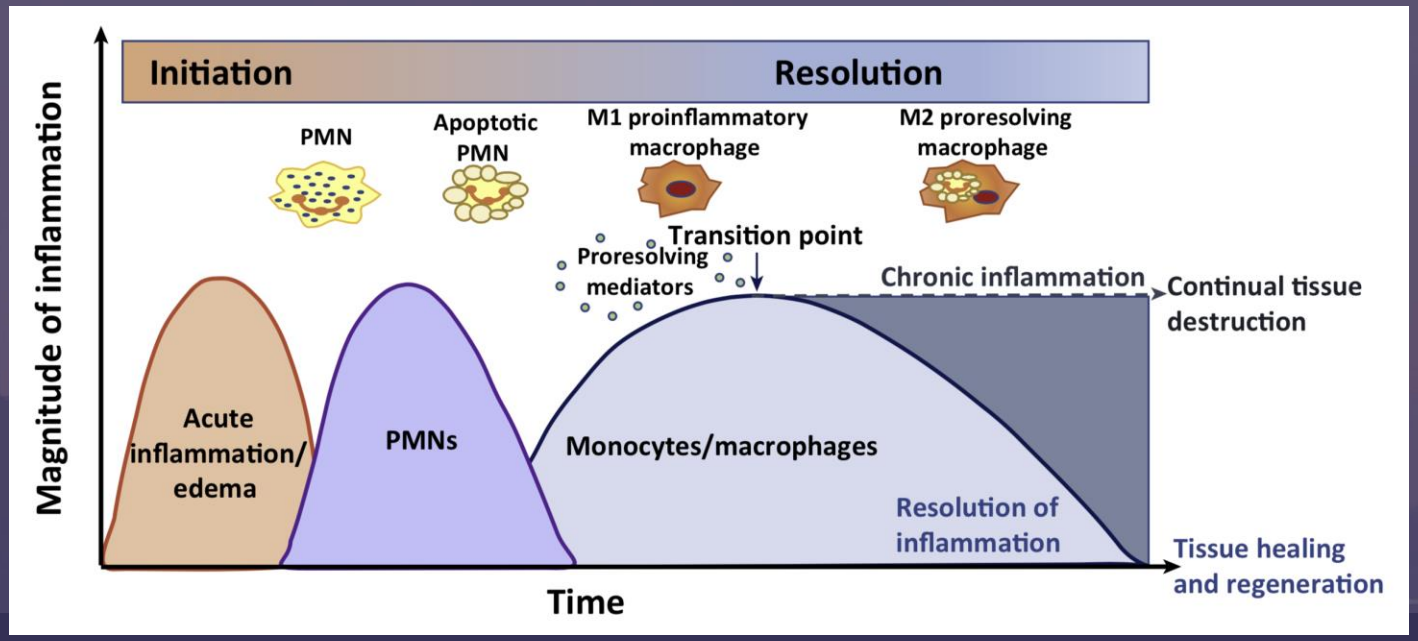
What happens if we stimulate the immune system instead of suppressing it?

Regenerative medicine is a branch of translational research in tissue engineering and molecular biology which deals with the "process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function".



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PAIN 50th Anniversary Supplement

PAIN 166 (2025) S60–S64

PAIN

How people resolve pain: insights from human transcriptomics into immune activation and therapeutic innovations

Andrey Bortsov[a], Sahel Jahangiri Esfahani[b], Lucas V. Lima[b], Ru-Rong Ji[a], Jeffrey S. Mogil[b], Luda Diatchenko[b,*]

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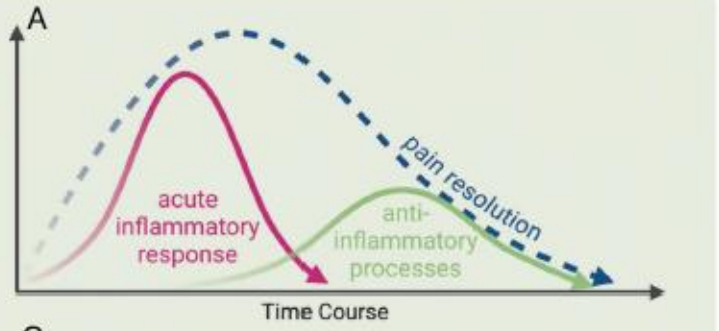
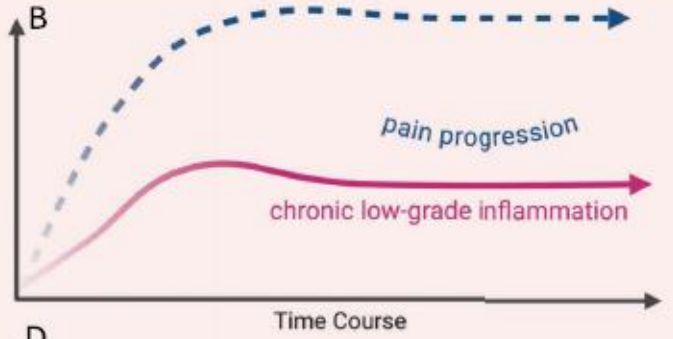
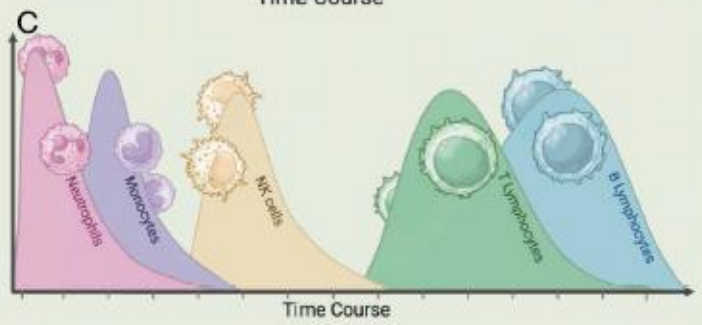
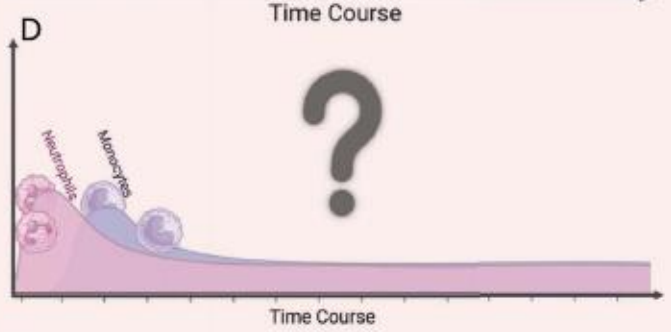






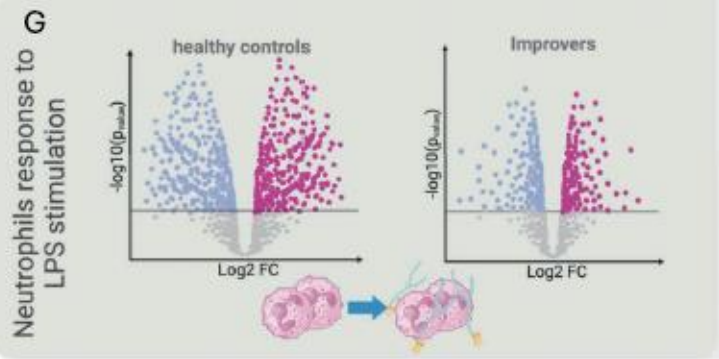


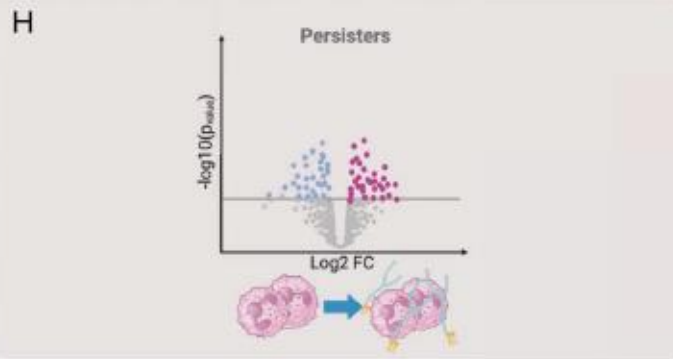
E

Pathway	Acute Pain Resolvers	
	Baseline	Follow-up
GO:0006954 Inflammatory response	↑↑↑	↓
GO:0042119 Neutrophil activation	↑↑↑	↓
GO:0043312 Neutrophil degranulation	↑↑↑	↓
GO:0042116 Macrophage activation	↑↑↑	↓

F

Pathway	Acute Pain Persisters		Chronic TMD
	Baseline	Follow-up	
GO:0006954 Inflammatory response	↓↓	↓	↑
GO:0042119 Neutrophil activation	↓↓	↓	↑
GO:0043312 Neutrophil degranulation	↓↓	↓	↑
GO:0042116 Macrophage activation	↓		





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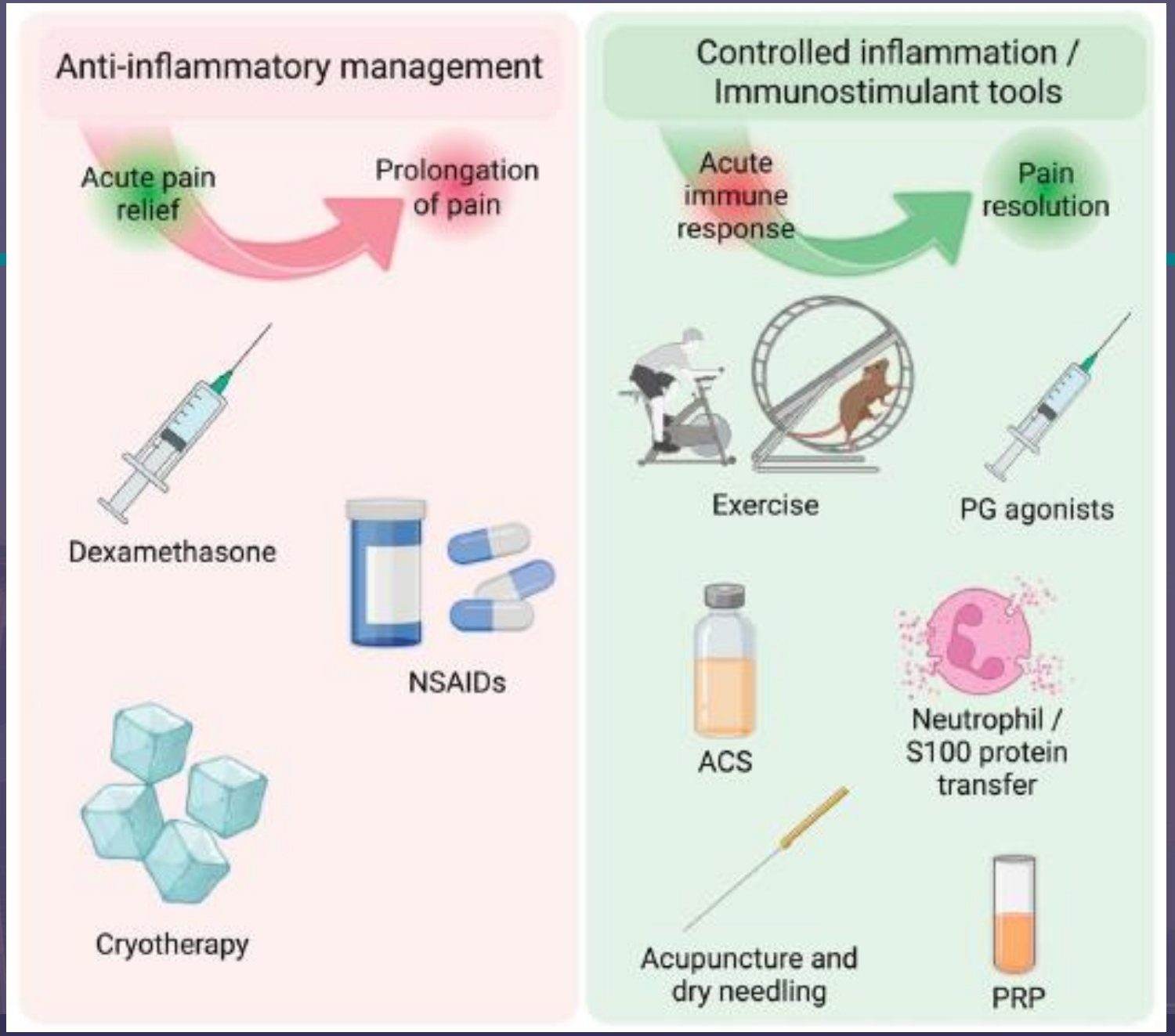

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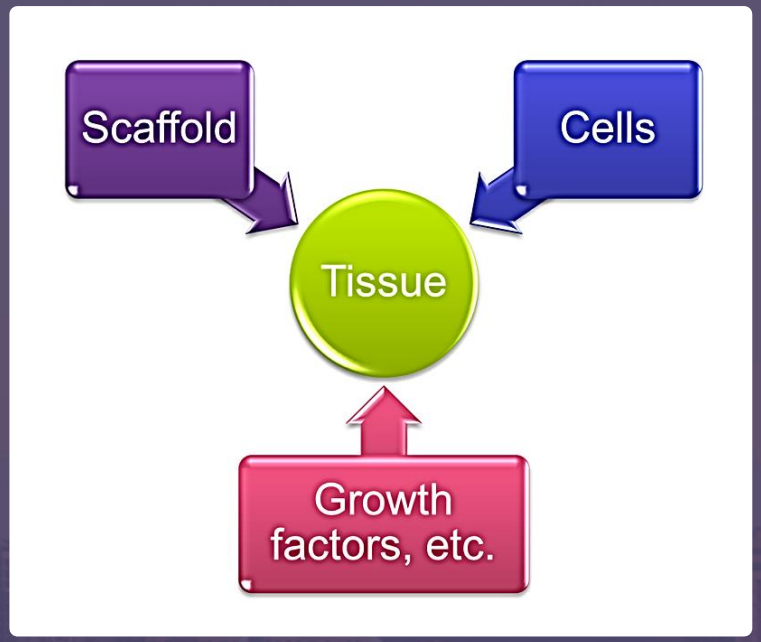
Framework for Regenerative Medicine

- Create living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage or congenital defects. (NIH.gov)
- Targets
  - Cells
  - Scaffold (niche)
  - Stimuli (GFs, etc.)
- Goal is Tissue:
  - Reduce pain
  - Improve function



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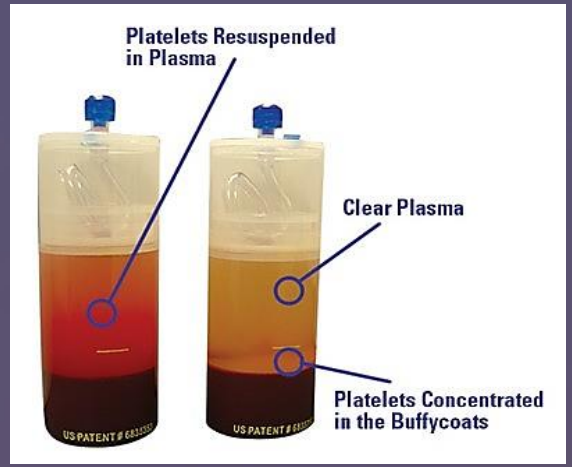
What is included in Regenerative medicine?

This includes:

- Platelet-rich plasma(PRP)
- Bone marrow aspirate concentrate (BMAC)
  - Mesenchymal stromal cells
- Prolotherapy
- Adipose derived stem cells
- Autologous concentrated serum(Regenokine/Orthokine)
- Stromal vascular fraction (SVF)
- Culture expanded cells
- Amniotic/ umbilical stem cells
- Alpha 2 Macroglobulin (A2M)



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(Mason C, et al. 2008)

What are common conditions regenerative medicine is used on?

- Osteoarthritis
- Osteonecrosis/ AVN
- Tendinopathy/ bursopathy
- Tendon and ligament tears
- Vampire facial
- Hair loss
- Erectile dysfunction
- Punctate keratitis
- Some research ongoing in neurological conditions
  - TBI, Stroke, Spinal cord injury

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Regulation

- FDA regulates HCT/Ps in 21 CFR 1271
- “Tissue rules” under section 361 PHSA
  - Category 1 – low risk, not subject to oversight
  - Category 2 – lower risk that meet specific criteria
    - Minimal manipulation
    - Homologous
    - Not combined
    - Systemic effect criteria/autologous
  - Category 3 – fail Category 2 ➔ 351 (i.e. a “drug”)
    - Require biologic license or IND
    - RMAT now an option

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Regulation

- You are a manufacturer of biological products & HCT/Ps
- Lawful marketing of a biological product under the Public Health Service Act (PHSA) requires license
  - Must register with the FDA
  - Submit list of all manufactured HCT/Ps
  - Comply with 21 CFR 1271
- Same day surgery exemption
  - Precludes need to comply with 21 CFR 1271
  - “rinse, cleanse, sizing, shaping, labeling, storing”

Federal Trade Commission

Protecting America’s Consumers

You should read all the guidelines at FDA website

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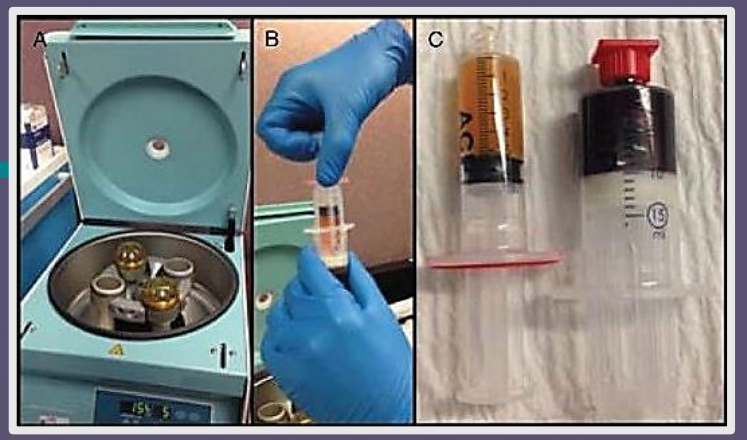
PRP- Platelet-rich plasma



- Platelet-Rich Plasma:
  - PRP is most simply defined as a volume of plasma that has a platelet (PLT) count above baseline (BL) blood levels.
- PRP is an autologous blood product that can be injected into damaged areas to deliver PLT-derived growth factors (GFs) and promote healing.
- <u>Rationale – supraphysiologic PLTs</u>
  - All purpose repair “cells”
  - Growth delivery vehicle
  - VEGF, TGF, PDGF, EGF, TGF, etc.
  - Modulate inflammation
  - Promote healing

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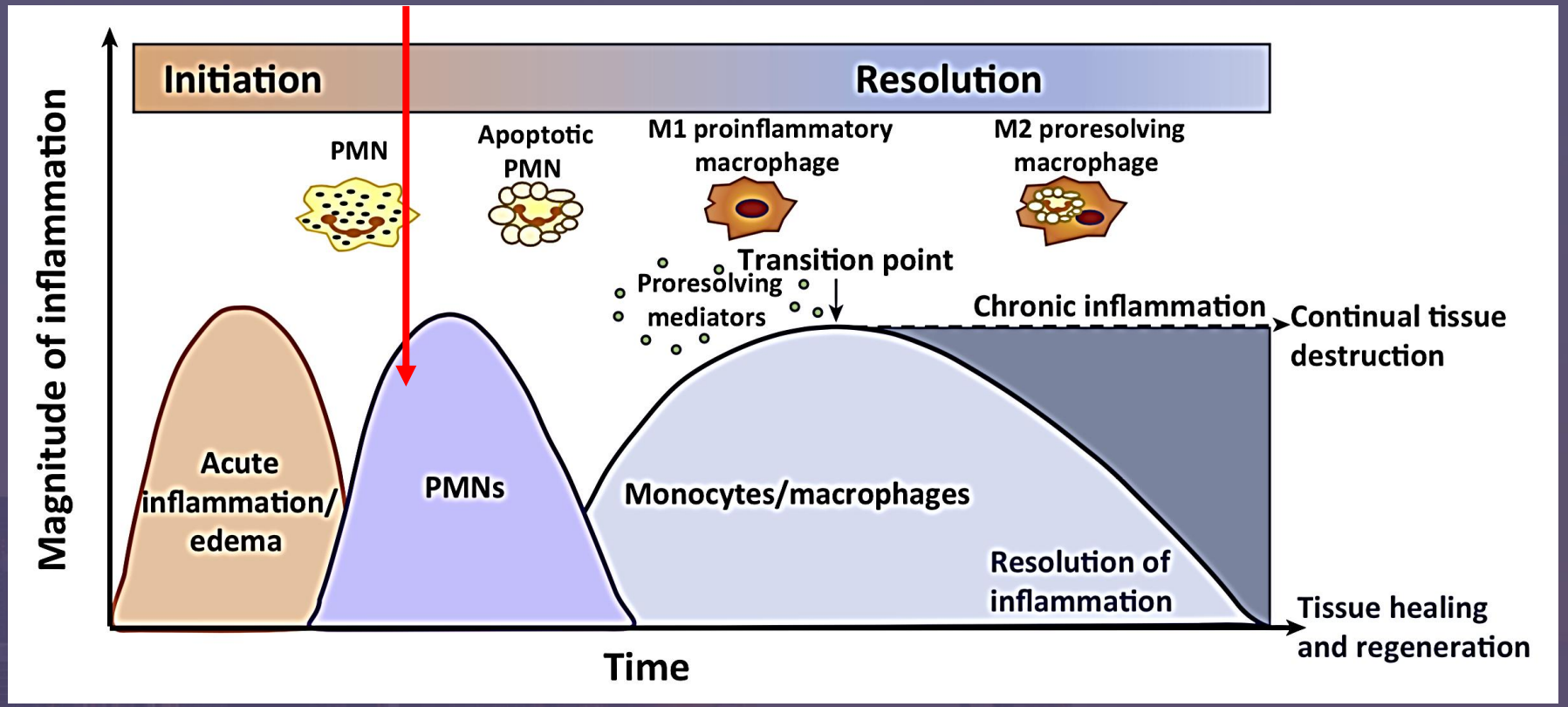
Pourcho AM, et al. 2014 Am J PM R, Fadadu Reg Anesth Pain Med 2019;Chahla Arthroscopy 2018; Le Curr Rev Musc Med 2018; Xu Sci Rep 2017;Fitzpatrick AJSM 2017; Alshahir et al. 2025

PRP within the healing cascade

PRP



Lumelsky et al: Autotherapies: Enhancing endogenous healing and regeneration. 2018

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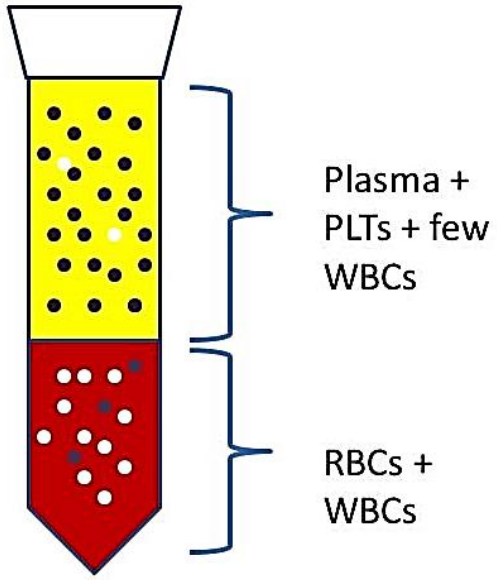
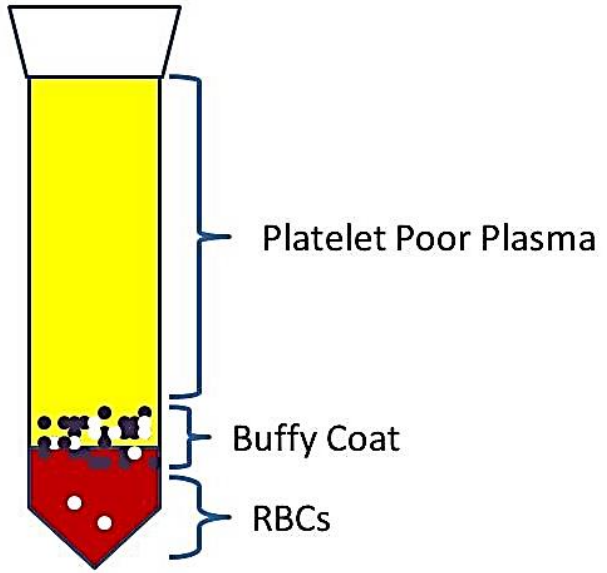
PRP – Not All PRP IS SAME

Leukocyte Poor PRP



Smaller WB draw
Shorter spin time
Lower PLTs
Very low RBCs & WBCs

Leukocyte Rich PRP



Larger WB draw
Longer spin time
Higher PLTs
RBCs & WBCs

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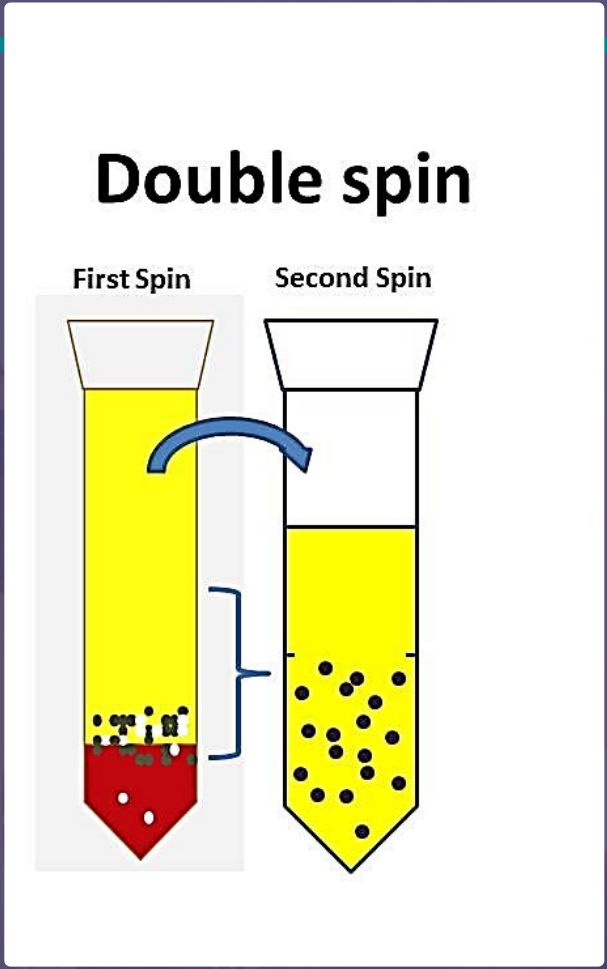
PRP – Not All PRP IS SAME



Second spin:
-Increases PLTs dramatically -
Reduces RBCs dramatically
-Reduces WBCs, esp. PMNs

Goal of DS PRP Systems:
-High PLT
-RBC poor
-LP (w/respect to PMNs)

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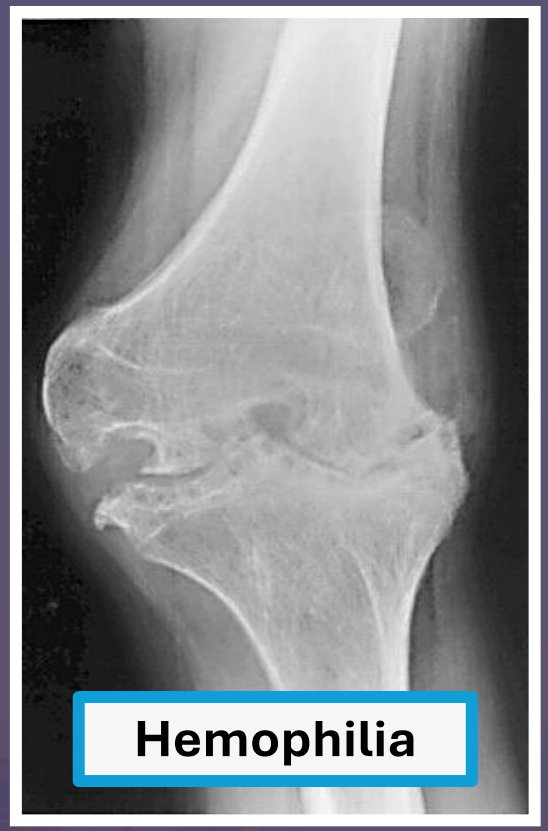
PRP – Composition May Be Important

- RBCs → pro-inflammatory
  - Joints → chondro- & synoviotoxic
  - Tendons & ligaments - ?
- WBCs (e.g. LR-PRP)
  - Pro-inflammatory, likely PMNs
  - Increase GFs, cytokines, etc.
  - PLT/PMN may be as important
  - Joints – probably bad
  - Tendons/soft tissue – may be good



Fadadu Reg Anesth Pain Med 2019;Chahla Arthroscopy 2018; Xu Sci Rep 2017; Fitzpatrick AJSM 2017;Mautner PMR 2015;Braun AJSM 2014; Dragoo AJSM 2012;Zimmerman Transfusion 2001

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Does it work?

- Literally thousands of peer-reviewed manuscripts: here are a few notable ones
- Achilles tendon
  - De jonge et al 2011, 2016; Kearney et al., 2021; de Vos et al., 2010
- Hamstring tendons
  - Rettig et al 2013, Wetzel et al 2013
- Jumper's knee (Patellar tendon)
  - Filardo Et al 2010; Andriolo et al., 2019; Belk et al., 2021
  - Dragoo et al., 2014; Vetrano et al., 2013
- General tendinopathies
  - Mishra et al 2009; Fitzpatrick et al 2017
- Lateral Epicondylitis (tennis elbow)
  - Mautner et al 2013,2018, Thanasas et al 2011;
  - Arirachakaran et al., 2016; Dong et al., 2020
- Plantar Fascia-
  - Martinelli et al. 2013; Franceschi et al., 2014
  - Ling et al., 2018; Hurley et al., 2020; Jain et al., 2018
- Gluteal tendons
  - Fitzpatrick, J. et al 2019

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PRP For Tendon Disorders

- Meta-analysis of RCTs
- Strong evidence that safe and LR-PRP improves outcomes in tendinopathy > LP-PRP/ACP)
  - Some effect of LP-PRP noted
- Optimal technique indeterminate, but suggested:
  - Minimize use of local anesthesia in tendon
  - Single Injection, but can repeat
  - Peppering technique
  - Ultrasound guidance

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Fitzpatrick AJSM 2017; Dragoo Et al 2018, 2022

But PRP doesn't always work: patient selection likely also matters

JAMA | Original Investigation

Effect of Intra-articular Platelet-Rich Plasma vs Placebo Injection on Pain and Medial Tibial Cartilage Volume in Patients With Knee Osteoarthritis
The RESTORE Randomized Clinical Trial

Kim L. Bennell, PhD; Kade L. Paterson, PhD; Ben R. Metcalf, BSc; Vicky Duong, DPT; Jillian Eyles, PhD; Jessica Kasza, PhD; Yuanyuan Wang, PhD; Flavia Cicuttini, PhD; Rachelle Buchbinder, PhD; Andrew Forbes, PhD; Anthony Harris, MSc; Shirley P. Yu, MPH; David Connell, MMed; James Linklater, MBBS; Bing Hui Wang, PhD; Win Min Oo, PhD; David J. Hunter, PhD

JAMA | Original Investigation

Effect of Platelet-Rich Plasma Injections vs Placebo on Ankle Symptoms and Function in Patients With Ankle Osteoarthritis
A Randomized Clinical Trial

Liam D. A. Paget, MD; Gustaaf Reurink, PhD; Robert-Jan de Vos, PhD; Adam Weir, PhD; Maarten H. Moen, PhD; Sita M. A. Bierma-Zeinstra, PhD; Sjoerd A. S. Stufkens, PhD; Gino M. M. J. Kerkhoffs, PhD; Johannes L. Tol, PhD; for the PRIMA Study Group

Hyaluronic Acid Versus Platelet-Rich Plasma

A Prospective, Double-Blind Randomized Controlled Trial Comparing Clinical Outcomes and Effects on Intra-articular Biology for the Treatment of Knee Osteoarthritis

Brian J. Cole,*†‡§‖¶ MD, MBA, Vasili Karas,# MD, MS, Kristen Hussey,† MS, David B. Merkow,† BA, Kyle Pilz,†¶ MMS, PA-C, and Lisa A. Fortier,** DVM, PhD, DACVS
Investigation performed at the Rush University Medical Center, Chicago, Illinois, USA

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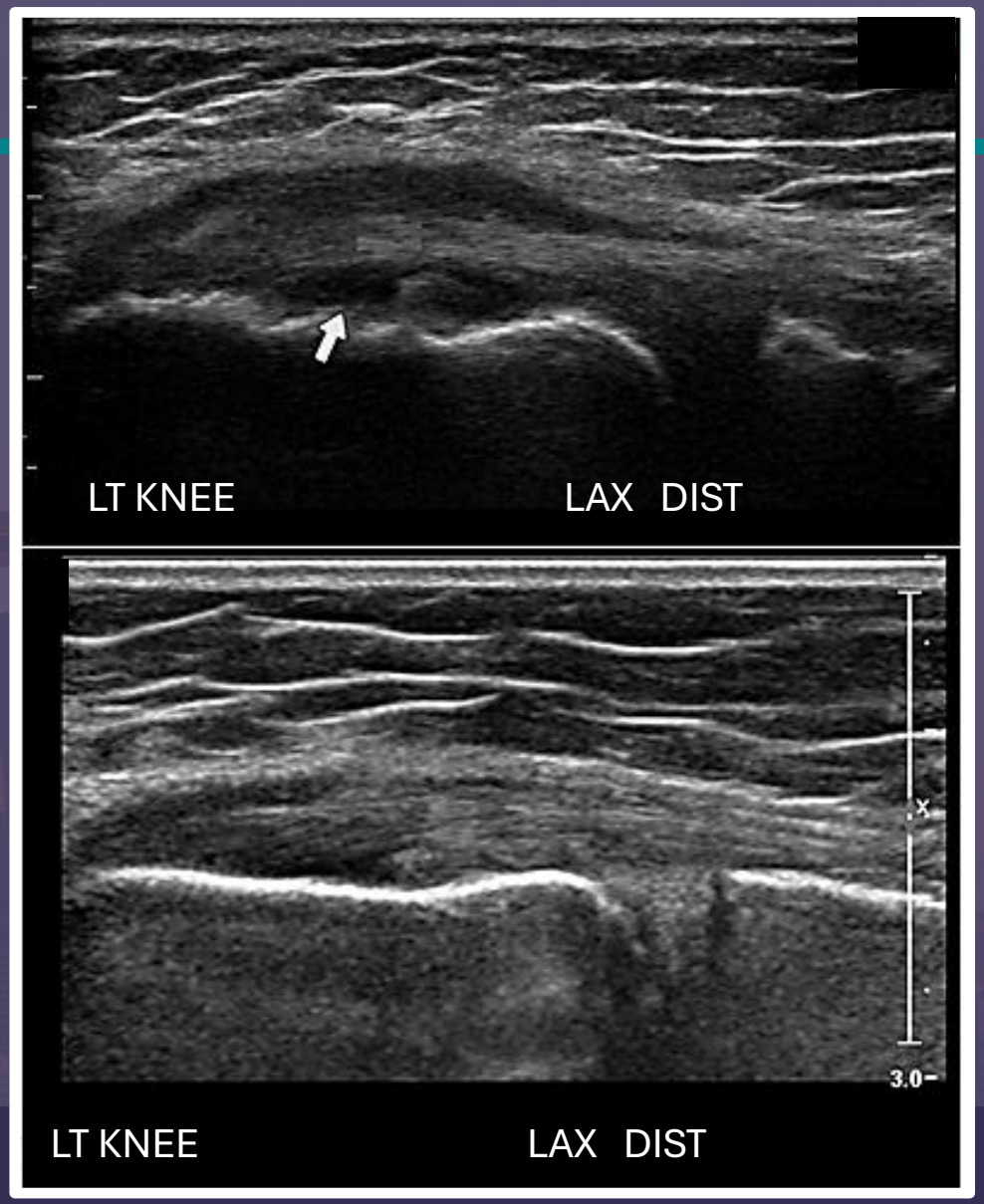
Does it work?: Ligament tears

Initial POC US

⇩

6-week POC US



- 38 y.o. F
- 2 years out MCL tear
- Still with medial knee pain

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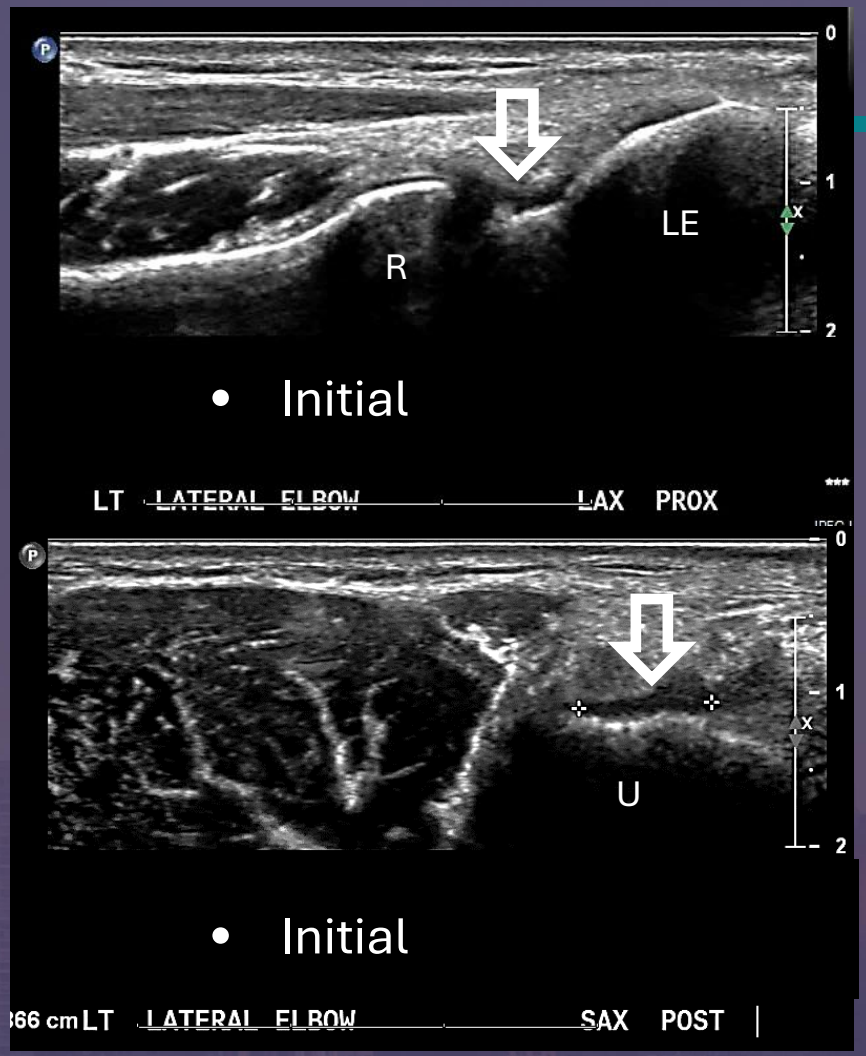
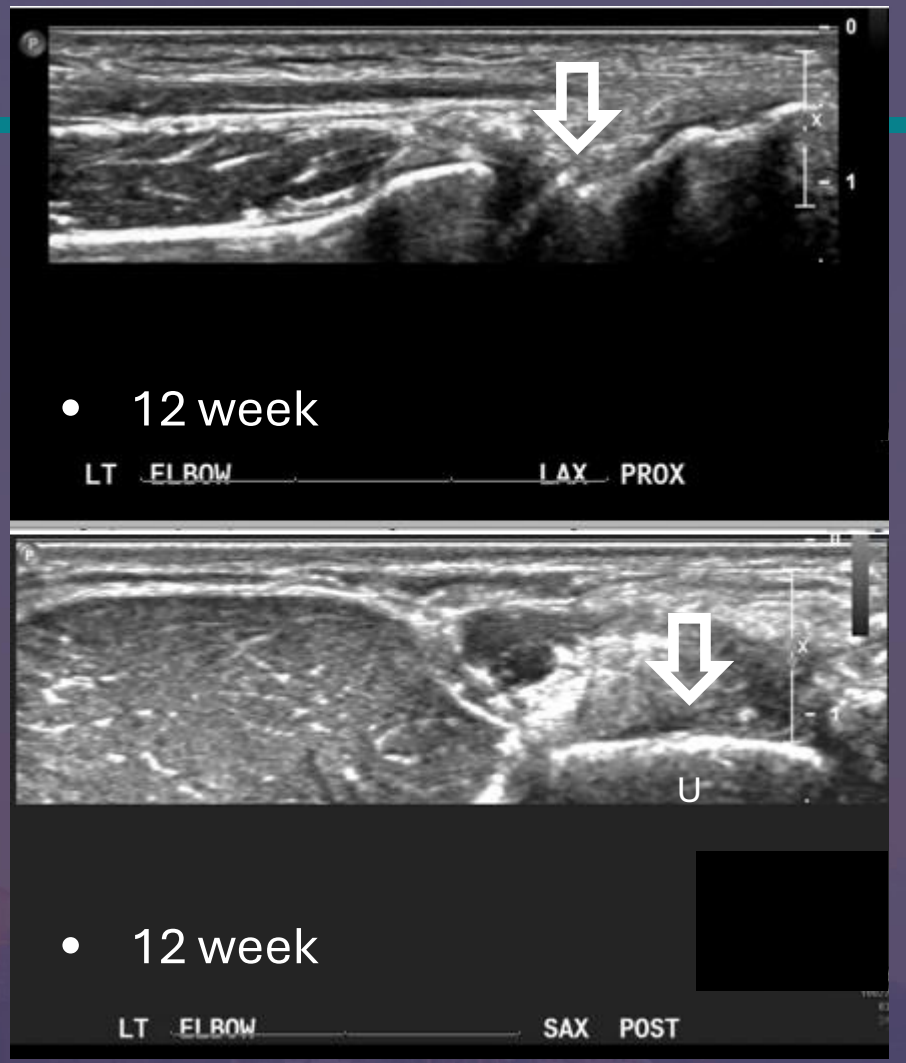
RCL tear pain for 1 year



- Initial

- Initial



- 12 week

- 12 week

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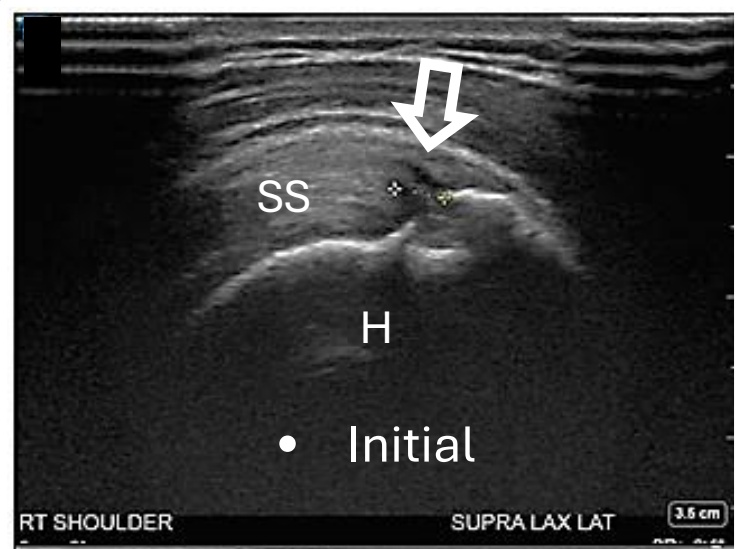
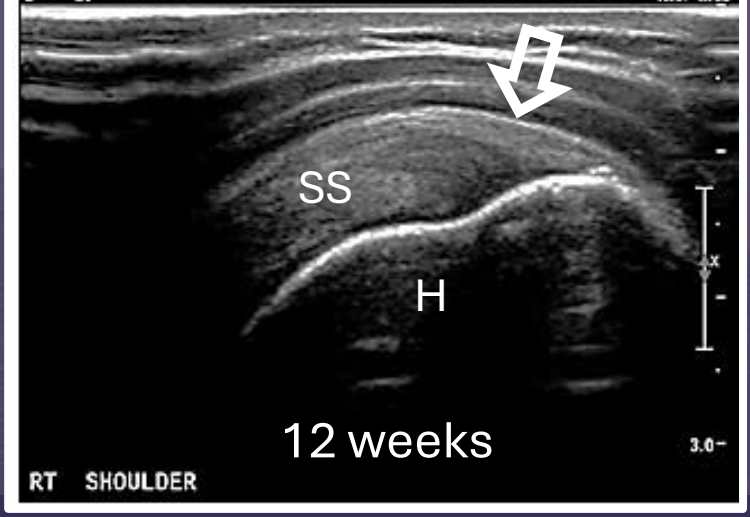
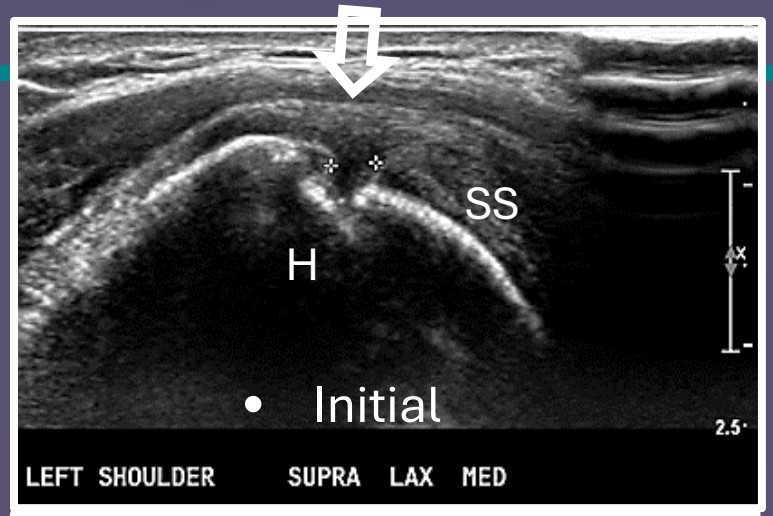
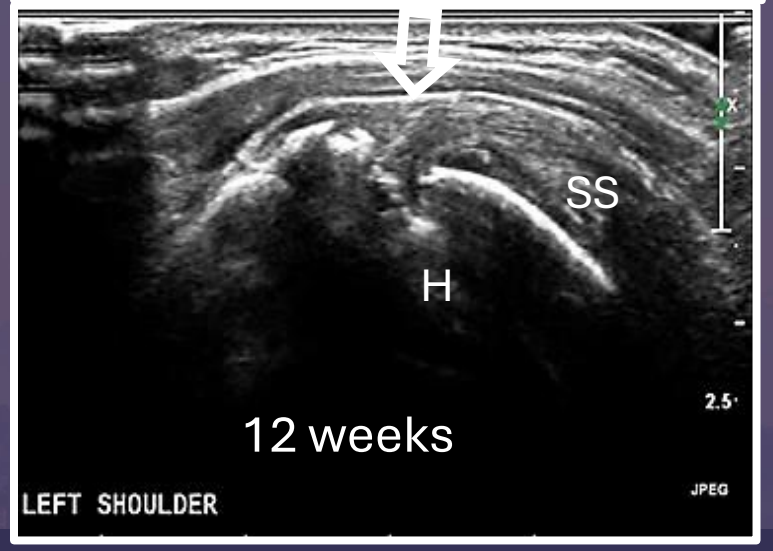
Does it work? : Tendons





- SS Partial tears
- (two diff patients)

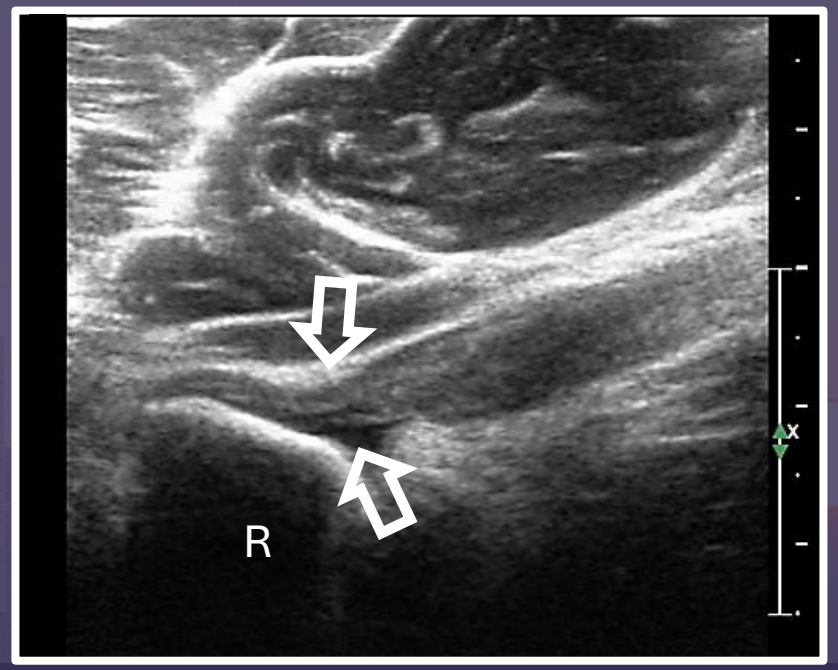




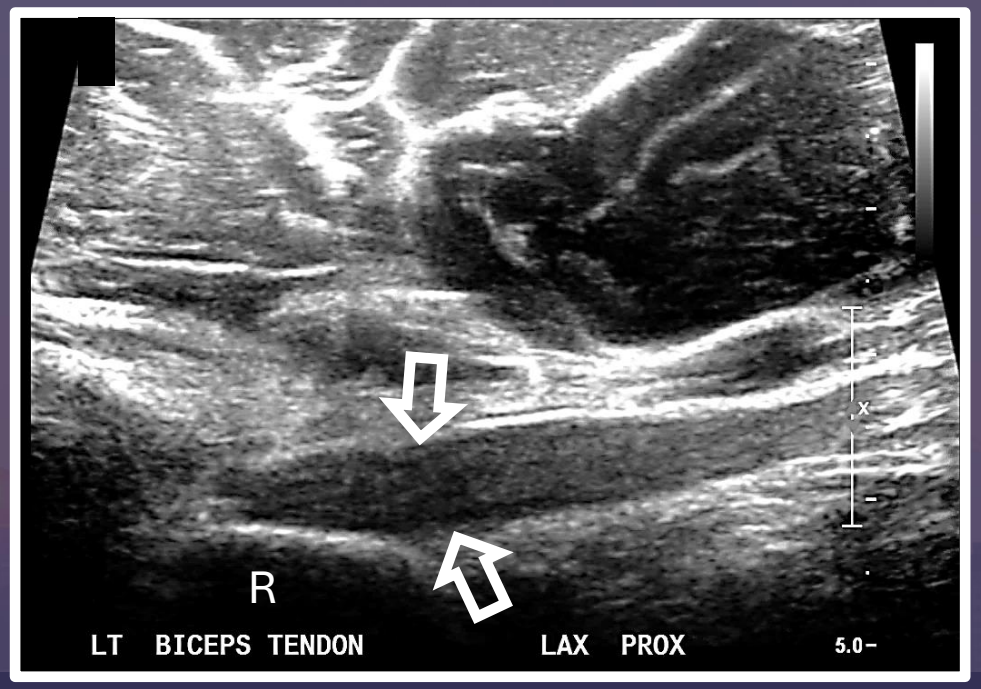
Distal Biceps tendon chronic partial rupture

- 46 y.o. M - 12 months of pain
- High grade partial rupture of distal biceps tendon

Initial POC US



12 week US



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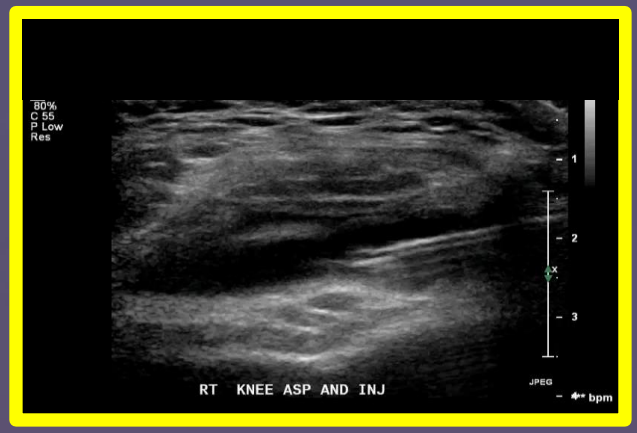
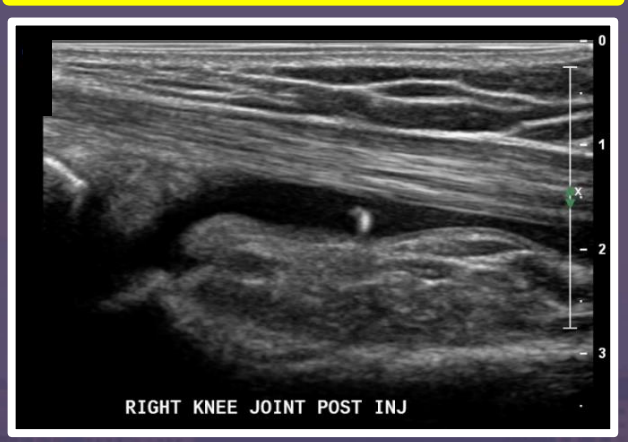
PRP For Osteoarthritis – Knee

- Multiple meta-analyses/systematic reviews RCTs & PCS
- In general:
  - Reasonably safe: AEs < HA, saline
  - <u>LP-PRP > HA, Saline pain & function</u>
  - LR-PRP less effective
  - Single injection, but can repeat
  - Slow onset ➔ last 6-12 months
  - More effective in less severe OA
  - New evidence of disease modulation





Delanois J 2019;Di 2018; Dai 2017; Riboh 2016;Filardo 2015, 2012; Patel 2013; AJSM 2012;Sanchez 2012;

Original Research

Randomized, Placebo-Controlled Analysis of the Knee Synovial Environment Following Platelet-Rich Plasma Treatment for Knee Osteoarthritis

Jason D. Tucker, MD, Lance L. Goetz, MD, Michael B. Duncan, PhD, Jared B. Gilman, MD, Lynne W. Elmore, PhD, Scott A. Sell, PhD, Michael J. McClure, PhD, Peter V. Quagliano, MD, Caroline C. Martin, MD

- Novel biomarkers including levels of interleukin (IL)-5, IL-6, IL-10, and tumor necrosis factor-α were measured in synovial fluid 10 days after PRP treatment.
- **Altered gene expression profiles in MSCs from patients treated with PRP were observed for matrix metalloproteinases and inflammatory markers (IL-6, IL-8, CCL2, TNF-α).**
- ***A2M protease was significantly increased following PRP treatment*** (P = .005).
- WOMAC scores declined for up to 3 months from baseline levels and remained low at 6 and 12 months in the PRP group.

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How about osteoarthritis?

Journal of Stem Cells & Regenerative Medicine
ISSN 0973 - 7154

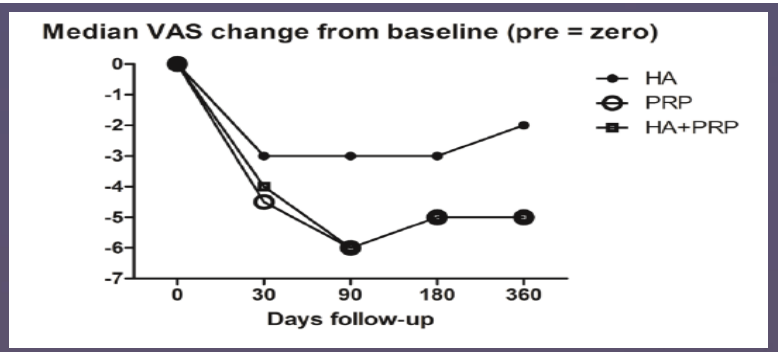
RESEARCH ARTICLE

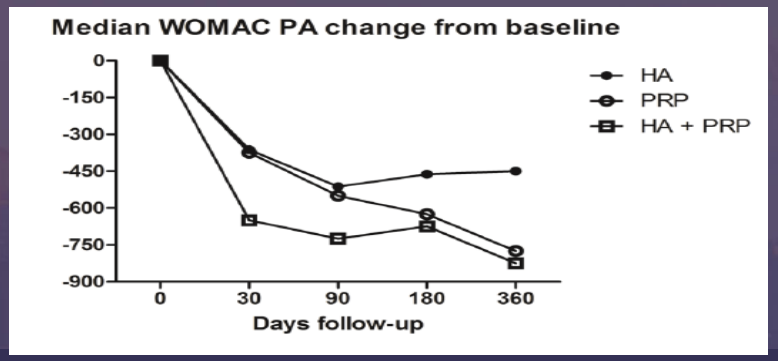
JSRM Code: 012020300011

Randomized controlled trial comparing hyaluronic acid, platelet-rich plasma and the combination of both in the treatment of mild and moderate osteoarthritis of the knee

Lana JFSD[1,4], Weglein A[3], Sampson S[2], Vicente EF[1], Huber SC[1,7], Souza CV[4], Ambach MA[5], Vincent H[6], Urban-Paffaro A[7], Onodera CMK[7], Annichino-Bizzacchi JM[7], Santana MHA[8], Belangero WD[8]

- RTC: n=105
- Baseline Pain: 7/10
- 3 mo: 1/10
- 12 mo: 2/10
- WOMAC PA: 988→213





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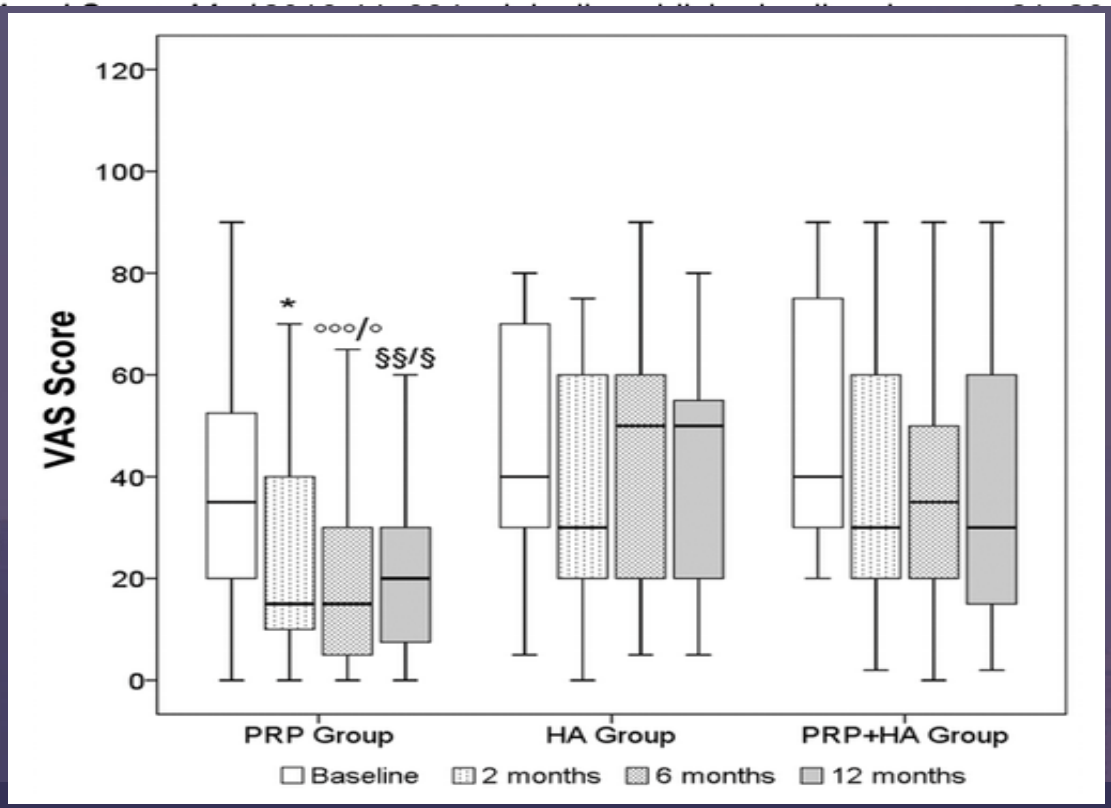
How about hip arthritis?

The American Journal of Sports Medicine

Ultrasound-Guided Injection of Platelet-Rich Plasma and Hyaluronic Acid, Separately and in Combination, for Hip Osteoarthritis: A Randomized Controlled Study

Dante Dallari, Cesare Stagni, Nicola Rani, Giacomo Sabbioni, Patrizia Pelotti, Paola Torricelli, Matilde Tschon and Gianluca Giavaresi



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How about augmenting surgery?

Clinical Study

A Prospective, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study Evaluating Meniscal Healing, Clinical Outcomes, and Safety in Patients Undergoing Meniscal Repair of Unstable, Complete Vertical Meniscal Tears (Bucket Handle) Augmented with Platelet-Rich Plasma

Rafal Kaminski,[1] Krzysztof Kulinski,[1] Katarzyna Kozar-Kaminska,[2] Monika Wielgus,[3] Maciej Langner,[1] Marcin K. Wasko,[4] Jacek Kowalczewski,[5] and Stanislaw Pomianowski[1]

- Level 1 data
- 37 patients with complete vertical meniscus tears.
- Patients received an intra-repair site injection of either PRP or sterile 0.9% saline
- After 18 weeks, the meniscus healing rate was significantly higher in the PRP-treated group than in the control group (85% versus 47%, $P = 0.048$).
- Functional outcomes were significantly better 42 months after treatment than at baseline in both groups. The IKDC score, WOMAC, and KOOS were significantly better in the PRP-treated group than in the control group.
- No adverse events were reported.

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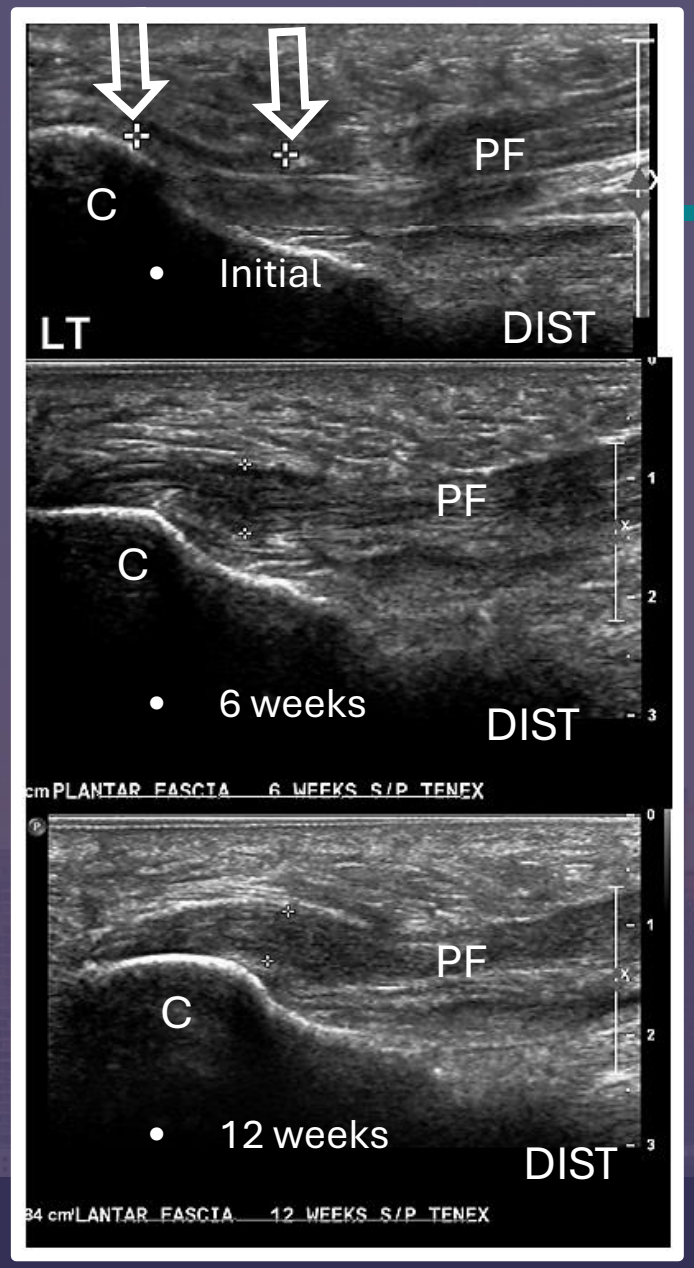
What about augmenting with ultrasonic tenotomy with PRP?



- 33-year-old female
  - 4 years of PF pain
  - High grade partial rupture of central band with avulsion (*arrows)*
  - Treated with ultrasonic tenotomy and LR- PRP same day
  - Pain free by 12 weeks
  - Back to full running by 3 months

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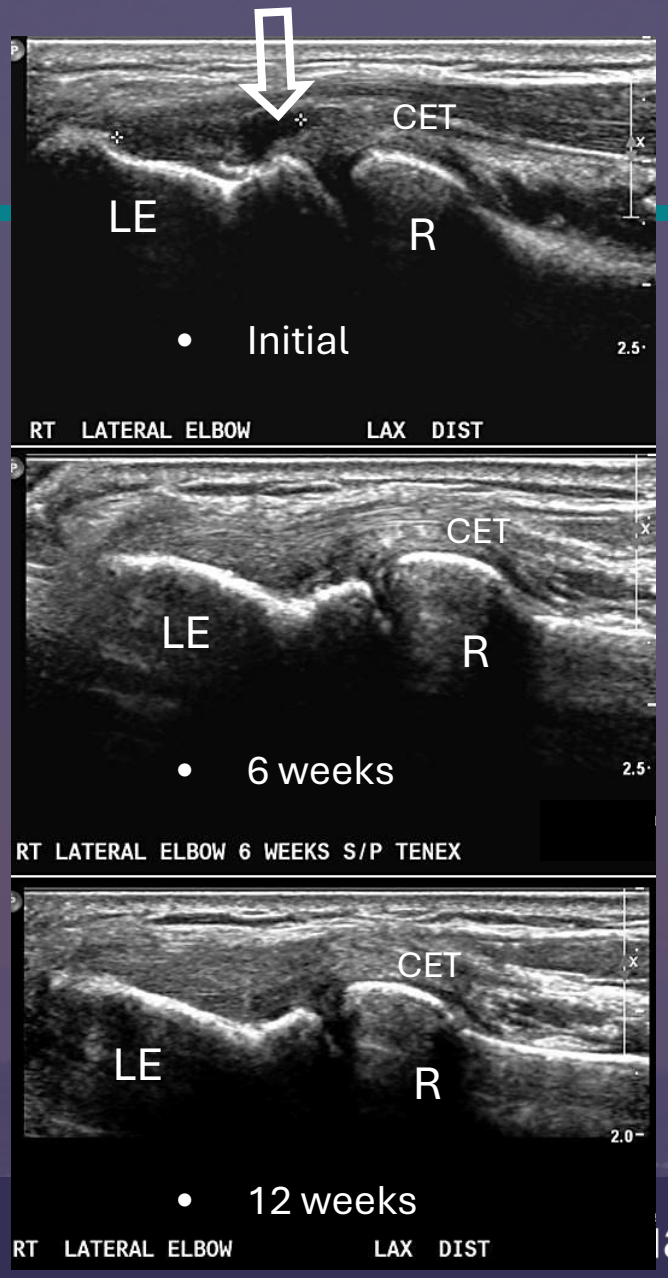
What about augmenting with ultrasonic tenotomy with PRP?

- 38-year-old male
- 9 months of pain
- High grade CET partial thickness rupture
- Treated with UT and PRP with A2M same day
- Pain free by 6 weeks
- Full return to hockey at 8 weeks

This is my elbow!



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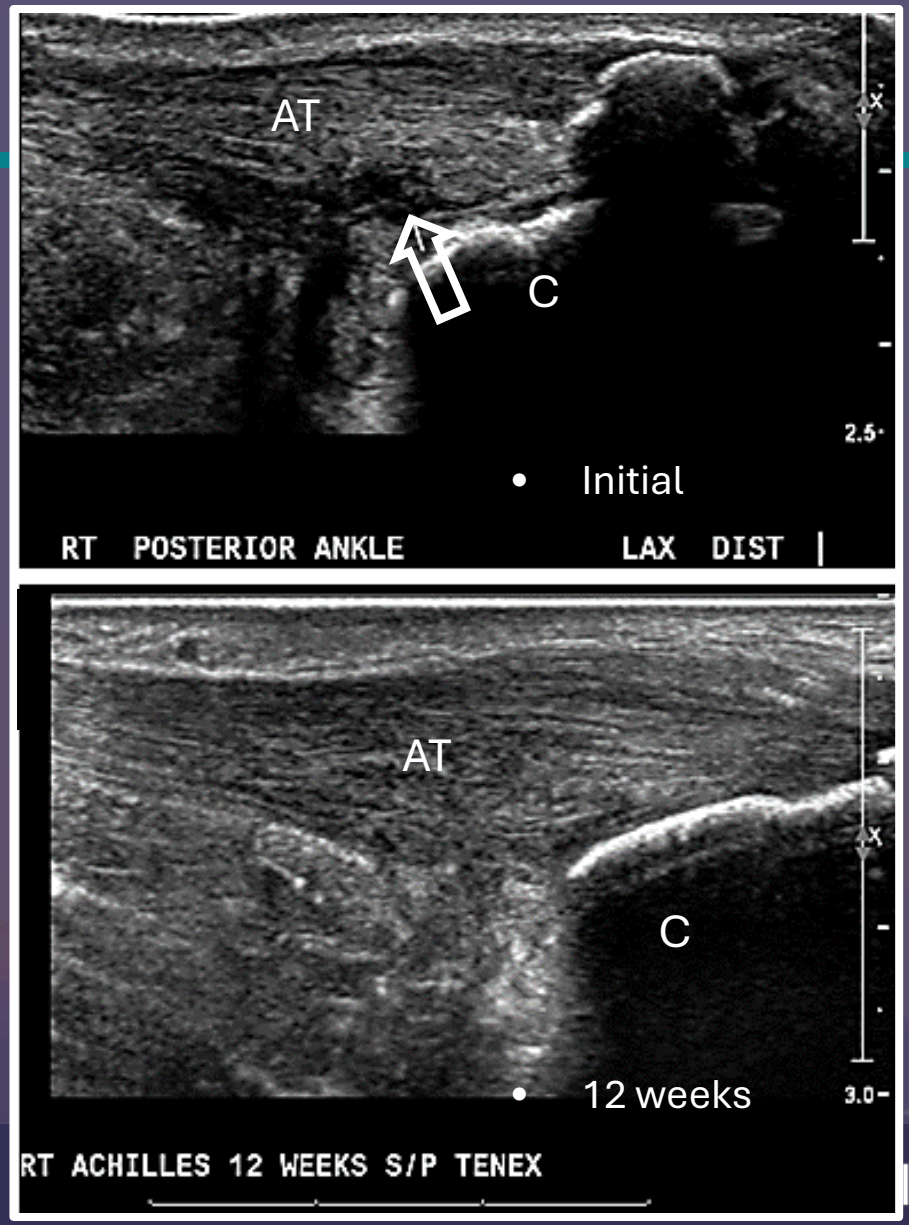
What about augmenting UT with PRP?

- 56-year-old Tennis player
- > 10 years of pain
- Insertional Achilles tendiniopathy with Haglund's deformity, enthesopathy, and partial thickness tearing
- Treated with UT with removal of enthesophyte and PRP same day
- Pain free by 4.5 months
- Back to tennis full at 5 months



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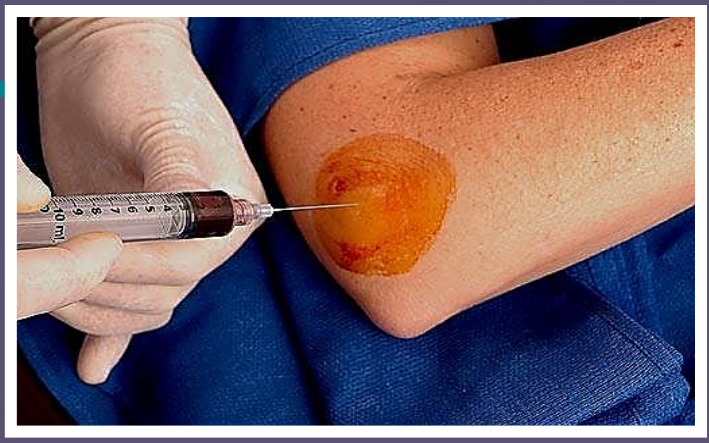
PRP – Clinical Considerations



- Evidence consistently shows that Platelet-Rich Plasma (PRP) is more effective than corticosteroid (CS) injections for long-term (3–12+ months) pain relief and functional improvement in knee osteoarthritis and chronic tendinopathies, offering superior sustained benefits. While steroids provide better pain relief within the first 4–6 weeks, PRP outperforms them over time, with fewer risks of tissue degeneration.
- **Key Evidence Supporting PRP Over Steroids**
- **Knee Osteoarthritis:** Multiple studies show PRP offers superior long-term pain relief (6–12 months) compared to steroids. A 2022 randomized trial indicated PRP provided better long-term functional improvement than steroid injections.
- **Chronic Tendinopathy:** PRP is strongly favored over steroids for conditions like lateral epicondylitis (tennis elbow) and gluteal tendinopathy, with studies indicating better pain and function improvements at 12–24 weeks and 12 and 24 month follow-up.
- **Rotator Cuff Injuries:** Research suggests PRP is better for sustained, long-term improvement (24 weeks, 6 months and 1 year) in shoulder function compared to steroids.
- **Safety Profile:** Unlike corticosteroids, which can weaken tendons and cartilage over time, PRP poses minimal risks and may improve tissue structure.

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Delanois J Arthroplasty 2019;Lamplot AJSM 2019; Fadadu Reg Anesth Pain Med 2019;Mautner PM&R 2013

“Stem cells”

- Clinically available products
  - Placental – Micronized dehydrated human amnio-chorionic matrix (mDHACM)
  - Bone marrow concentrate
  - Adipose – Micro-fragmented fat

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How patients think “stem cells” work…

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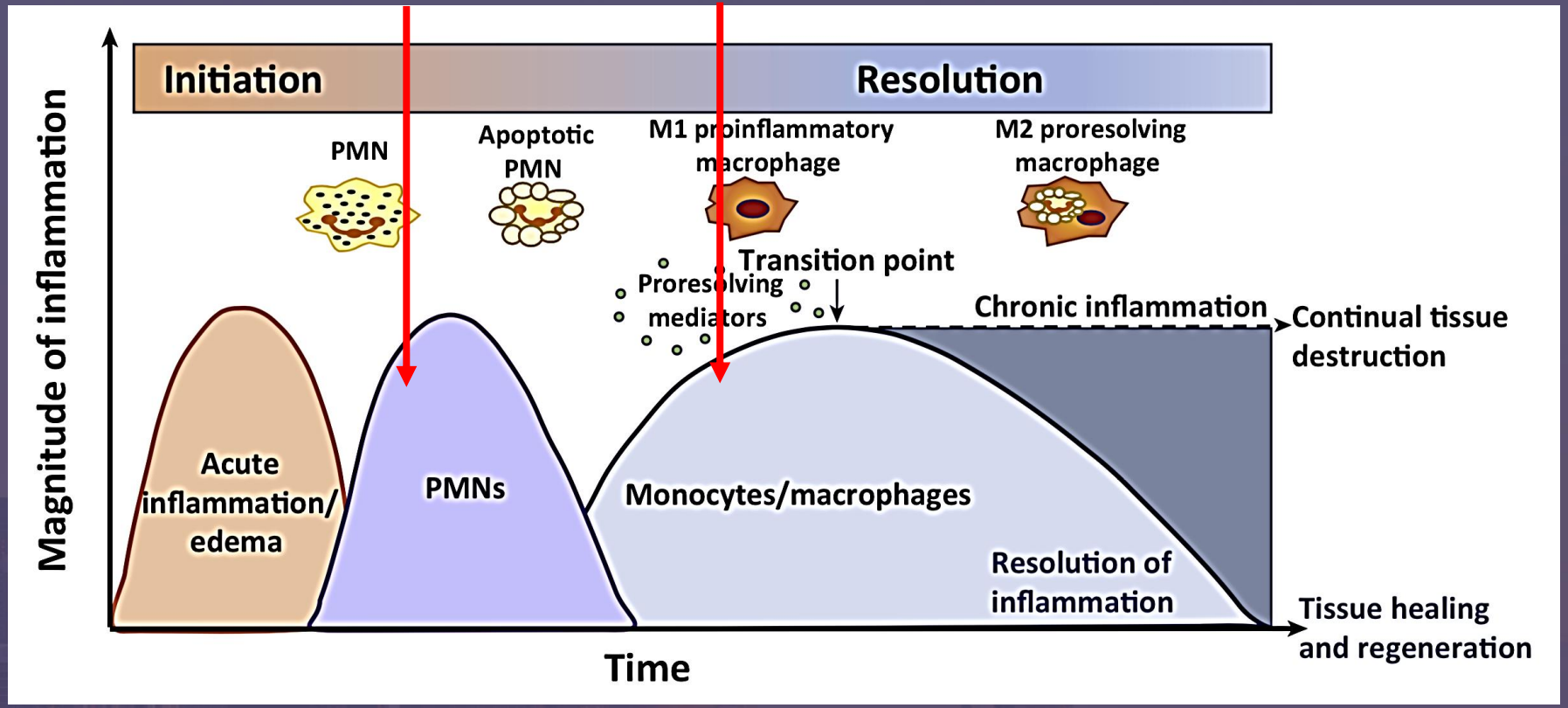
MSCs within the Immune Cascade

PRP MSC



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Sources of MSCs

- Sources of MSCs include:
  - embryonic SCs (ESCs),
  - induced pluripotent stem cells (iPSCs),
  - hematopoietic stem cells (HSCs), and
  - Mesenchymal stromal cells (MSCs)

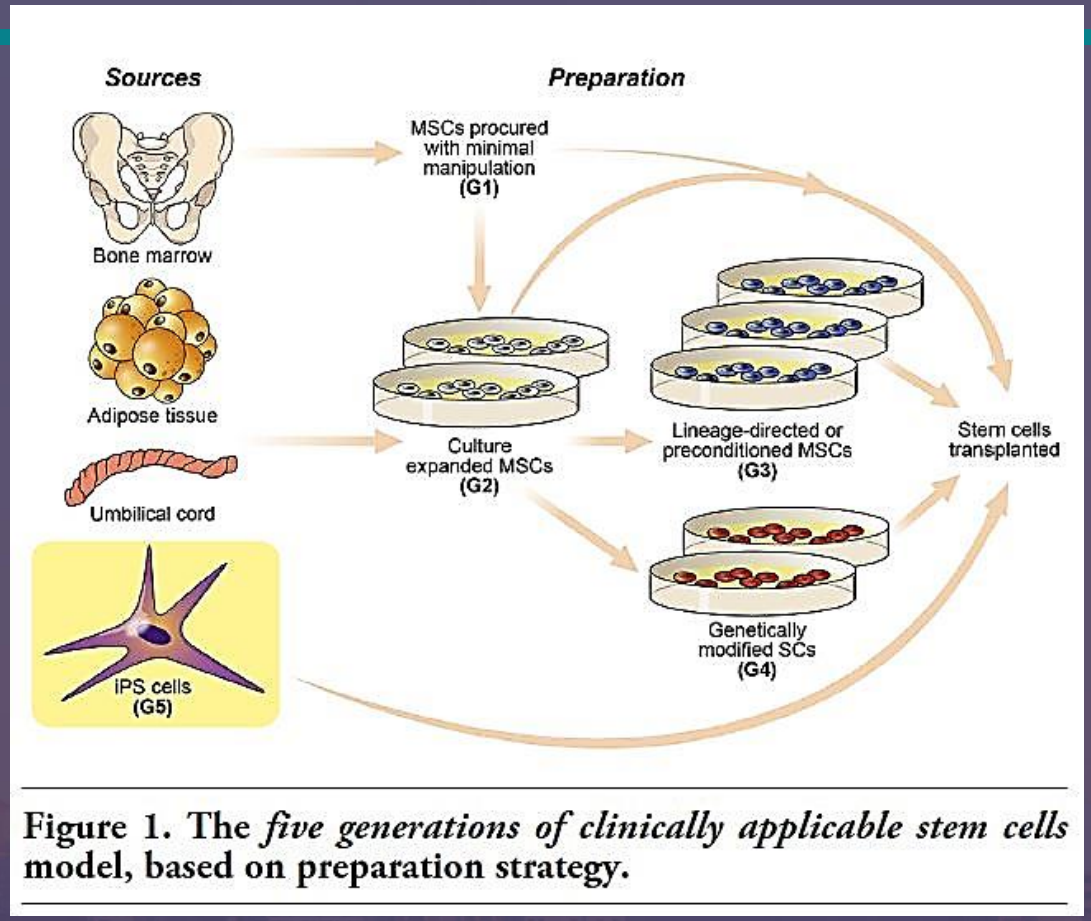
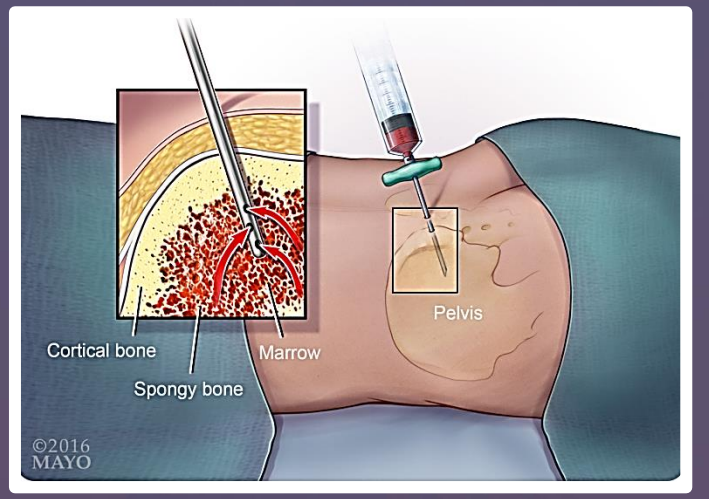


Figure 1. The *five generations of clinically applicable stem cells* model, based on preparation strategy.

Hunt, CL et al 2017

What is Bone Marrow Aspirate Concentrate (BMAC) ?

- The process involves harvesting cells concentrating then in a centrifuge with the goal of obtaining the mesenchymal stem cells/ mesenchymal signaling cells (MSCs)
- Autologous, stem-cell product
- Rationale – concentrate PCs
  - MSCs, HSCs, and others
  - Bioactive proteins like PRP
    - Higher IL-1Ra vs. PRP
- Goal - improve pain & function
  - More powerful than PRP?
  - Disease modification ?
- Most articles present the use of BMAC derived MSCs as a safe procedure and report good results.



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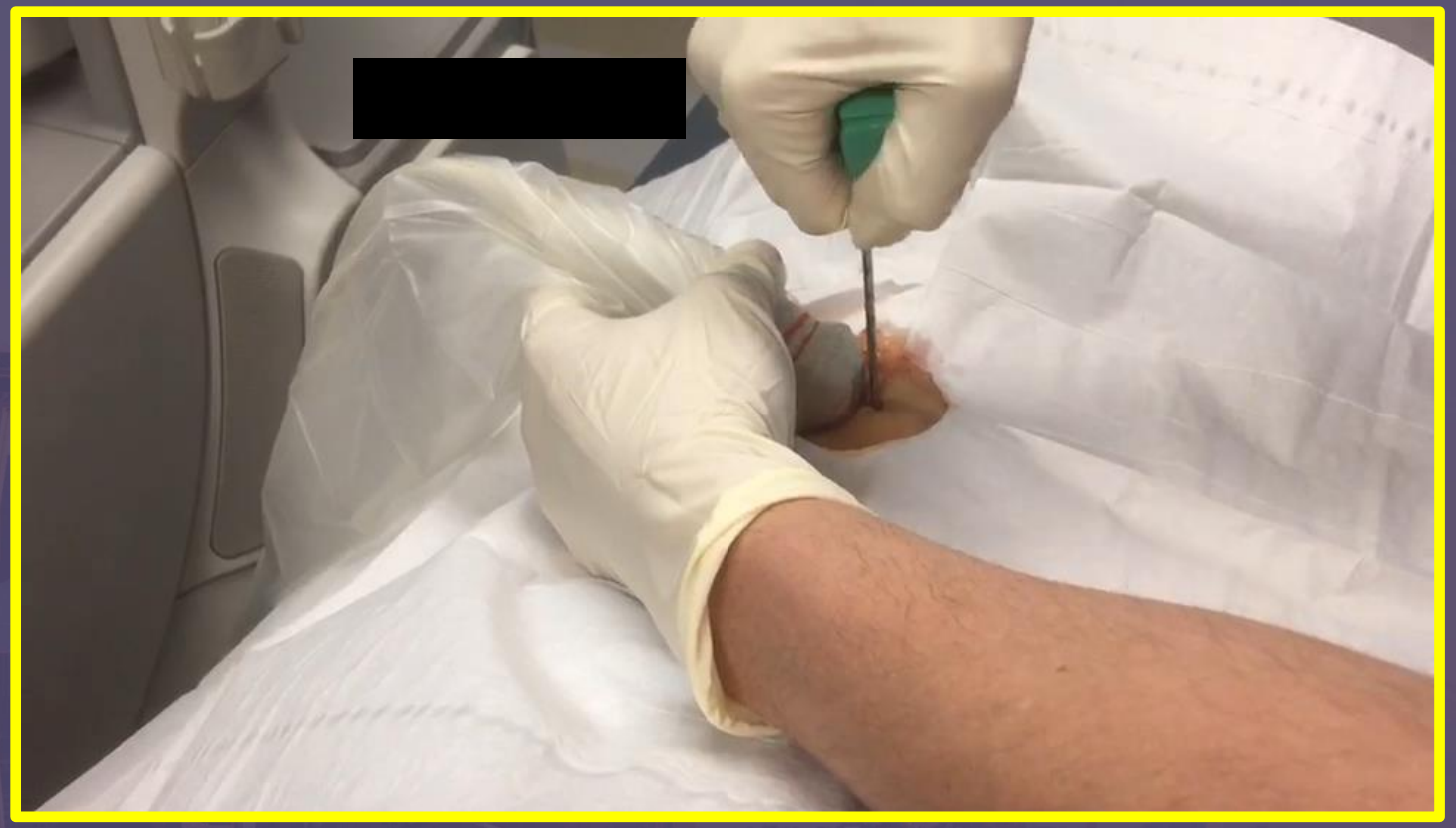
Centeno et al. 2016; Hernigou P. et al. 2005,2014 Hendrich C. et al. 2009, Sampson S. et al 2015. Steinert AS, 2011; Delanois J Arthroplasty 2019

Procedure



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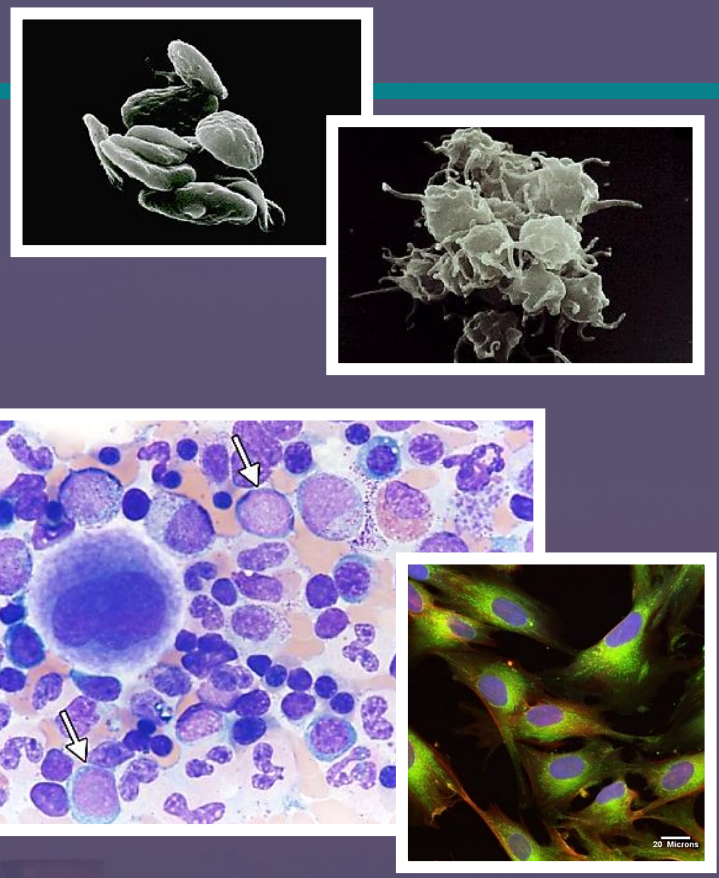
Mesenchymal Stromal Cells (MSCs)

- MSC = one of many PCs in BMAC
- Smart cells
  - Adaptive vs. reflexive
- Potential therapeutic effects:
  - Homing to site of injury
  - Drug making factory
    - Medicinal Signaling Cells
    - Major mechanism
  - Multipotency ➔ new tissue
    - Not major mechanism!



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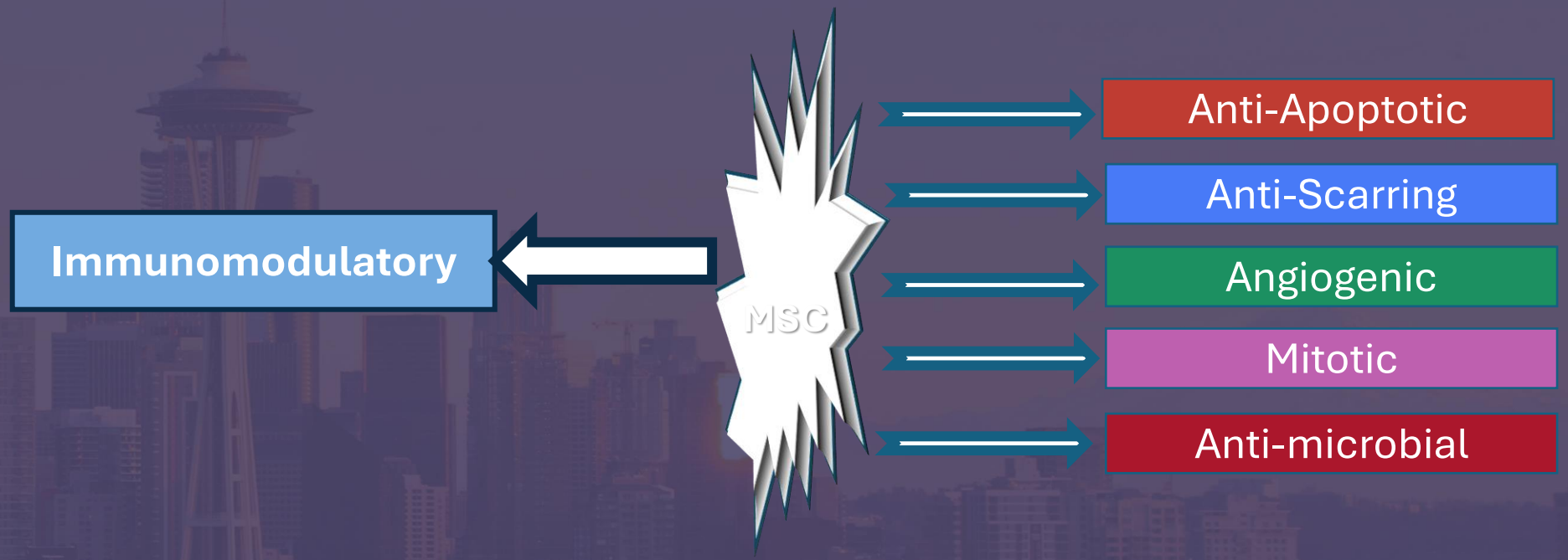
Delanois J Arthroplasty 2019; Pak J Biomed Sci 2017;
Caplan Stem Cells Trans Med 2017;Dominici Cytotherapy 2006

Mesenchymal Stem Cells (MSCs)

<u>Paracrine effects</u> = secreted bioactive proteins & mRNA (like mini-drugstores)



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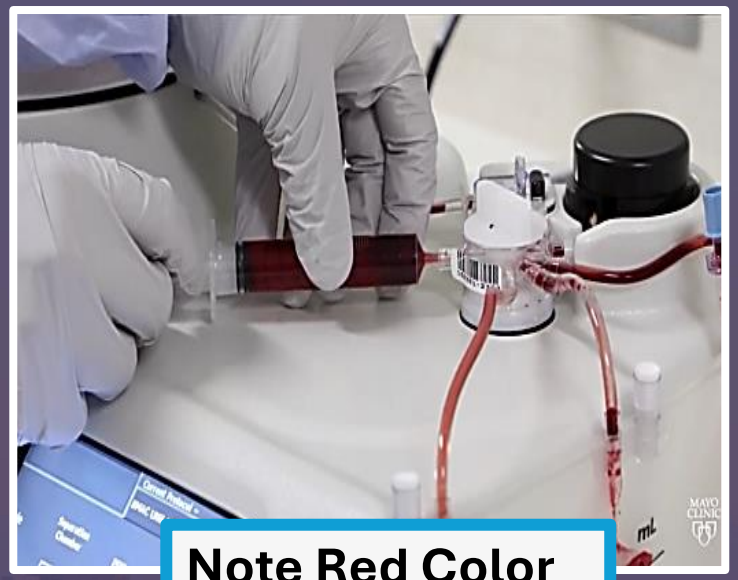
Delanois J Arthroplasty 2019; Pak J Biomed Sci 2017; Caplan Stem Cells Trans Med 2017

Bone Marrow Aspirate Concentrate (BMAC)

- Extract BMAC (some combine with cell poor)
  - Some also inject PRP, etc.
- Inject → MSK same day
  - OA >> Tendon/Ligament
  - ~ 60-90 minute procedure
- Dosing?
  - Not standardized
  - Whatever the kit makes
  - Dose-response not conclusive
  - Knee OA: > $4X10^8$ PCs (maybe)



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Bone Marrow Aspirate Concentrate (BMAC)

- Regulatory
  - Not FDA approved
  - FDA compliant if minimally manipulated
  - Should use GTPs & register with FDA
  - Avoid marketing as a “stem cell treatment”
  - Cash pay

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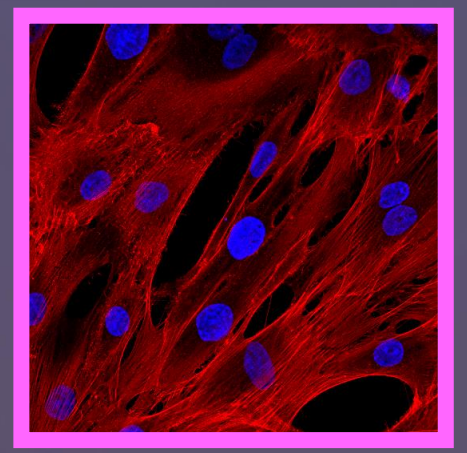
Culture Expanded MSCs Knee OA

- All are case series
- Most use bone marrow, some adipose
- No SAEs at doses $1X10^6$ - $1X10^8$
- Consistent but variable improvement
- Some disease modification!!!
  - Improved MRI and/or arthroscope parameters
- Mechanism mostly “hit and run” mode of action
  - Paracrine effects, not multipotency



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Naji Cellular Mol Life Sci 2019;Jayaram PMR 2019;Jo AJSM 2017; Zwolanek JCI Insight 2017;Orozco Transplantation 2013; von Bahr Stem Cells 2012

Not All BMAC Is The Same

- Variable quantities
  - Bioactive proteins
  - PCs, including MSCs
- Optimal system?
  - Mechanism of action?
  - May not be MSCs
- How many MSCs?

Compare with clinical trials using culture expanded MSCs

TABLE 2
Cellular Characterization[a]

	n	Median (Range)
Pre-spin measures		
Viability, %	24	97.8 (75.2-99.4)
MNCs, %	25	38.5 (26.0-57.5)
Total MNCs/μL	25	6100 (1950-27,000)
HSCs, %	25	3.2 (0.04-21.0)
MSCs, %	25	0.03 (0.00-0.60)
Total MNCs × MSCs, %	25	198 (0-2673)
WBCs, 1000/μL	25	13.0 (3.9-62.8)
RBCs, Mil/μL	25	3.33 (0.17-4.44)
HCTs, %	25	32.0 (1.6-38.2)
Platelets, 1000/μL	25	95 (7-399)
Post-spin measures		
Viability, %	22	97.0 (85.4-99.6)
MNCs, %	23	56.2 (25.8-87.9)
Total MNCs/μL	23	16,000 (2900-210,000)
HSCs, %	23	4.4 (1.2-14.0)
MSCs, %	23	0.05 (0.0-0.9)
Total MNCs × MSCs, %	23	688 (8.7-28,980)
WBCs, 1000/μL	23	31.4 (5.6-97.2)
RBCs, Mil/μL	23	0.96 (0.63-3.65)
HCTs, %	23	8.5 (3.5-34.0)
[illegible]	[illegible]	[illegible]
Total HSCs injected	23	4,620,000 (174,000-130,200,000)
Total MSCs injected	23	34,400 (435-1,449,000)

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Gaul Cartilage 2018;Cassano Knee Surg Sport Traumatol Arthr 2018; Shapiro AJSM 2017;Fortier JBJS 2010;Kasten Euro Cell Mater 2008; Hernigou JBJS 2005

BMAC – Clinical Considerations

- Rationale → cell based, more powerful vs. PRP/mDHACM
  - Different than non-cell based orthobiologics
    - ***not clear if superior***
  - No currently published comparative trials
- Science in infancy but rapidly evolving
- Reasonably safe (long term?)
- Viable option for symptomatic Rx of joint (? soft tissue)
  - 50% chance of >50-70% improvement
  - May take ≥ 3 months for effect, last ≥ 1 year (vs. PRP)
  - Failed PRP or mDHACM or other orthobiologic
  - Patient preference (informed consent)
  - Potential for disease modification

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BMAC For Osteoarthritis – Knee

- Significantly fewer studies than PRP
  - Same if not greater methodological variability
- Case series, prospective case series
  - Reasonably safe
  - 50-70% response rate (>50% VAS reduction)
  - Not all patients respond
  - Mechanism of action unknown – likely complex
- Pro-RCT BMAC vs. Normal saline same patient
  - No significant difference → both knees improved
- No conclusive but potential evidence of disease modification

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Delanois J Arthroplasty 2019;Lamplot AJSM 2019;Shapiro Cartilage 2018, AJSM 2017;Piuzzi JBJS 2018;Sampson Reg Med 2016; Centeno Biomed Res Int 2014

Clinical Study

Efficacy of Autologous Bone Marrow Concentrate for Knee Osteoarthritis with and without Adipose Graft

Christopher Centeno,[1] John Pitts,[1] Hasan Al-Sayegh,[1] and Michael Freeman[2]

- 840 procedures/681 pts, K-L I-IV
- Pre-Rx 12.5% dextrose 2-5 days prior
- 1-3 ml BMAC + LP-PRP/PL + (616 no graft, 224 fat graft)
- 11-12% patients received additional PRP
- 10-11 month f/u

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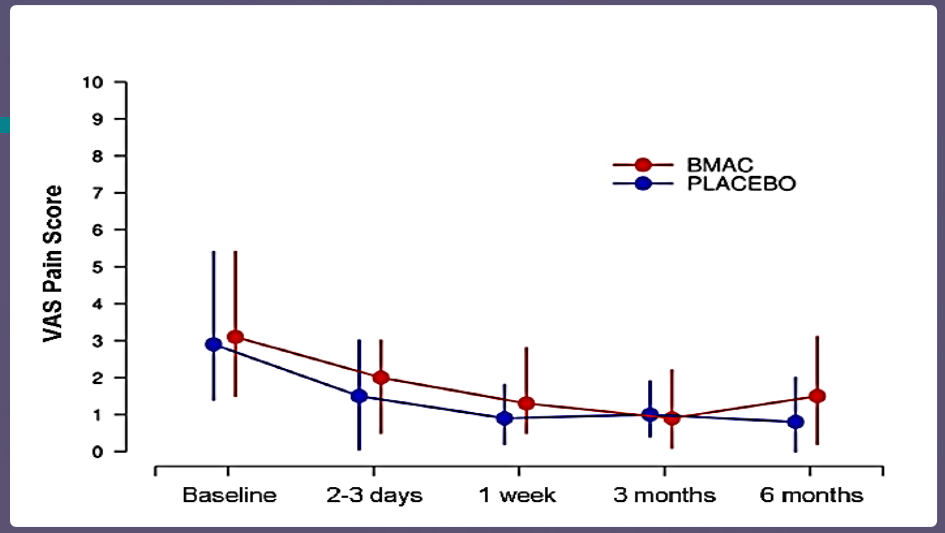
BMAC For Osteoarthritis – Knee

- No BMC related SAEs
  - Transient pain & swelling common
- 40-50% improvement at 10-12 months
  - NPS 4 ➔ 2.6 (MCID ≥ 2)
- Additional experience similar
  - 50%-70% response rate
    - >50% improvement
  - Knees better than hips
  - Shoulder data published
  - 1 year durability



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Shapiro Cartilage 2018, AJSM 2017;Sampson Reg Med 2016;
Centeno J Pain Res 2015;Biomed Res Int 2014

A Prospective, Single-Blind, Placebo-Controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis

Shane A. Shapiro,*† MD, RMSK, Shari E. Kazmerchak,† BSN, Michael G. Heckman,‡ MS, Abba C. Zubair,§ MD, PhD, and Mary I. O'Connor,†‖ MD
Investigation performed at the Mayo Clinic, Jacksonville, Florida, USA

- 25 patients, level 2 data
- There were no serious adverse events from the BMAC procedure. OARSI Intermittent and Constant Osteoarthritis Pain and VAS pain scores in **both knees** decreased significantly from baseline at 1 week, 3 months, and 6 months (P .019 for all).

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- N = 12
  - Patients with late-stage Kellgren-Lawrence knee- OA osteoarthritis
- received a single intra-articular injection of 1, 10, or 50 million (BM-MSCs)
- There were no serious adverse events.
- There were significant overall improvements in KOOS pain, symptoms, quality of life, and WOMAC stiffness relative to baseline;
  - the 50 million dose achieved clinically relevant improvements across most PROMs.
- Pro-inflammatory monocytes/ macrophages and interleukin 12 levels decreased in the synovial fluid after MSC injection.

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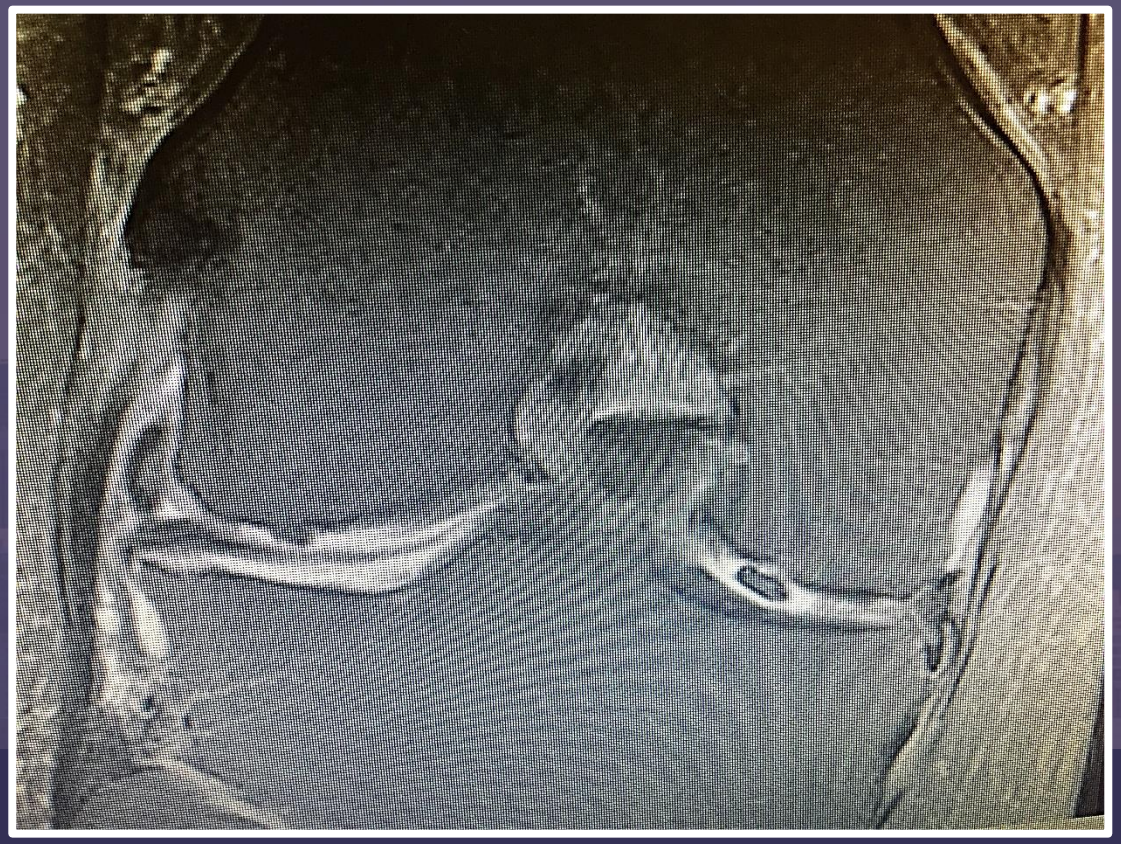
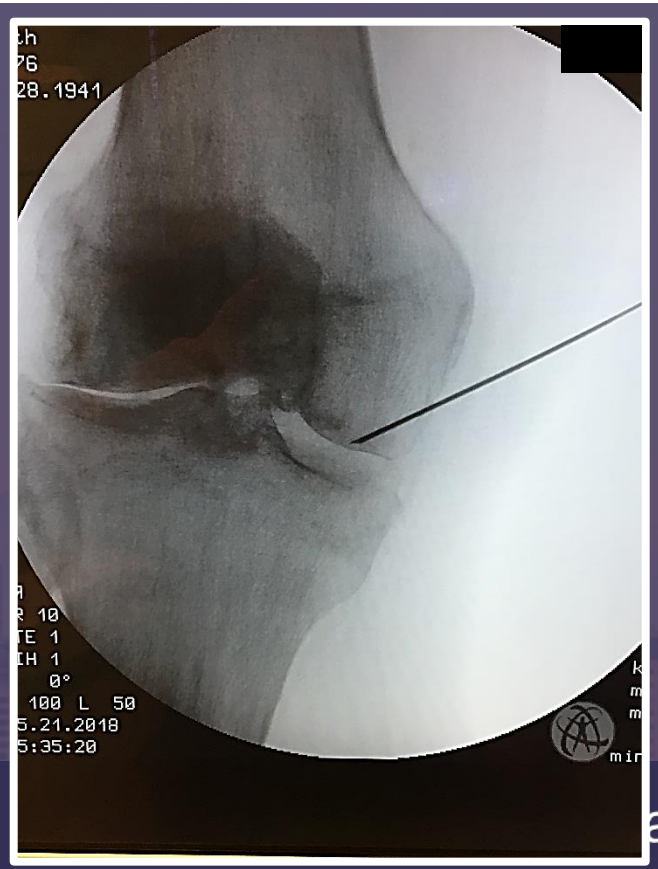
How about subchondral MSCs?

Subchondral stem cell therapy versus contralateral total knee arthroplasty for osteoarthritis following secondary osteonecrosis of the knee

Philippe Hernigou[1] · Jean Charles Auregan[1] · Arnaud Dubory[1] · Charles Henri Flouzat-Lachaniette[1] · Nathalie Chevallier[1] · Helene Rouard[1]





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Subchondral stem cell therapy versus contralateral total knee arthroplasty for osteoarthritis following secondary osteonecrosis of the knee

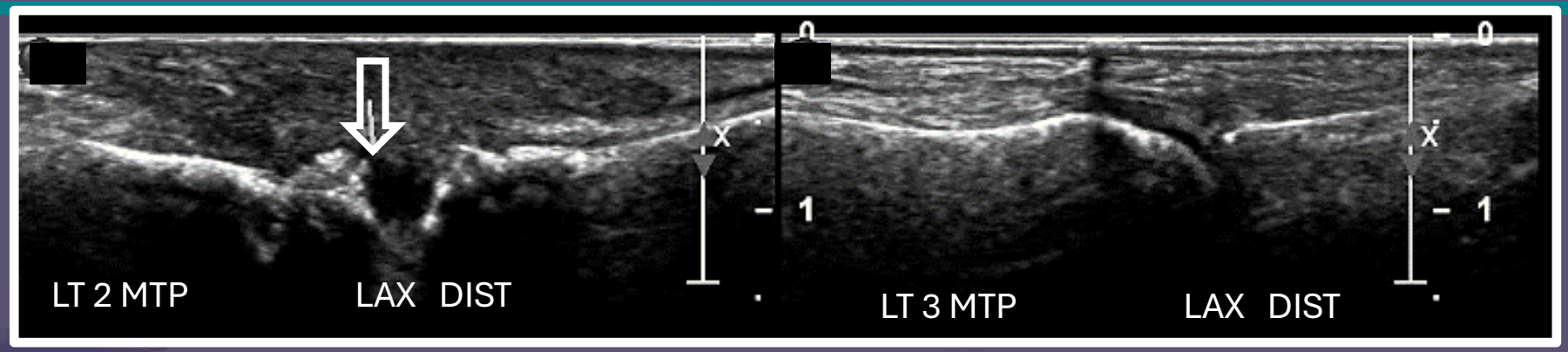
Philippe Hernigou[1] · Jean Charles Auregan[1] · Arnaud Dubory[1] · Charles Henri Flouzat-Lachaniette[1] · Nathalie Chevallier[1] · Helene Rouard[1]

- A prospective randomized controlled clinical trial –
  - 60 knees of 30 patients (mean age 28 years, 18–41) who presented bilateral osteoarthritis secondary to knee ON related to corticosteroids
  - During the same anesthesia, one knee received TKA; for the other knee, a bone marrow graft subchondrally
- Outcomes:
  - Anesthesia related to the TKA side was longer than for the cell therapy group.
  - Medical and surgical complications were more frequent after TKA. A higher number of thrombophlebitis was observed on the side with TKA (15%) versus none on the side with cell therapy (0%).
  - At the most recent follow-up (average of 12 years, range 8 to 16 years), six (out of 30) TKA knees needed subsequent surgery versus only one with cell therapy.
  - The Knee Score had improved and remained similar in the TKA and cell therapy groups (respectively 80.3 points ± 11 versus 78.3 ± 23); 21 patients preferred the knee with cell therapy and 9 preferred the knee with TKA.

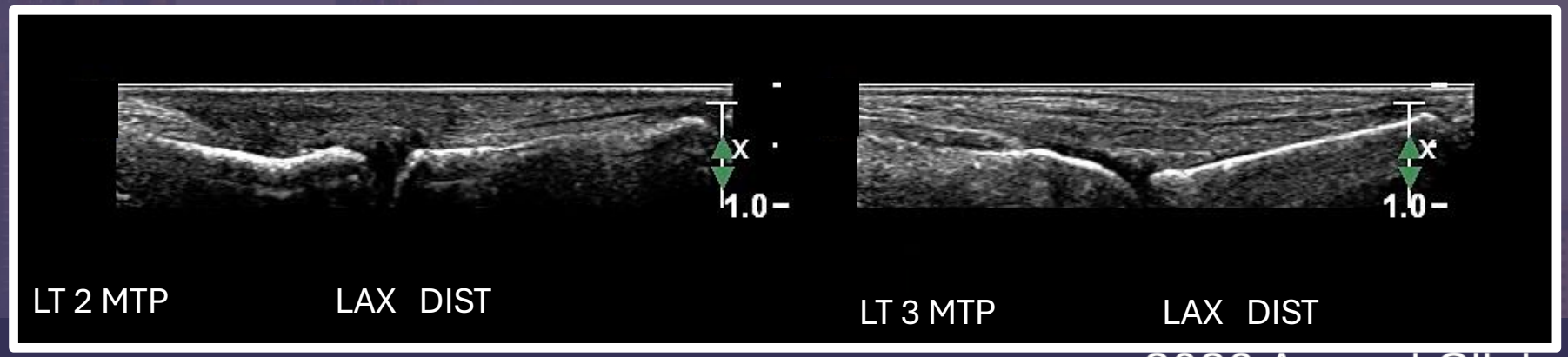
A few cases

17-year-old F

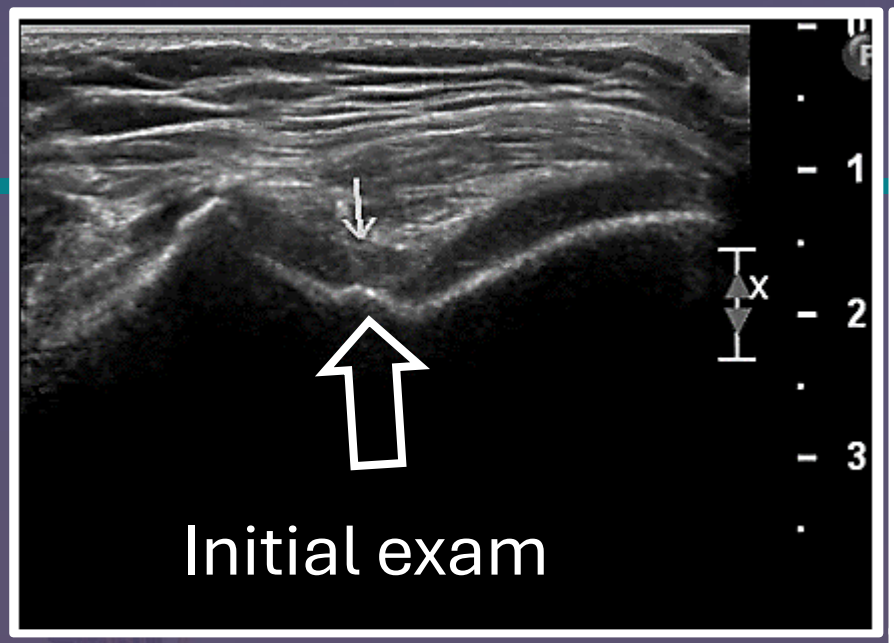
18 months AVN 2nd MTP Freiberg's disease

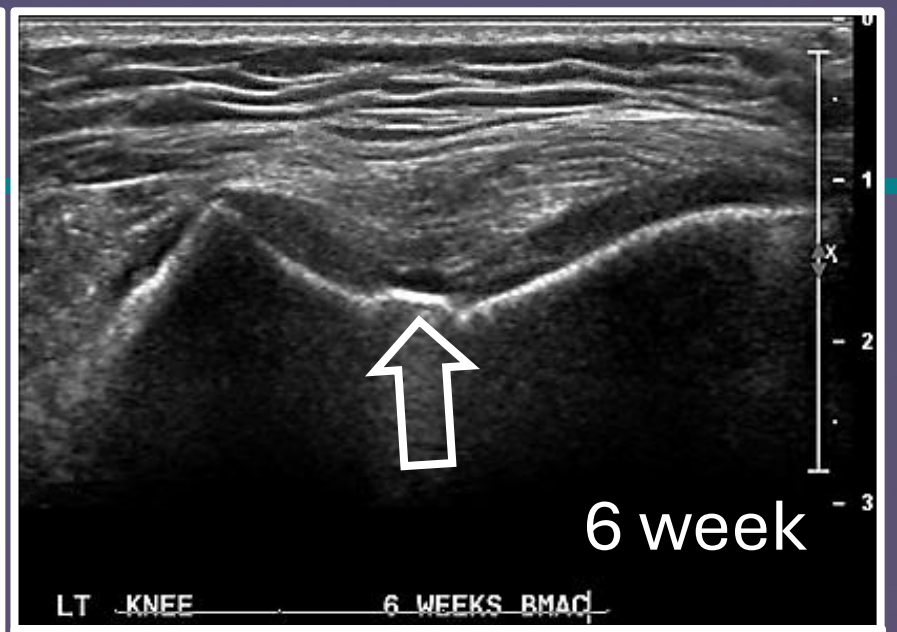


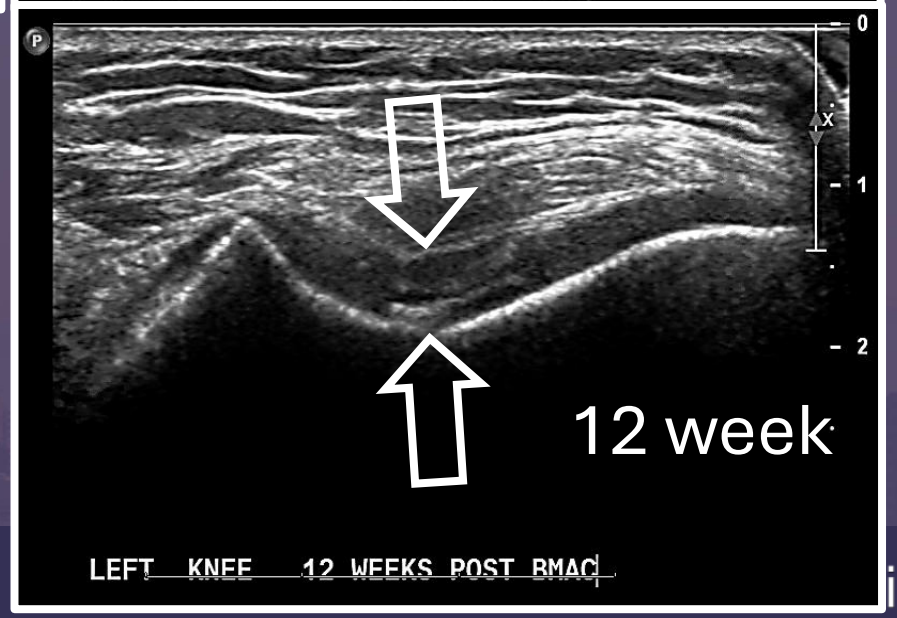
3-month follow-up



Case presentation Subchondral for ON







- 37 yo F
- Osteonecrosis after PG steroid injection
- Treated with subchondral BMAC for focal defect

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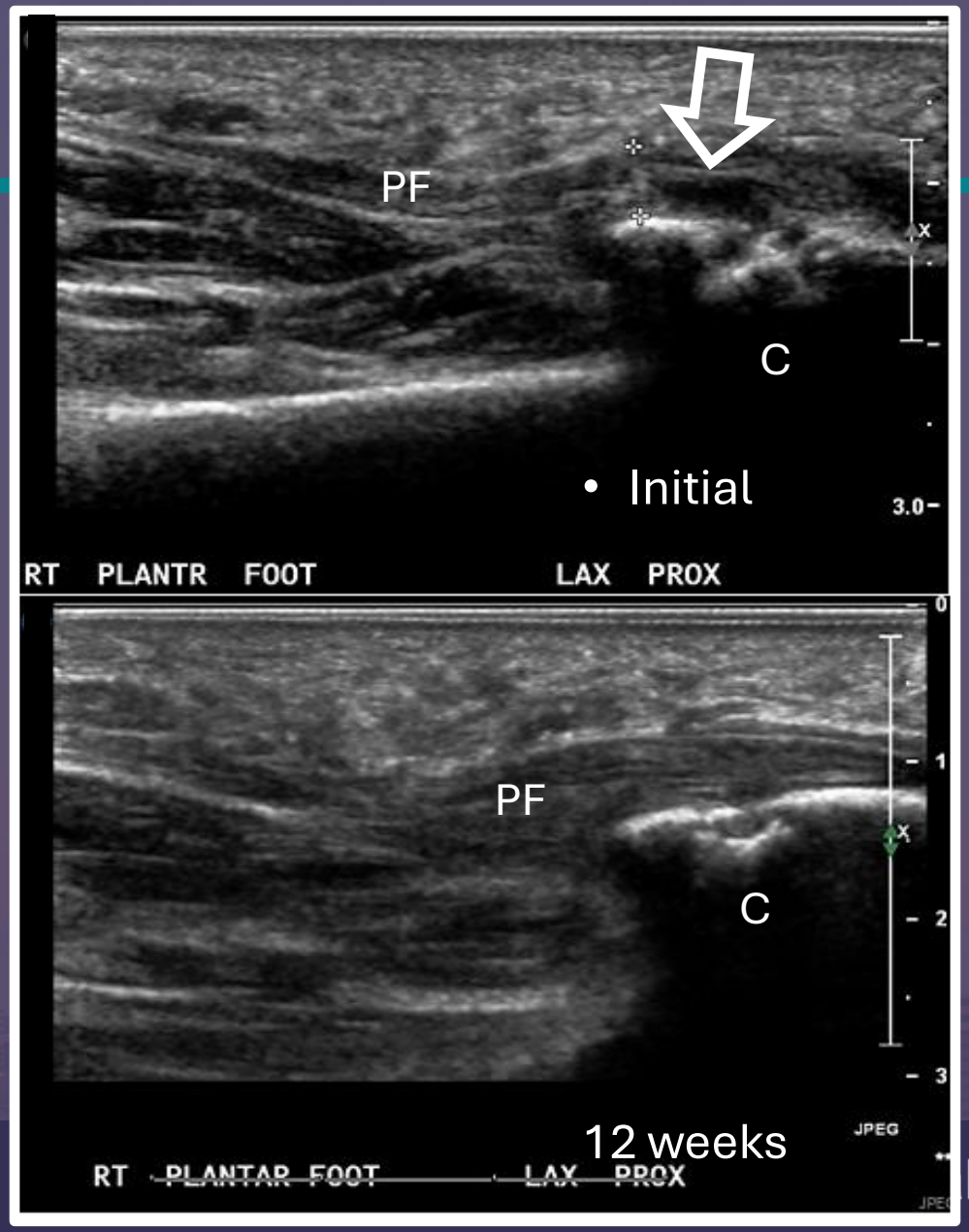
A few cases

- 56-year-old marathon runner
- 3 years of pain
- High grade central band PF rupture with calcaneal fracture
- Treated with BMAC



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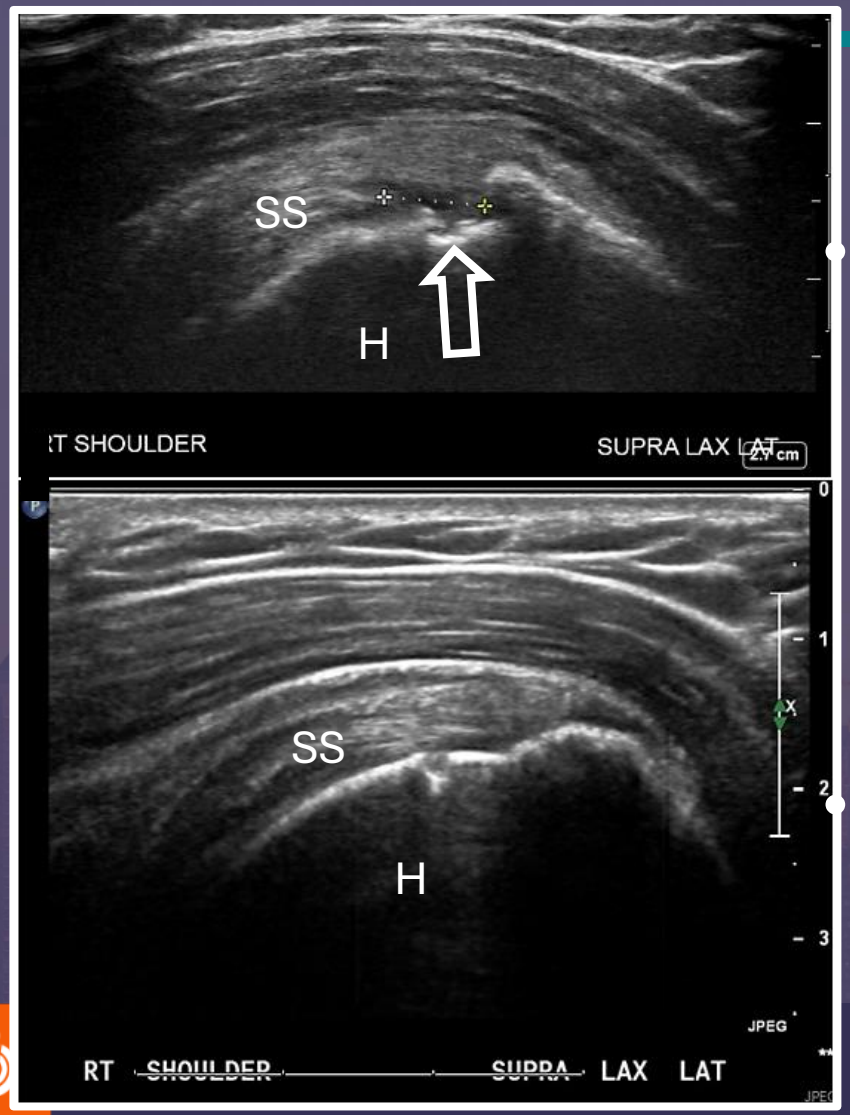
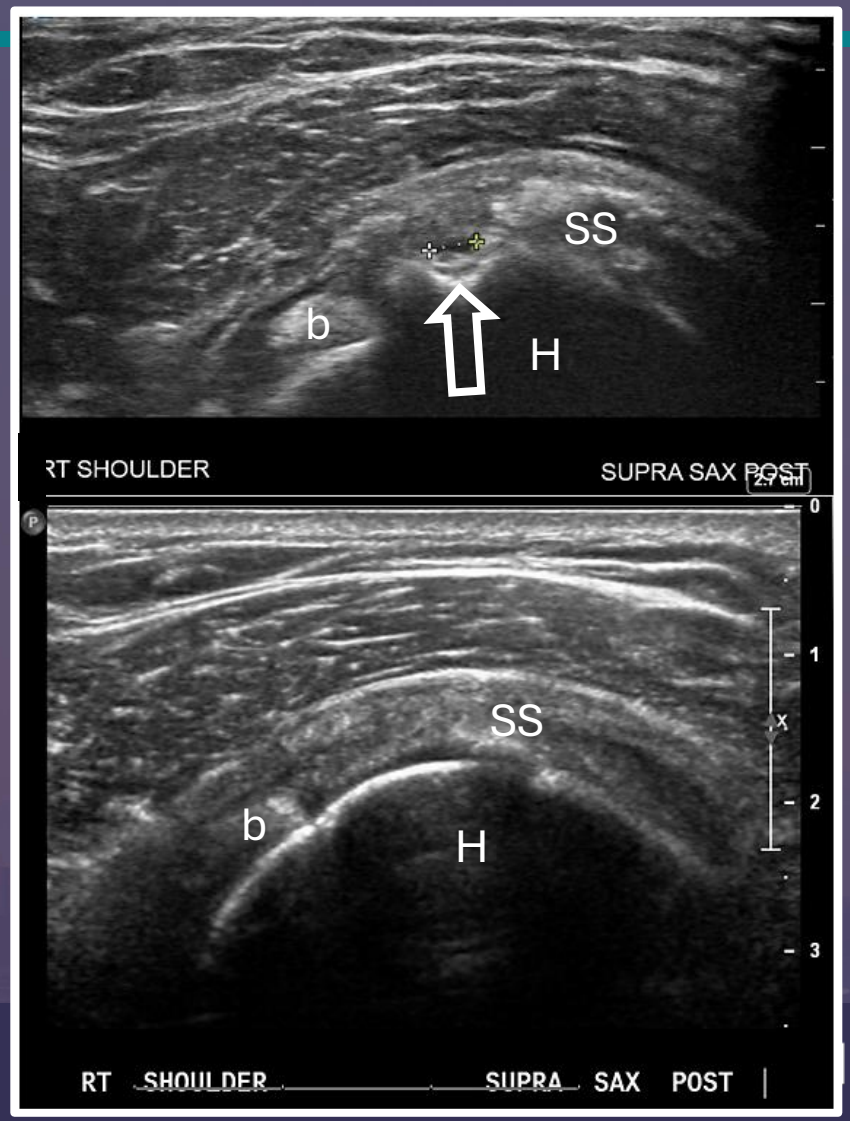
A few cases



Initial

12wks



- 55 y o male- 10 months of pain
- ss partial thickness tear

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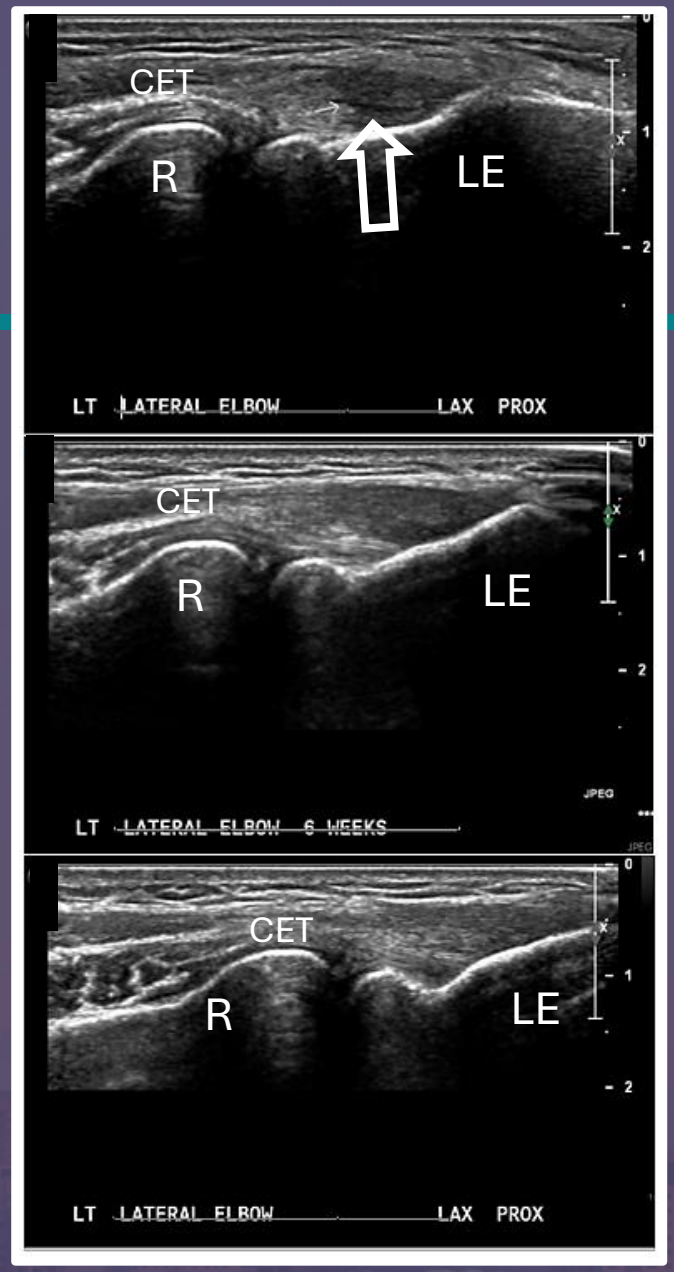
A few cases

- 38-year-old M
- Left common extensor tendinopathy with partial thickness tearing



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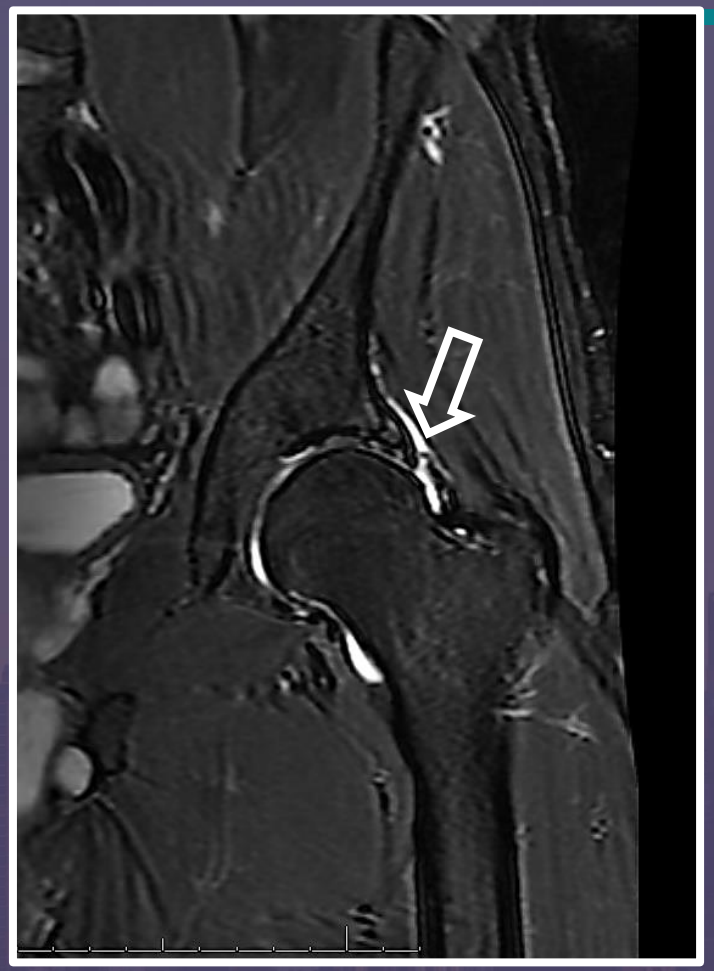
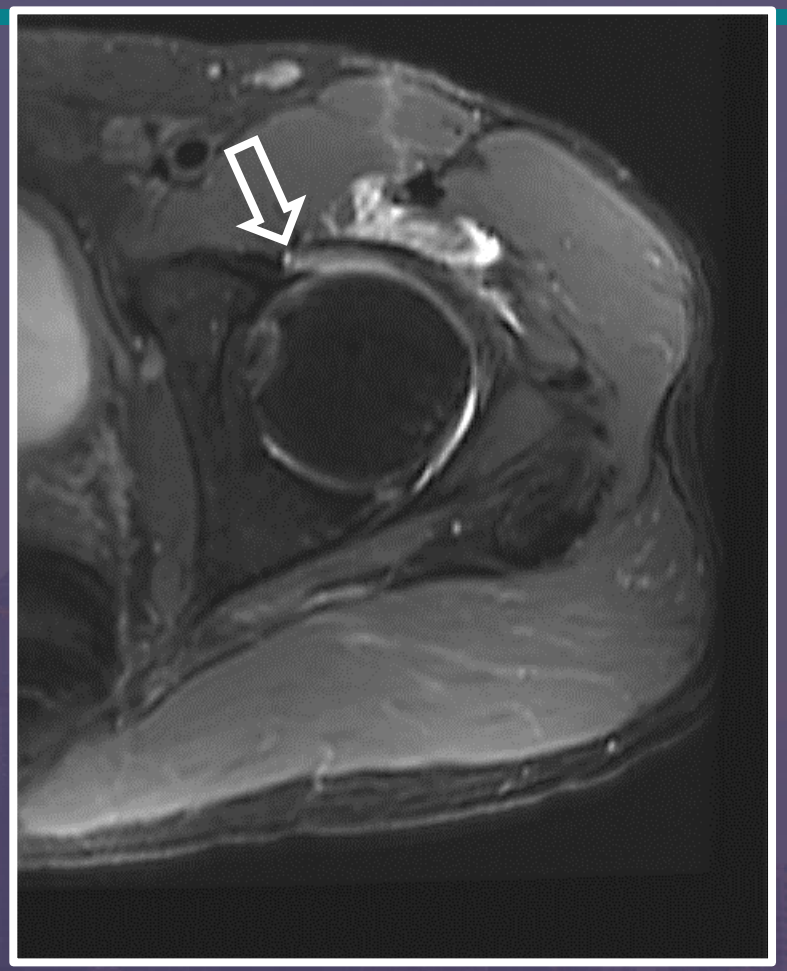
A few cases





- 19 y o male wrestler with anterior hip pain
- Partial thickness labral tear

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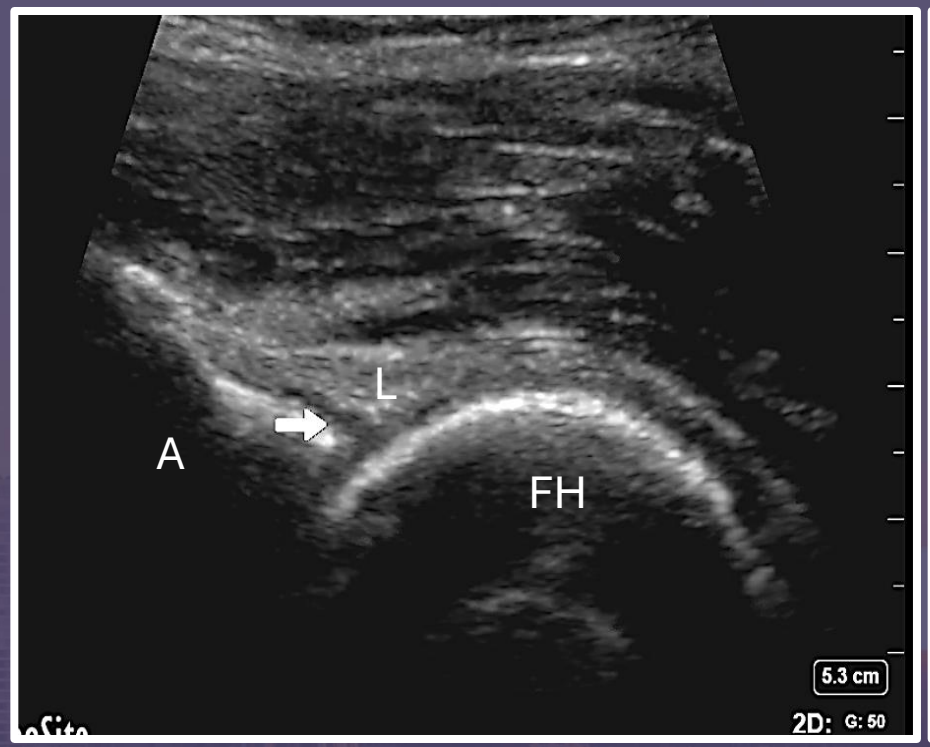
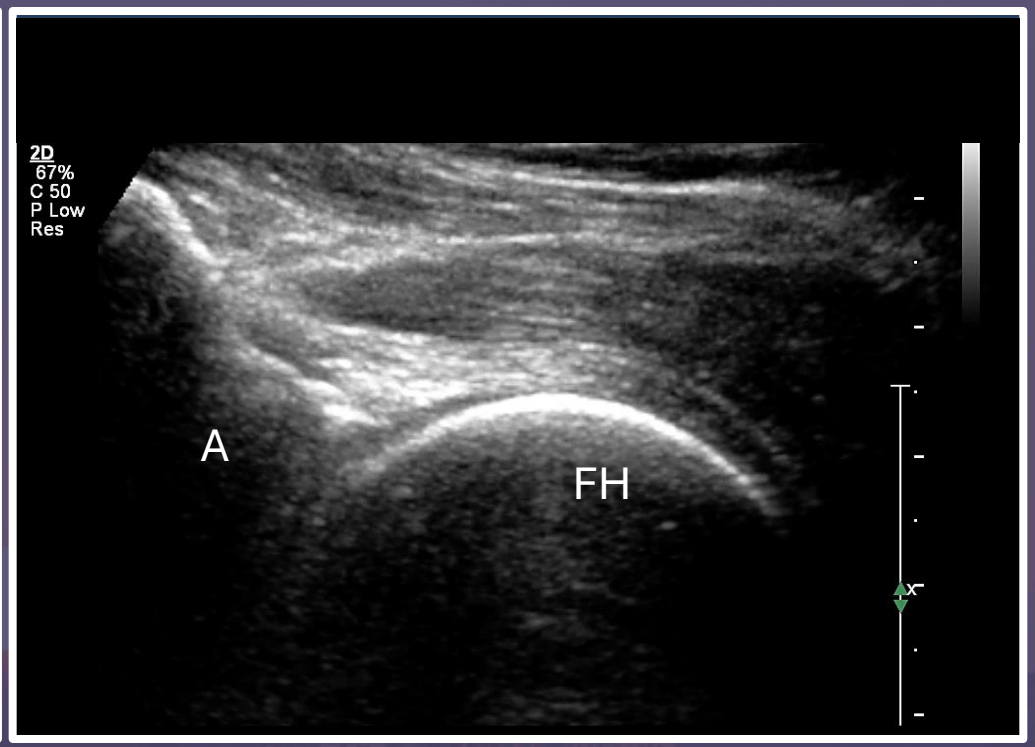
A few cases

- Initial



- 12 weeks



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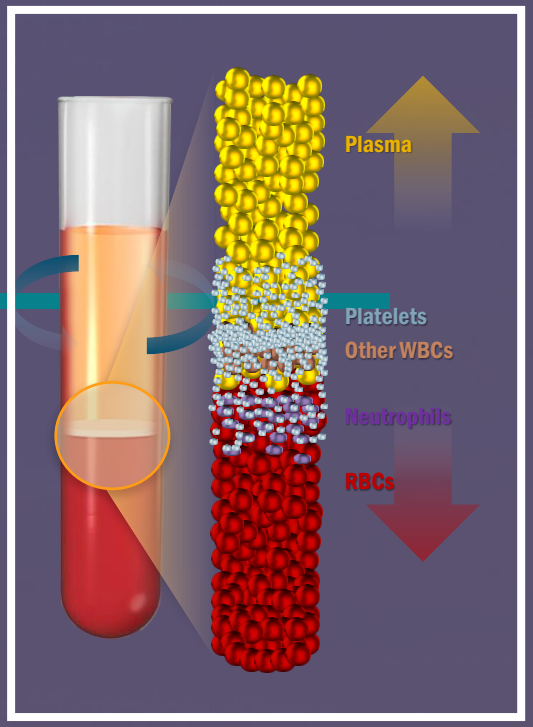
What is Alpha-2-Macroglobulin?



- Along with the cellular components of blood there are acellular molecules/proteins, found in the Platelet-poor plasma (PPP) that have anti-inflammatory properties, one of which is Alpha-2 Macroglobulin (A2M) another is Interleunkin receptor antagonist protein (IRAP).
- Alpha 2 macroglobulin (A2M) is a naturally occurring autologous protein found in the platelet-poor-plasma (PPP) at relatively high levels (2-4 mg/ml), as well in the joint fluid at lower concentrations.
- Concentrated injections of A2M have demonstrated chondral (cartilage) protection in knee Osteoarthritis in animal models.

Tortorella MD, Et al. 2004; Wan R. Et al 2012; Kaneko M. Et al 2001; Maiotti M et al, 2000; Kapila S. Et al 1995, Rengel Y. et al 2007; Wilkinson DJ et al 2019; Wang S. Et al 2014.; Brighton et al. 2008.

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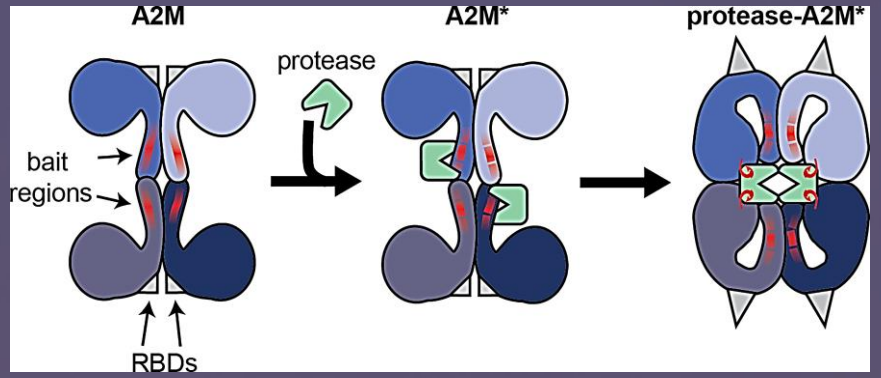
How does Alpha-2-Macroglobulin work?

- A2M is known as a ubiquitous proteinase inhibitor, which contains a ‘bait region’, resulting in a cleavage site for proteinases and is identified as one of the active substances in PRP.
- Among the mechanisms responsible for cartilage degradation in the setting of OA, disintegrin-metalloproteinases with thrombospondin motifs (ADAMTSs) and the matrix metalloproteinases (MMPs) have been identified as key players.
- It has been established that ***in early OA, ADAMTSs are the main proteinases responsible for the breakdown of aggrecan and cartilage oligomeric matrix protein (COMP)***, a prominent non-collagenous component of cartilage leading to progression of further cartilage loss.
- ***Later in the OA process, MMPs are more prominent in the continued degradation of collagen***.[6] Of the collagenases, MMP-13 cleaves primarily type II collagen while MMP-1 and MMP-8 cleaves types III and I.



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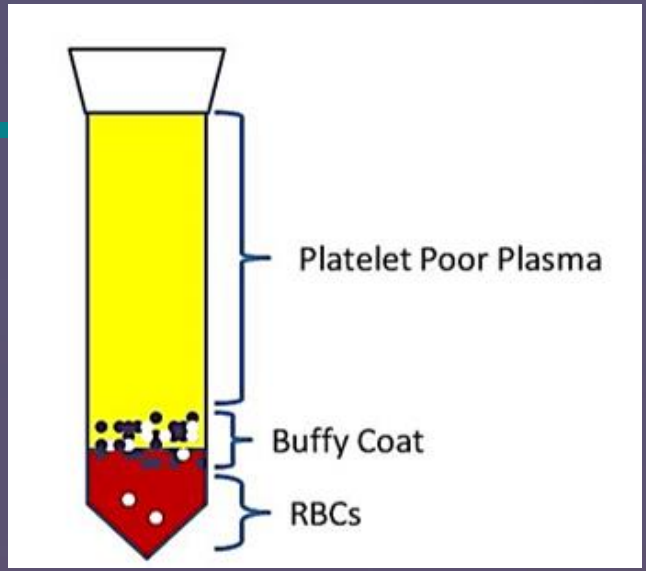
How does Alpha-2-Macroglobulin work?



- Concentrated injections of intra-articular A2M has demonstrated chondral protection in post-traumatic knee OA decreasing both matrix metalloproteinase (MMP) and IL-1, indicating a potential disease modulating effect (slowing effect) in osteoarthritis.
- It has furthermore been demonstrated that ***lower intrinsic levels and inhibition of A2M result in increased progression of osteoarthritis.***
- Therefore, intra-articular autologous concentrated A2M with its ability to bind pro-inflammatory molecules such as tumor necrosis factor-α (TNF- α), tumor necrosis factor- β (TNF-β), matrix metalloproteinase (MMP), interleukin-1β (IL-1β), and ADAMTS may be of benefit in treating and slowing progression of OA.

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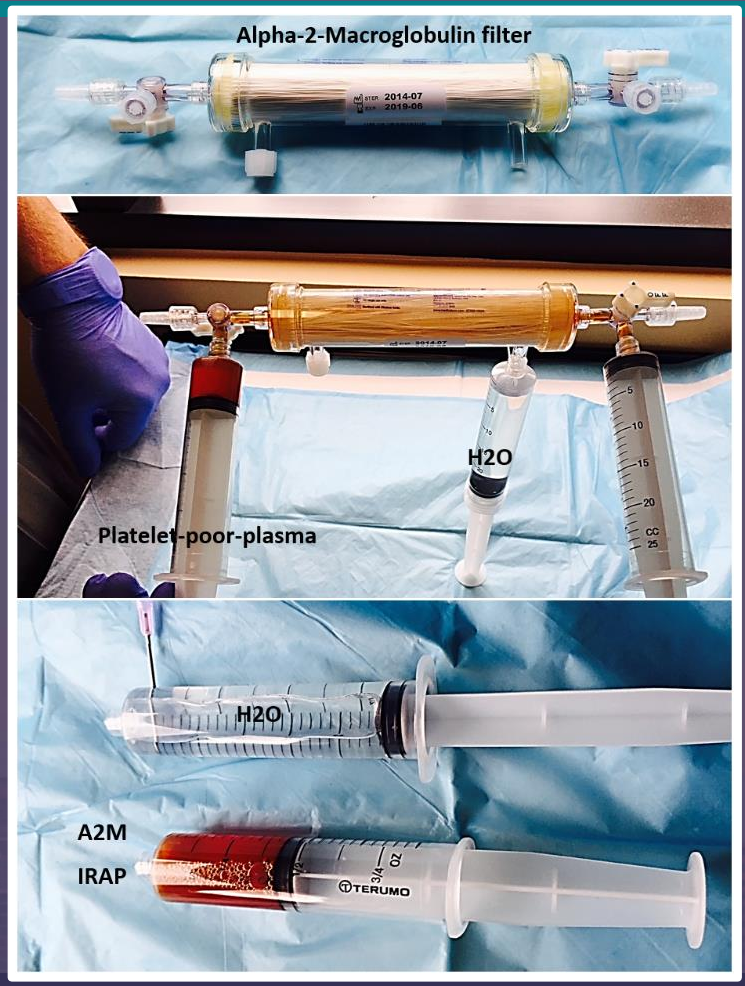
Tortorella MD, Et al. 2004; Wan R. Et al 2012; Kaneko M. Et al 2001; Maiotti M et al, 2000; Kapila S. Et al 1995, Rengel Y. et al 2007; Wilkinson DJ et al 2019; Wang S. Et al 2014.; Brighton et al. 2008.; Iuan et al 2008

How is it harvested?

- It is harvested by taking 60-180cc (depending on treatment area) of blood from the patient and spinning it in a centrifuge separate the platelet-rich-plasma (PRP), from the platelet poor plasma (PPP).
- The PPP is then cycled through a filter system, which has a high molecular weight cutoff designed to trap larger molecules including A2M (720 kDa).
- This results in a concentrated amount of A2M proteins.
- These are then reinjected with or without PRP.



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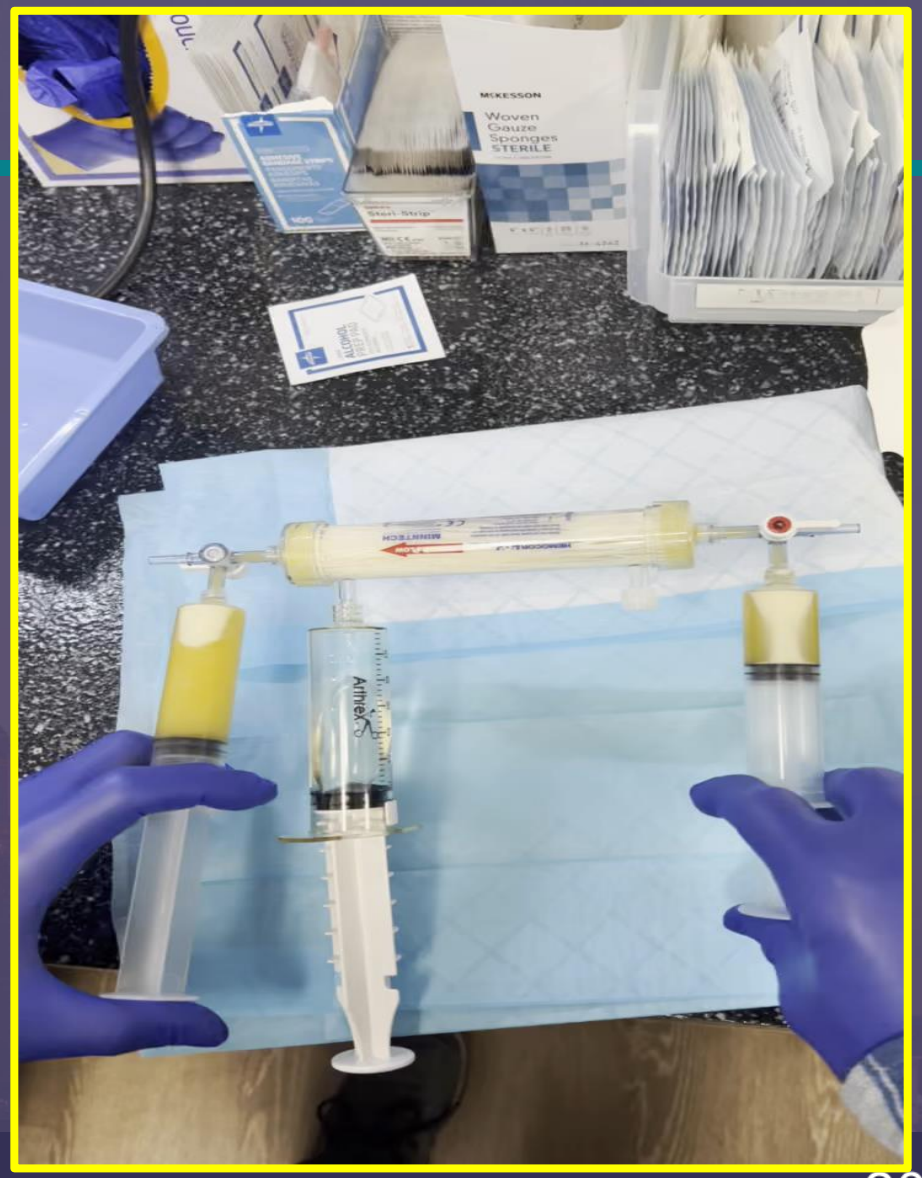
How is it harvested?



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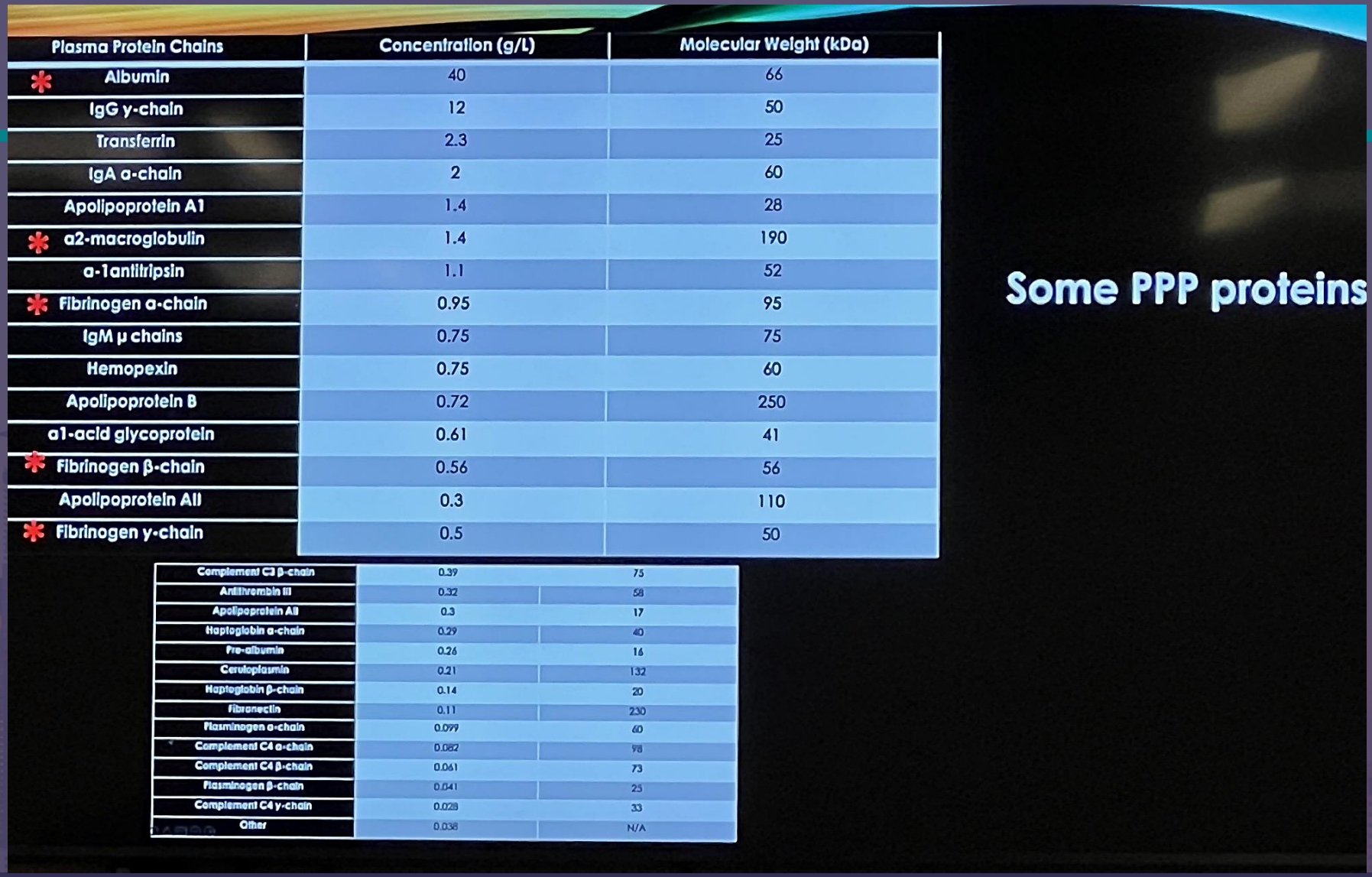
What other goodies are in the PPP?



Plasma Protein Chains	Concentration (g/L)	Molecular Weight (kDa)
* Albumin	40	66
IgG γ-chain	12	50
Transferrin	2.3	25
IgA α-chain	2	60
Apolipoprotein A1	1.4	28
* α2-macroglobulin	1.4	190
α-1antitripsin	1.1	52
* Fibrinogen α-chain	0.95	95
IgM μ chains	0.75	75
Hemopexin	0.75	60
Apolipoprotein B	0.72	250
α1-acid glycoprotein	0.61	41
* Fibrinogen β-chain	0.56	56
Apolipoprotein AII	0.3	110
* Fibrinogen γ-chain	0.5	50
Complement C3 β-chain	0.39	75
Antithrombin III	0.32	58
Apolipoprotein AII	0.3	17
Haptoglobin α-chain	0.29	40
Pre-albumin	0.26	16
Ceruloplasmin	0.21	132
Haptoglobin β-chain	0.14	20
Fibronectin	0.11	230
Plasminogen α-chain	0.099	60
Complement C4 α-chain	0.082	98
Complement C4 β-chain	0.061	73
Plasminogen β-chain	0.041	25
Complement C4 γ-chain	0.028	33
Other	0.038	N/A

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Can the concept be taken further?
What is autologous concentrated serum?

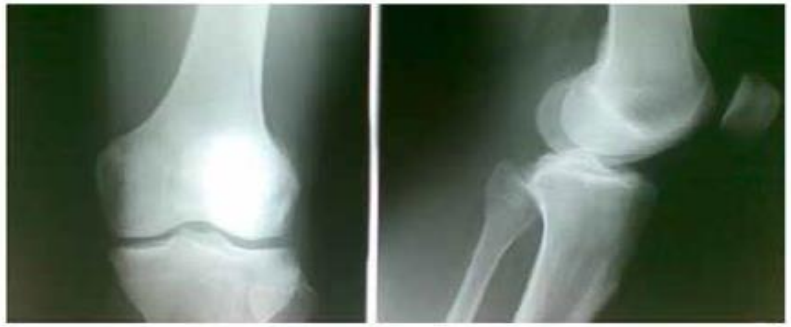
The Atlantic

HEALTH

An Arthritis Treatment Worthy of the Pope and Kobe

LLOYD SEDERER OCTOBER 15, 2012

Regenokine isn't approved by the FDA (yet), but the treatment for joint pain is promising.



mtkopone/Flickr

The likes of Kobe Bryant, Alex Rodriguez, Vijay Singh, and Pope John Paul II are among a growing number -- myself included -- who have sought a novel form of anti-inflammatory arthritis/tendinitis treatment that, until recently, was only available in Germany. If you haven't already heard about it, it's called Regenokine, and it's among a trend moving orthopedics away from operating rooms and into the realm of the molecular -- from mining titanium to mining the anti-inflammatory molecules coursing through our veins.

[...]

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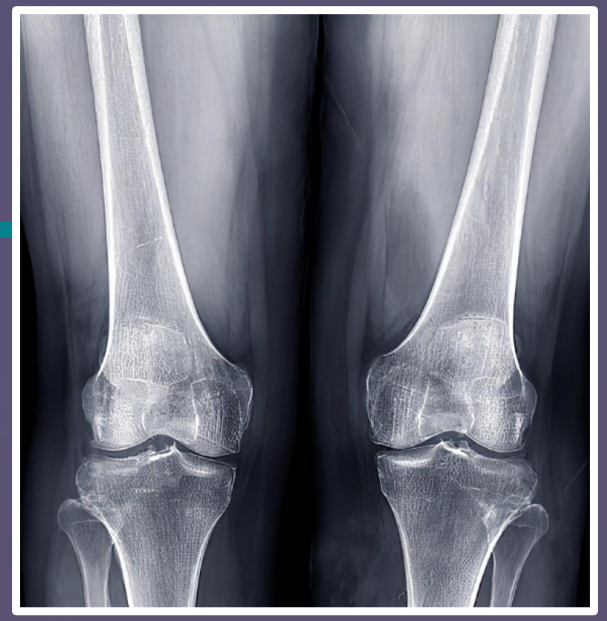
What is the autologous concentrated serum?



- The treatment was developed by Dr. Peter Wehling, a German spinal surgeon, and has been approved for use in Germany.
- After continuing his research with humans, Wehling's formulation was approved for human use in 2003 by the German equivalent of the FDA.
- The procedure concentrates the multiple pro and anti-inflammatory proteins in the blood with a goal of stimulation of the immune system.
- The processed serum is then injected back into the affected joint. The serum has no red blood cells or white blood cells that can cause irritation.
- The serum may also be called autologous conditioned serum, Regenokie, Orthokine or ACS

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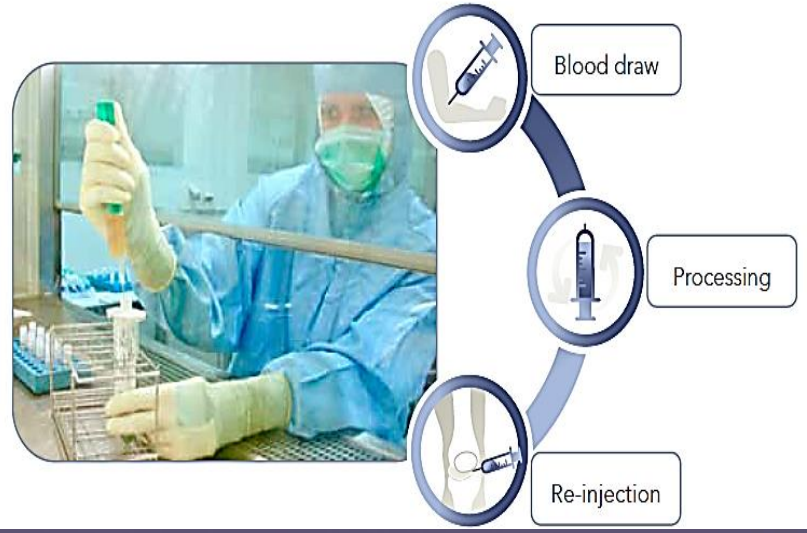
How is it harvested?



- It is harvested by taking blood from the patient. The temperature of the blood sample will be slightly elevated and processed for up to 30 hours in a sterile lab environment. It will then be placed in a centrifuge to:
  - separate the blood products
  - concentrate the anti- and pro-inflammatory proteins
  - create a cell-free serum
- The treated sample is then frozen and put into syringes for injection. The processed serum can then be reinjected into the patient in a series of 4-5 injections. (This can also vary based off site location and tissue being treated)

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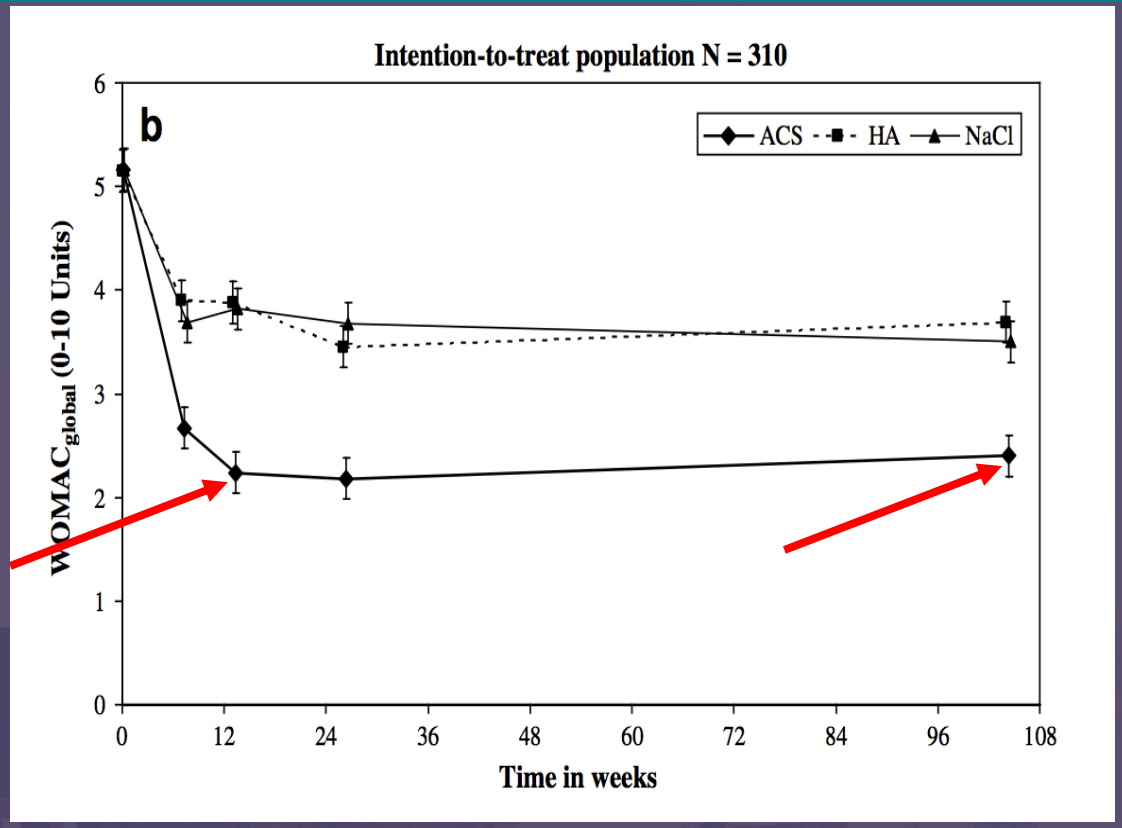
ACS produces long-term analgesia in patients with OA



Baltzer A. et al. Osteoarthritis and Cartilage 2009

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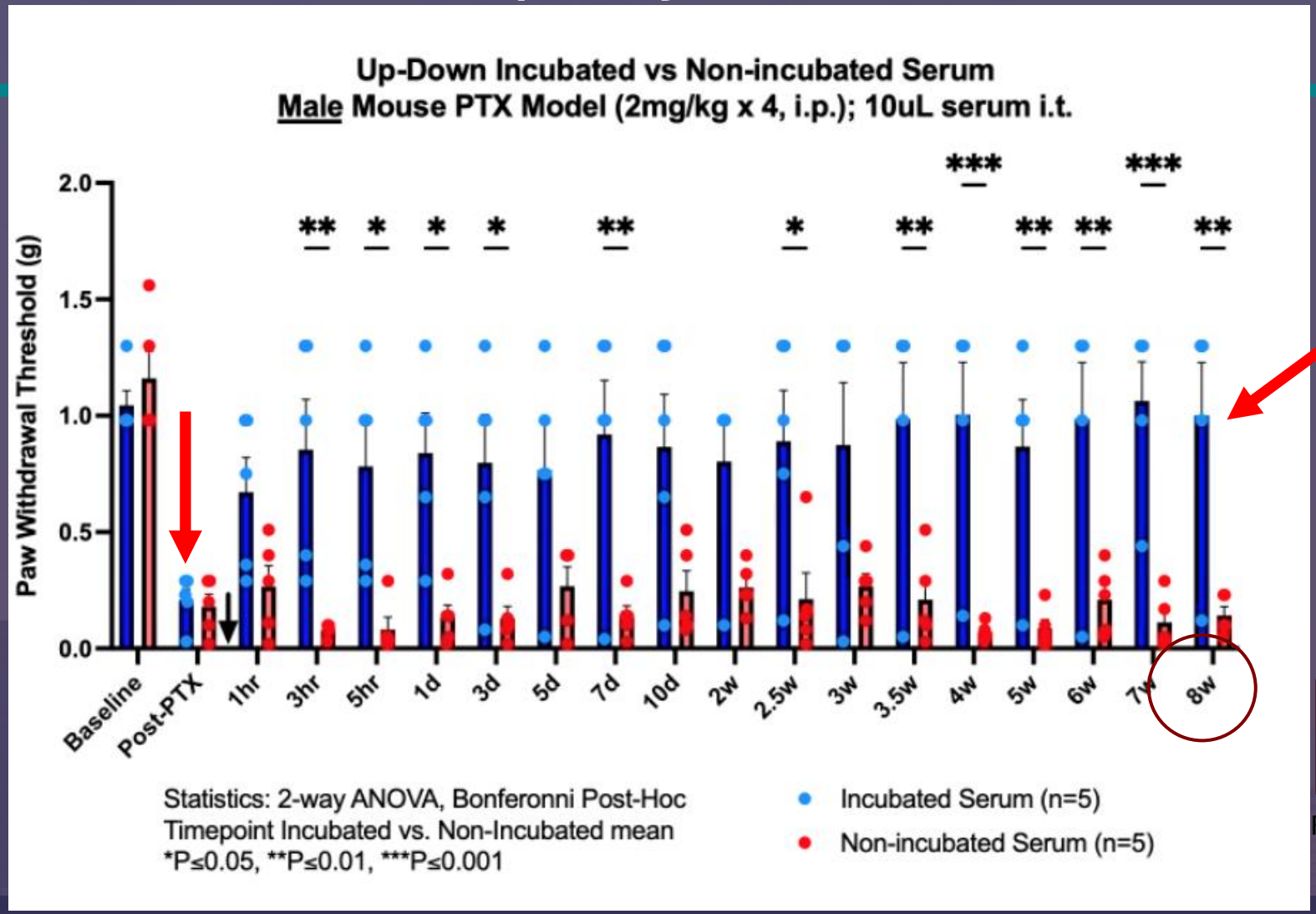
ACS produces long-term analgesia in animal models of neuropathy

- Notice the difference between
- incubated serum (Blue) and
- non-incubated serum (Red)



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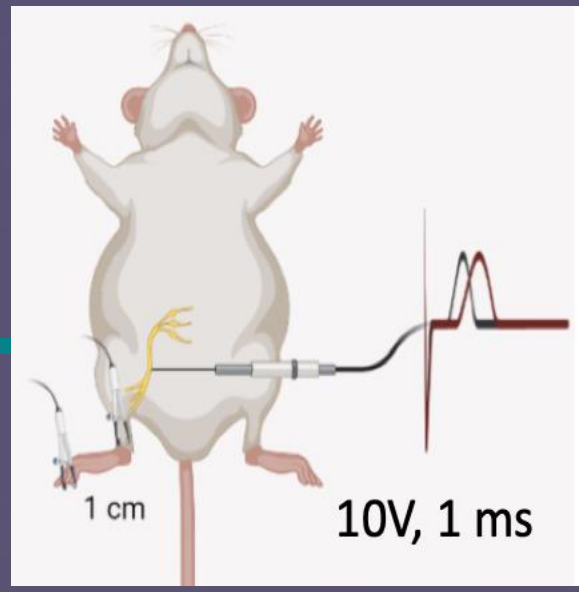
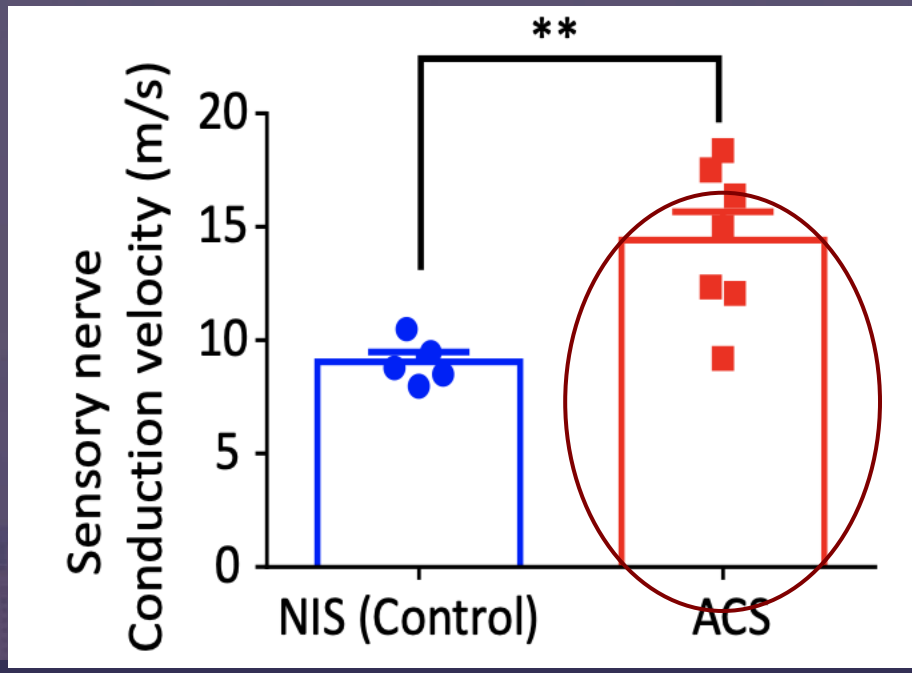
Demonstrated potential improvement nerve conduction on animal model



- Intrathecal ACS treatment significantly improves nerve conduction velocity in mice with CIPN.
- (A) Schematic of sensory conductance measurement. Two stimulation electrodes were inserted into a hind paw with 1 cm between them and the recording cuff electrode was inserted to the sciatic nerve (1 ms stimulation 10V).
- (B) Representative nerve conductance trace. left: control mice. right: ACS-treated mice. (C,D) Quantification of nerve conductance velocity (C) and amplitude (D).
- n = 5 mice for control (NIS), n = 7 mice for ACS. **p<0.01, unpaired t-test.
- SNAP: sensory nerve action potential amplitude: improvements.
- This is an under powered experiment.



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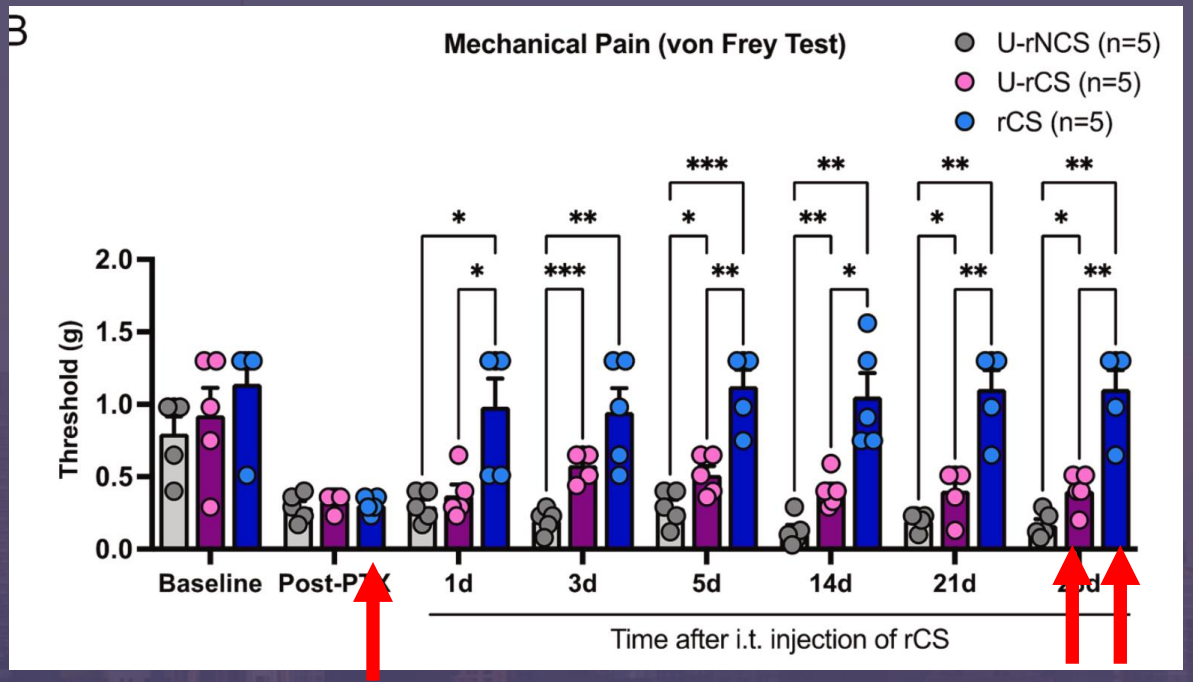
Intrathecal administration of conditioned serum from different species resolves Chemotherapy-Induced neuropathic pain in mice via secretory exosomes

Thomas Buchheit[a,b,*,1,2], Yul Huh[a,c,1], Andrew Breglio[a], Sangsu Bang[a], Jing Xu[a], Yutaka Matsuoka[a], Ran Guo[a], Andrey Bortsov[a], Julio Reinecke[d], Peter Wehling[a,d], Tony Jun Huang[e], Ru-Rong Ji[a,c,f,*]

rCS or U-rCS intrathecal injection into male PTX mice



- Exosomal removal significantly reduces analgesia
- Exosomal replacement restores analgesia

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	Treatment Class	ES Pain	ES Function	NNT	Side-effects
INTRA-ARTICULAR OPTIONS	***ACS***	***0.56[1]***	***0.67[1]***	***5.29[1]***	***Low***
	GC	*0.07[2]*	*0.06[2]*	*49.60[2]*	*Low*
	HA	*0.34[2]*	*0.30[2]*	*9.26[2]*	*Medium*
	PRP	*0.005[3]* *0.37[4]* *0.16[5]*	*0.04[3]* *0.40[5]*	*713[3]* *8.43[4]* *20.90[5]*	*Medium*
	Stem cells	*0.24[6]* *0.11[7]*	*0.01[6]* *0.12[7]*	*13.60[6]* *31.10[7]*	*Unclear*
ORAL OPTIONS	**NSAIDs**	*0.33[2]*	*0.37[2]*	*9.57[2]*	*High*
	Acetaminophen	*0.30[2]*	*0.32[2]*	*10.6[2]*	*Medium*
	Opiods	*0.20[2]*	*0.31[2]*	*16.5[2]*	*High*

[1-5] according references where data is derived from can be found in the Reference section

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One more argument for early intervention

This athlete played 3.5 weeks after this injury with early intervention!

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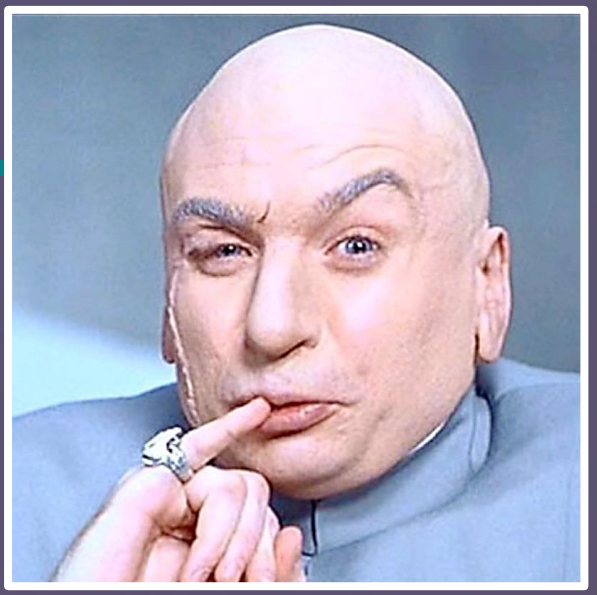
Possible considerations of Regenerative Medicine?



- Acutely in trauma?- My own case that I presented.
- Failed conservative management
- Limited time off work/sport
- Surgical Contraindications- other options exhausted
- Failed surgical management
- Buying time till definitive treatment is more appropriate
- Poor surgical tissue/ bone quality
  - Augmenting surgical procedures
- Surgical outcomes for condition are poor
  - Degenerative meniscal tears?
  - a recent meta-analysis shows that **only 20% of what is done** in orthopedics has level 1 data. (Lohmander LS, et al 2016; Blom et al 2021)
- Patient preference

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Things that we don’t know?

Does it work? Early intervention vs Late? Is more better?

1. MSCs + PRP?
2. MSCs + PRP + HA?
3. MSCs + PRP + Glucosamine?
4. MSCs + PRP + ACS?
5. MSCs + PRP + A2M?
6. ACS + PRP?
7. Single vs multiple injections?
8. Augmenting surgeries?
9. Who are the best patients?
10. What is the optimal dose/ volume?
11. How can we increase concentration?
12. What are the long-term results?

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Summary: A Paradigm Shift

- OA and tendinopathy is a chronic process that requires immune stimulation for the active *resolution* of inflammation
- The regenerative therapies act at different points within the healing cascade
- Orthobiologics provide a unique combination of inflammation-resolving cytokines, growth factors, and epigenetically active exosomes
- Think: Not how can I stop inflammation… But how can I stimulate the immune response to gain the desired outcome.

<u>Fighting inflammation and immune suppression impair natural healing cycles.</u>

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Questions?

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