Updates in Regenerative Medicine

Finding the Signal in the Noise

Jamie Lewis, MD

Spokane Pain Conference · October 16, 2026

Learning objectives

1. Describe how orthobiologics act through cell signaling rather than tissue replacement
2. Explain current evidence on platelet dose, leukocyte content, and delivery site for PRP and BMAC
3. Discuss why autologous treatments differ from donor-derived cell and exosome products, including the FDA framework
4. Summarize the current evidence and regulatory status of peptides such as BPC-157 and TB-500

Signal, not replacement

Platelets and cells act like a drug factory.

- They release growth factors, cytokines, and extracellular vesicles
- These signals shift tissue from breakdown toward repair
- PRP: activated platelets release PDGF, TGF-β, VEGF, and IGF-1 from alpha granules
- PRP concentrates the opening signal of normal wound healing

BMAC: bricklayer or general contractor?

Old model: bricklayer

Stem cells engraft and become new cartilage

Current model: general contractor

Cells read the injured environment, calm inflammation, and direct the patient's own cells to rebuild

- MSCs are about 0.001 to 0.01% of marrow nucleated cells
- Injected cells do not persist long in the joint
- BMAC also carries platelets, monocytes, growth factors, and IL-1Ra
- Caplan (2017): rename MSCs "medicinal signaling cells"
- BMAC in cuff repair: MRI retear 57% vs 18%, no difference in patient-reported outcomes

Caplan, Stem Cells Transl Med 2017; Cassano et al., KSSTA 2018; Cole et al., AJSM 2023

The target: inflammation in the arthritic joint

IL-1β and TNF-α

Main inflammatory signals in OA



Switch ON breakdown

MMP-13 (cuts type II collagen), ADAMTS-4/5 (degrade aggrecan)

Switch OFF building

COL2A1 and ACAN, the cartilage-building genes

Result: the joint tears down faster and builds slower.

Why the research is slow

	A drug (e.g., steroid)	An orthobiologic (PRP, BMAC)
The product	Identical in every vial	Different in every patient
The dose	Printed on the label	Depends on the patient's blood and the device
The variables	Dose + anatomy	Patient blood × equipment × anatomy

When a trial says "PRP failed," ask: which PRP?

Three buckets of variables

1. The patient's blood

Platelet count 150,000 to 400,000/µL (about a 2.5× range). Leukocytes, red cells, age, sex, baseline inflammatory state.

2. Equipment and protocol

Spin method, leukocyte-rich vs poor, draw and final volume. Same marrow, three cleared devices: 25% to 82% progenitor recovery.

3. Anatomy and delivery

Joint, tendon, or ligament. Disease stage. One site or several. Image guidance. Single injection or series.

About 70% of published BMAC studies never reported what was in the product.

Dragoo et al. 2020; Piuzzi et al., JBJS 2018

Dose: the first strong signal

Lateral epicondylitis meta-analysis: 13 RCTs, 791 patients, sorted by platelet concentration

−1.31

VAS mean difference, high-dose PRP (more than 3× baseline)

0.08

VAS mean difference, low-dose PRP (no effect)

58.5%

of between-study heterogeneity explained by platelet concentration

Oeding et al., AJSM 2025;53(10):2489–2496

Dose in knee OA: key studies

Study	Design	Dose	Result
Chu 2022	610 patients, double-blind, sham saline	Leukocyte-poor, ~4.16B × 3	Exceeded MCID, 6 to 60 months
Bansal 2021	RCT vs hyaluronic acid	Leukocyte-poor, 10.45B, single	Better than HA to 12 months
Hooper 2026	Meta-analysis, 32 trials, vs HA	5–10B vs more than 10B	SMD 1.48 vs 0.68

A sweet spot, not a ceiling.

Chu et al., KSSTA 2022; Bansal et al., Sci Rep 2021; Hooper et al., PM&R 2026

Practical dose targets

Joints (knee, hip OA)

≈10 billion platelets total

Soft tissue (tendon)

≥3.5 billion per injection

Rotator cuff: better above 6 billion

- Concentration is not total dose: 5× in 2 mL can hold fewer platelets than 3× in 8 mL
- Gluteal tendinopathy: negative trial, est. 3–5B split across two sites; positive trial, est. 6–9B into one structure

Buford, IOF/TOBI MAX 2026; Corsini et al., J Clin Med 2025; Atchia et al., JBJS 2025; Fitzpatrick et al., AJSM 2018

Leukocytes and dose travel together

Head-to-head trials

- Leukocyte-rich vs poor, platelets matched: no efficacy difference (n=192; n=132)
- Leukocyte-rich roughly doubles post-injection pain (OR 1.97)

The confound

- Platelets and white cells both concentrate in the buffy coat
- High-dose PRP in the literature tends to be leukocyte-rich
- Two strongest positive knee trials were high-dose and leukocyte-poor
- Measure platelets and white cells on the final product

Di Martino et al., AJSM 2022; Romandini et al., AJSM 2024; Driscoll et al., Arthroscopy 2026; Chu 2022; Bansal 2021

Where you put it: the subchondral bone

- OA is a whole-joint disease; the subchondral bone is involved early
- Bone marrow lesions on MRI are associated with pain and progression
- Cartilage has no nerves; subchondral bone does
- Intra-articular injection does not reach the bone

If cells direct repair, deliver them where the disease is.

Felson et al., Ann Intern Med 2001

Intraosseous delivery: the evidence

Study	Finding
Zhang 2024, rat OA model	IO + IA beat IA alone on pain and cartilage
Hernigou 2021, bilateral knee OA, 15 yr	Fewer knee replacements on the subchondral side
Hernigou, IOF 2026, shoulder, 15 yr	Arthroplasty 45.7% control vs 7.1% IO BMC
Oliver, IOF 2026, 455 patients, 5 yr	Pain: IA 5.87 to 5.21; IA + IO 5.93 to 3.43
Systematic review 2025, 298 knees	Subchondral better than IA; ~80% avoided TKA at 13 yr
Systematic review 2026, 1,109 patients	Cell products: most favorable long-term results
Barman 2022, RCT, IO PRP, n=50	No added benefit at 6 months; more injection AEs

Zhang, AJSM 2024; Hernigou, Int Orthop 2021; Nallakumarasamy, World J Stem Cells 2025; Abu Salem/Kon, Cartilage 2026; Barman, Injury 2022

Why do some patients not respond?

Same dose. Same device. Same joint. Different result.

Responders at baseline (60 of 109)

- Higher total antioxidant capacity
- Lower oxidative stress
- Lower TNF-α, PTX3, and PDGF-AA
- Distinct immune-cell profile

Not explained by

- Age
- Sex
- Prior treatment

Outcome = dose × the patient's biology

Granata et al., Front Immunol 2026 (knee OA, 1-year follow-up); Zila et al., OJSM 2026

The body's own brakes on inflammation

IL-1Ra

Binds the IL-1 receptor without activating it, blocking IL-1β

Soluble TNF receptors

Decoy receptors that bind TNF-α before it reaches the cell

Alpha-2-macroglobulin

Traps cartilage-degrading proteases; too large to enter the joint easily

All three circulate in plasma.

What happened when we used them

Approach	Result	Lesson
Recombinant IL-1Ra (anakinra) into the knee	No better than placebo	Cleared within hours
Autologous conditioned serum, as a series	Better than HA and saline	Own biology, repeated
A2M concentrate	Positive in animals; not better than PRP in one human comparison	Strong mechanism

Delivery, dose, and persistence decide whether it helps.

Chevalier et al., Arthritis Rheum 2009; Baltzer et al., Osteoarthritis Cartilage 2009; Wang et al., Arthritis Rheumatol 2014; Klein et al., OJSM 2020

Keeping what we used to throw away

- A centrifuge concentrates cells (platelets), not dissolved proteins or small particles
- Standard PRP keeps a few mL; most of the plasma (PPP) is discarded
- PPP carries IL-1Ra, soluble TNF receptors, A2M, and extracellular vesicles
- Extracellular vesicles: membrane packages (exosomes 30–150 nm) carrying proteins, lipids, and microRNA
- The membrane protects the cargo: vesicle-packaged IL-1Ra survived enzyme digestion; free IL-1Ra did not

Qu, IOF/TOBI MAX 2026; ISEV MISEV guidelines 2018/2023

Platelet-poor plasma vesicles: the data

- Plasma small vesicles are mostly platelet-derived; PRP and PPP vesicles are similar; both protect synoviocytes from IL-1β
- PPP vesicles lowered inflammatory genes and restored COL2A and ACAN in IL-1β-stressed OA chondrocytes

Multicenter registry (9 clinics)	**Standard PRP**	**PRP + processed PPP**
Baseline pain (NPRS)	4.72	4.73
Platelet dose	11.2 billion	11.2 billion
Pain reduction, 24 months	38% (n=1,973)	57% (n=52)
Knee MCID, 24 months	59%	80%

Piening et al., AJSM 2025; Papadimitriou et al., J Orthop Surg Res 2024;19:789; registry summary provided by the system manufacturer, 2026

Why autologous is where the science is

1. More than stem cells

MSCs are 0.001–0.01% of marrow cells; the effect comes from the whole fresh mix: platelets, monocytes, growth factors, IL-1Ra

2. Donor cells arrive dead

Independent labs found no live cells in commercial birth-tissue products

3. Infection and contamination

One product line: 20 infections, 65% of unopened vials contaminated. FDA safety notice on exosome products (2019)

4. Clinical data

Placebo-controlled trial of donor vesicles in knee OA: no difference from saline at 2 and 6 months

Becktell et al., Cartilage 2021; Berger et al., AJSM 2021; Panero et al., AJSM 2019; Hartnett et al., JAMA Netw Open 2021; Bolandnazar et al., BMC Musculoskelet Disord 2024

Where the FDA draws the line

Medical procedure

- The patient's own tissue
- Minimally manipulated
- Returned in the same procedure
- FDA clears the processing devices

Drug: requires FDA approval

- More than minimally manipulated (e.g., culture expansion)
- Donor (allogeneic) birth-tissue products
- None approved for musculoskeletal use

Courts: US v. US Stem Cell (11th Cir. 2021); US v. California Stem Cell Treatment Center (9th Cir. 2024); certiorari denied October 2025

Peptides: approved vs. unapproved

Approved

- Teriparatide
- Abaloparatide
- Semaglutide
- Tirzepatide
- Tesamorelin

BPC-157 and TB-500

- BPC-157: no published human RCTs
- TB-500: no human data (FDA briefing, July 2026)
- April 2026: removed from 503A Category 2 (not approval)
- July 2026: advisory vote 8–6 to recommend; FDA has not acted
- Not lawfully compoundable; WADA-prohibited

Regulatory status as of October 2026

Adjuncts: shockwave and laser

Shockwave (ESWT)

- Acoustic pressure waves: a mechanical signal
- Randomized trials of PRP + shockwave in tendinopathy, including a sham-controlled lateral epicondylitis trial
- Of interest where PRP alone is weak (patellar tendinopathy)

Laser (photobiomodulation)

- Light used to stimulate cell activity
- Combined with PRP: lab and animal data only for joints and tendons

Arch Phys Med Rehabil 2025; Knee Surg Relat Res 2024

Take-homes

1. Orthobiologics work by signaling, not tissue replacement
2. Research is slow because of variables: blood × equipment × anatomy
3. Dose is the first strong signal; count platelets and cells
4. Leukocytes and dose travel together
5. BMAC is a general contractor: location matters, and intraosseous is the frontier
6. Baseline patient biology predicts response
7. Plasma proteins and vesicles may be part of the medicine
8. Autologous, minimally manipulated care is where the science is

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