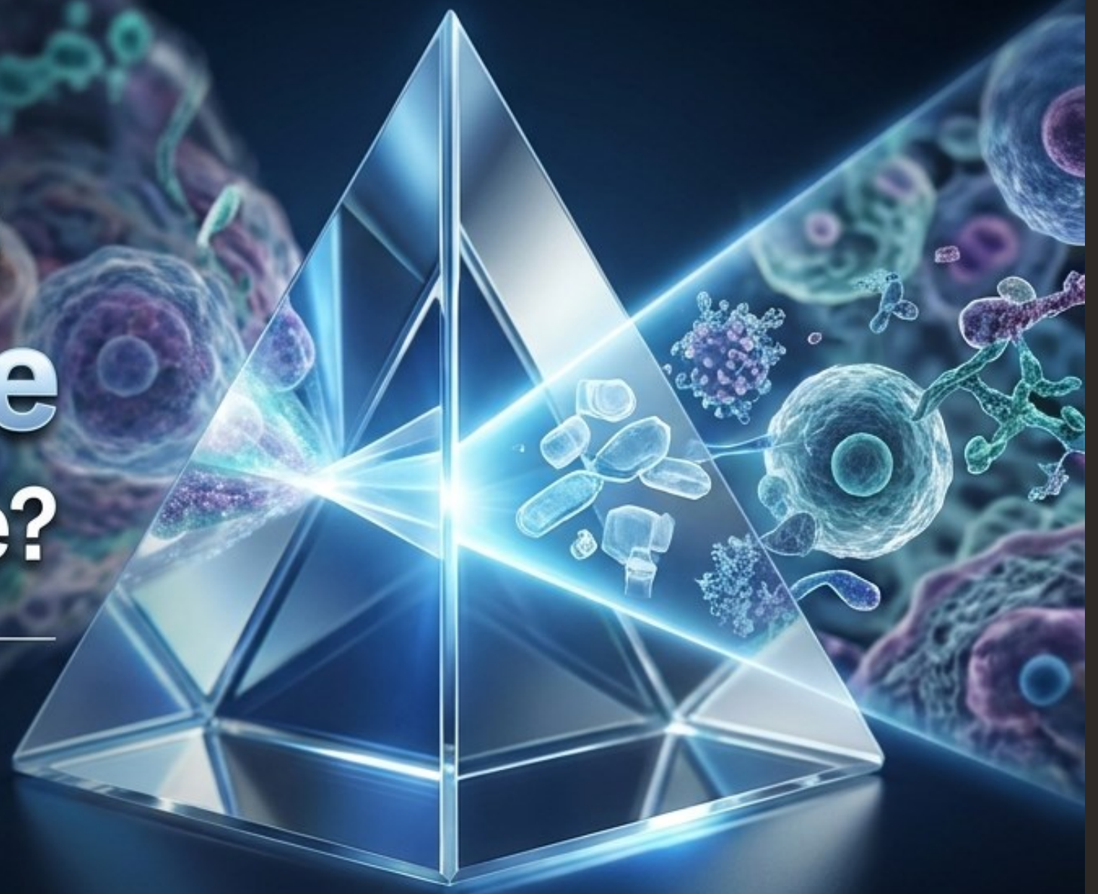
Orthobiologics in Pain Medicine

Evidence, Hype, or Hope?



Dr. Reza Aminnejad
Anesthesiologist & Pain Medicine Specialist

18–20 November 2026 · Tehran, Iran · From Innovation to Resilience

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Disclosure

Scientific Preparation & Use of AI

Evidence Base

65 | **review articles, systematic reviews and meta-analyses**

I personally studied these sources to develop the scientific content and critical appraisal presented here.

AI Assistance

- AI tools supported the visual design, slide layout and creation of illustrative graphics.
- AI was used as a presentation-design aid—not as a substitute for reviewing the scientific literature.
- The scientific appraisal, interpretation and final clinical messages remain my responsibility.

Transparent use of AI. Independent scientific responsibility.

The Translational Reality Check



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Ref: Hartvigsen et al. Lancet. 2018.

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The Unmet Need vs. Biological Plausibility

The Motivation

- **The Burden**: Chronic low back pain and degenerative disc disease remain major sources of disability.
- **The Limitation**: Current treatments focus on symptom control, not disease modification.



The Reality

- **Proposed Actions**: Immunomodulation, paracrine signaling, matrix homeostasis.
- **Translational Barriers**: Avascular and low-oxygen environments, poor cell survival, and product variability.

A plausible mechanism is a rationale for testing—not proof of clinical benefit.

Ref: Gradisnik et al. Bioengineering. 2026;1

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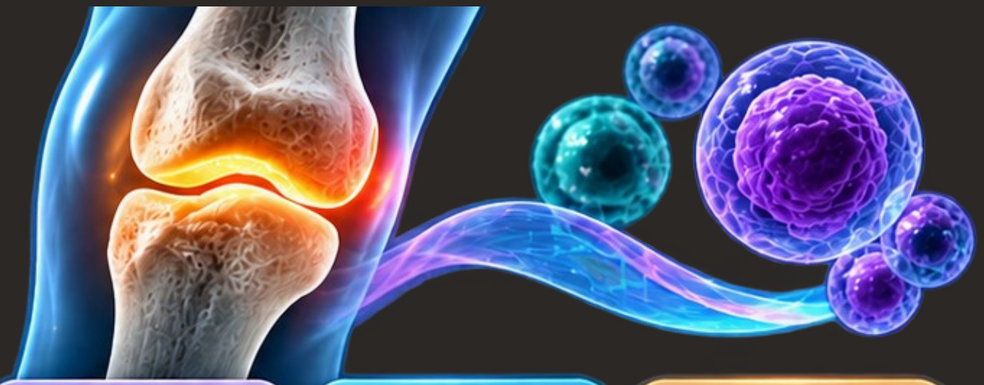
Orthobiologic Taxonomy
Seven Distinct Product Classes

Source, processing, composition and indication must be evaluated separately.



PRP


Platelet-Rich Plasma

Platelet-derived mediators in a plasma preparation.

BMC / BMAC


Bone Marrow Concentrate

A heterogeneous marrow-derived concentrate.

BM-MSC

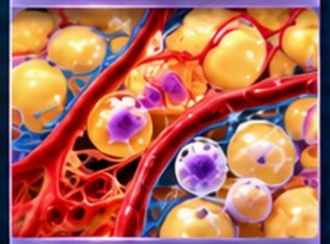

Bone Marrow MSCs

Culture-expanded mesenchymal stromal cells; autologous or allogeneic.

MPC


Mesenchymal Precursor Cells

A defined allogeneic cell product used in specific trials.

SVF


Stromal Vascular Fraction

Heterogeneous adipose-derived cell mixture; enzymatic or mechanical isolation.

ADSCs


Adipose-Derived Stromal Cells

Selected stromal cell population, often culture-expanded.

MFAT


Microfragmented Adipose Tissue

Mechanically processed adipose tissue; partial preservation of native architecture and ECM.

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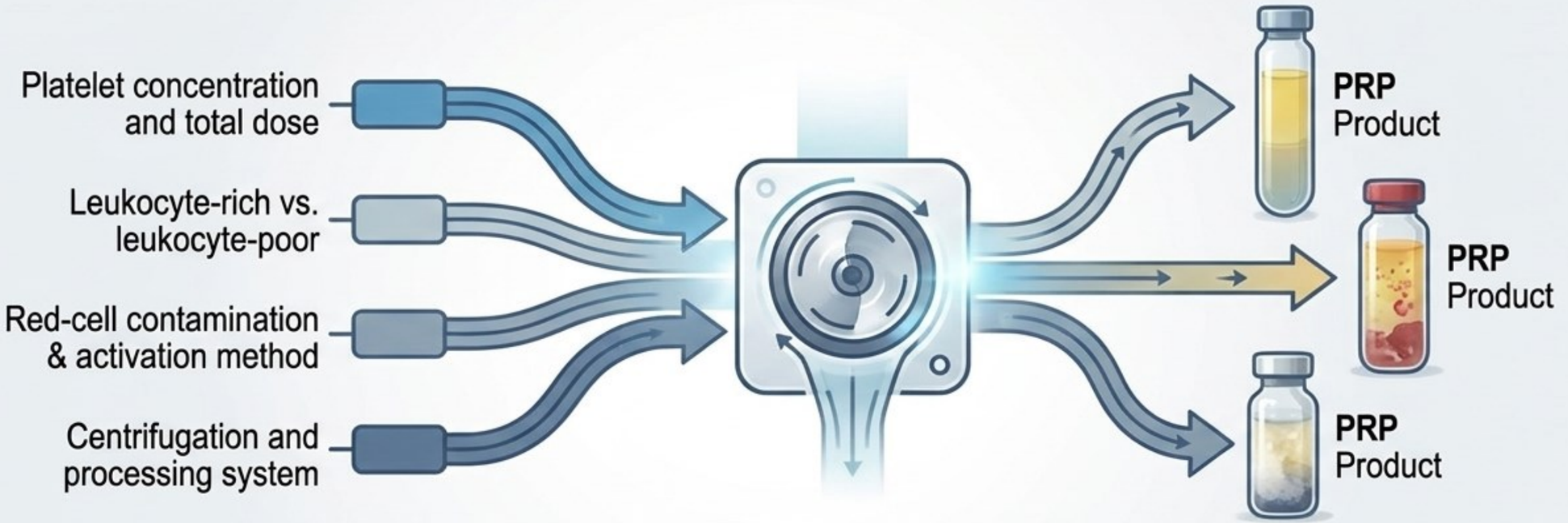
The Standardization Crisis: PRP is a Product Class, Not a Drug



Two studies labeled ‘PRP’ may test biologically different products. Preparation details are part of the intervention—not a technical footnote.

Refs: Marx RE. J Oral Maxillofac Surg. 2001; Dohan Ehrenfest

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TENDINOPATHY: PRP AS A SECOND-LINE OPTION

A systematic review focused on chronic cases that failed conservative treatment

9	**RCTs**	**488**	**patients**	**6**	**low-risk-of-bias RCTs pooled**

PAIN REDUCTION VS CONTROL

6 MONTHS

−0.83

95% CI −1.61 to −0.04

12 MONTHS

−1.11

95% CI −2.10 to −0.12

Mean difference in pain change; 24-month signal based on limited data.

WHAT THE REVIEW ACTUALLY SUPPORTS

POPULATION — Adults with chronic tendinopathy (>3 months) after unsuccessful first-line care, including physiotherapy.

SITES — Lateral elbow, rotator cuff/supraspinatus, patellar, gluteal tendinopathy and greater trochanteric pain syndrome.

FUNCTION — Some studies reported improvement; outcomes were too heterogeneous for pooled functional analysis.

CRITICAL LIMITS

Substantial heterogeneity (I^2 >75% across time points); varied PRP preparations, tendon sites and comparators. Functional outcomes could not be pooled. Results should not be generalized to every tendon, PRP formulation or first-line use.

CLINICAL TAKE-HOME | Consider PRP as a possible second-line option in selected refractory tendinopathy—not as a proven tendon-regeneration treatment.

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Nadeau-Valle M, et al. Pain Med. 2025;26:407–419. doi:10.1093/pm/pnaf022

When Promising Biology Meets Negative Clinical Trials

RESPINE Study | Allogeneic bone marrow–derived mesenchymal stromal cells (BM-MSCs) for chronic discogenic low back pain

PHASE IIb	N = 114	INTERVENTION	FOLLOW-UP
Multicentre • randomized • double-blind • sham-controlled	58 BM-MSC | 56 sham	Single intradiscal injection • 20 million allogeneic BM-MSCs	24 months

CLINICAL OUTCOME | PRIMARY ENDPOINT AT 12 MONTHS

74% — **68.8%**

BM-MSC group — Sham group

Responder definition: ≥20% and ≥20 mm VAS improvement, or ≥20% ODI improvement

p = 0.77 | No significant difference

STRUCTURAL OUTCOME | MRI

12 months	24 months
Disc-fluid content p = 0.77	Disc-fluid content p = 0.55

No between-group difference in modified Pfirrmann grade at 12 months (p = 0.94).

24-month MRI data: only 20 participants

WHAT THE TRIAL TELLS US

Biological plausibility did not translate into demonstrated clinical or MRI superiority over sham. The result applies to this allogeneic BM-MSC product, protocol and selected population—not to every cell therapy.

SAFETY SIGNAL

SAEs: 10 events in 7 BM-MSC patients vs 8 in 7 sham patients; no significant group difference. De novo donor-specific antibodies: 5/50.

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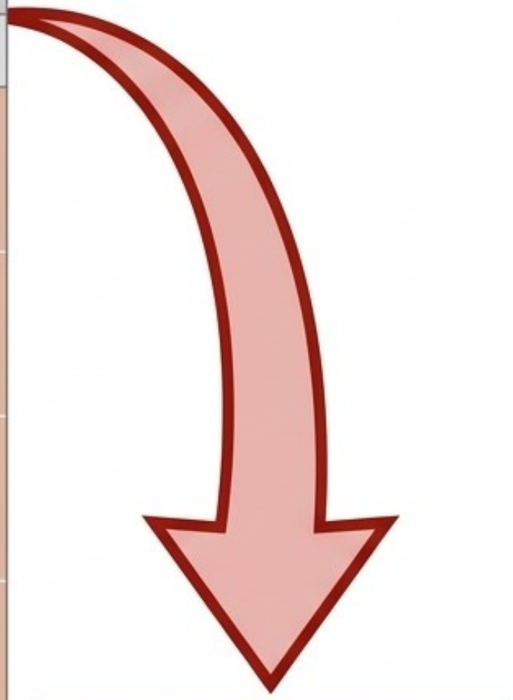
Pers Y-M, et al. Ann Rheum Dis. 2024. doi:10.1136/ard-2024-225771

Spine Trials Synthesis: The RCT Reality Check

Spine Efficacy Heatmap			
Trial	**Treatment**	**Clinical Data**	**Clinical Outcome**
Schepers 2022	PRP vs Saline	Pain response (PRP 48% vs Control 35%, P=0.244)	No significant clinical superiority over control.
Levi 2025	BMC vs Sham	12-month pain (BMC 44% vs Sham 56%, P=0.604)	No significant clinical superiority over control.
Vadalà 2025 (DREAM)	BM-MSC vs Sham	Short-term MRI signals, but no clinical superiority	No significant clinical superiority over control.
Pers 2024 (RESPINE)	BM-MSC vs Sham	Month-12 responders (BM-MSC 74% vs Sham 69%, P=0.77)	No significant clinical superiority over control.
Beall 2025	MPC vs Saline	Phase III primary composite endpoint NOT met	No significant clinical superiority over control.



No significant clinical superiority over control.

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Refs: Schepers (2022), Levi (2025), Vadalà (2025), Pers (2024), Beall (20

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BONE MARROW–DERIVED BIOLOGICS FOR DISCOGENIC PAIN

Systematic review | Her et al. | Journal of Pain Research, 2022

16	607	3	VERY LOW
STUDIES	PARTICIPANTS	RANDOMIZED TRIALS	GRADE CERTAINTY

CLINICAL SIGNAL

- Most studies reported reduced pain and improved physical function after intradiscal BMAC or culture-expanded BM-MSCs.
- Pain-score improvements of approximately 50–71% were reported in eight studies.
- Some benefits were maintained during long-term follow-up (up to 36–72 months in selected studies).

STRUCTURE & SAFETY

- MRI changes (Pfirrmann grade, disc height or water content) were inconsistent across studies.
- Reported adverse events were mainly injection-related pain; one case of discitis occurred.
- BMAC and culture-expanded BM-MSCs are distinct products and should not be considered interchangeable.

TAKE-HOME MESSAGE | Promising clinical signal, but very-low-certainty evidence; disc regeneration is not established.

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Her YF, et al. J Pain Res. 2022;15:3299–3318. doi:10.2147/JPR.S373345

Intradiscal PRP: High Platelet Concentration, No Clinical Superiority

Schepers et al. | Randomized controlled trial | Intervertebral disc degeneration without Modic changes

PRP PREPARATION & INJECTION

PLATELET CONCENTRATION

1.5×10^6 /µL

≈ 1.5 billion platelets/mL

32 mL	1.0 mL
Whole blood collected	Intradiscal PRP injected

SmartPReP 2 | 1,000 rpm × 15 min, followed by a second spin

PRP contained ~1% WBC; no further biochemical analysis was performed.

CLINICAL OUTCOMES AT 12 MONTHS

PRP: n = 44 1 mL intradiscal	Control: n = 45 Saline + 0.2 g Kefzol
Pain improvement	48% vs 35%
RMDQ improvement	50% vs 53%

No statistically significant between-group differences

SAFETY — 1 case of spondylodiscitis; required antibiotics and surgical debridement

KEY TAKEAWAY — **A very high platelet concentration did not translate into superior pain or functional outcomes.**

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Schepers MO, et al. Interv Pain Med. 2022;1:100011. doi:10.1016/j.inpm.2022.100011

EPIDURAL REGENERATIVE THERAPIES FOR SPINAL PAIN

Systematic Review & Meta-Analysis of Randomized Controlled Trials | 2026

9 RCTs included	**8 / 1** Positive / Neutral	**0** Epidural MSC RCTs	**III** Evidence level: Fair

WHAT THE REVIEW FOUND

Pain outcomes: No statistically significant pooled superiority of PRP over active comparators at 1, 3, or 6 months.

Function: No significant between-group differences at 1, 3, or 6 months.

Study design: All trials used active controls; none included placebo or sham controls.

CLINICAL INTERPRETATION

PRP: Promising, but superiority over epidural corticosteroid-based comparators is not established.

MSCs: No eligible randomized controlled trial of epidural stem-cell therapy was identified.

Recommendation: Moderate; overall evidence rated Level III (Fair).

KEY MESSAGE | Promising biologics should not be equated with proven clinical superiority.

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Manchikanti L, et al. Curr Pain Headache Rep. 2026;30:83. doi:10.1007/s11916-025-01448-2

ASIPP 2026 | FACET JOINT INTERVENTIONS

Updated Evidence-Based Guidelines for Chronic Spinal Pain

37	Guideline recommendations
48 / 39	Experts / Voting members
3	Spinal regions addressed
II–III	Evidence level: Diagnostic & therapeutic

KEY EVIDENCE & RECOMMENDATIONS

DIAGNOSIS

- Clinical features guide selection, but examination alone cannot confirm facet pain.
- Diagnostic medial branch blocks: lumbar Level I–II; cervical and thoracic Level II.
- Fluoroscopy or CT guidance is strongly recommended for all facet interventions.

TREATMENT

- RFA: Level II (cervical and lumbar); Level III (thoracic).
- Therapeutic medial branch blocks: Level II across all three regions.
- Intra-articular injections: weaker evidence, particularly lumbar (Level IV).

CLINICAL PRACTICE POINTS

PATIENT SELECTION

Consider axial pain for ≥3 months after failed conservative care; assess tenderness, reduced ROM, extension/rotation-provoked pain and absence of a radicular pattern.

PROCEDURAL SAFETY

Avoid opioids during diagnostic blocks; low-dose benzodiazepines may be used for mild sedation when appropriate. Perform sensory and/or motor testing before RFA. Antithrombotic therapy may often be continued after individualized risk assessment.

KEY MESSAGE | Accurate diagnosis and patient selection are central to successful facet interventions.

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Manchikanti L, et al. Pain Physician. 2026;29:S1–S228.

ASIPP 2026 | PRP IN FACET JOINT INJECTIONS

Clinical evidence from randomized comparative studies

3	Randomized trials
116	Participants (46 + 30 + 40)
2	Spinal regions Lumbar & cervical
No	Consistent superiority vs corticosteroid

CLINICAL EVIDENCE

LUMBAR FACET JOINTS

- Wu et al., 2017 (n=46): both groups improved; PRP showed better MRI synovitis grading. No placebo or controlled diagnostic blocks.

- Kotb et al., 2022 (n=30): both groups improved at 3 months. PRP favored some MRI and examination measures, but clinical relevance remained uncertain.

CERVICAL FACET JOINTS

- Allison et al., 2026 (n=40): no significant difference in ≥50% pain responders at 3 or 6 months.

CRITICAL INTERPRETATION

EVIDENCE APPRAISAL

- Three small randomized trials; all used active comparators.
- No consistent advantage in clinically meaningful pain or function outcomes.
- Imaging or examination changes do not necessarily mean meaningful patient benefit.

UNANSWERED QUESTIONS

- Optimal PRP composition, dose, volume and protocol.
- Long-term benefit and clinically meaningful responder rates.
- Comparative value versus established facet interventions.

KEY MESSAGE | PRP is promising, but current facet-joint trials do not establish consistent clinical superiority over corticosteroid injections.

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Manchikanti L, et al. Pain Physician. 2026;29:S1–S228 (Table 25, pp. S132–S134). | Allison DJ, et al. Reg Anesth Pain Med. 2026;51:33–40.

ASIPP 2025: REGENERATIVE THERAPIES IN CHRONIC LOW BACK PAIN

Evidence-based recommendations for targeted spinal biologic interventions

BIOLOGIC THERAPY IS TARGET-SPECIFIC — NOT A SINGLE "SPINAL PRP" TREATMENT

INTRADISCAL

PRP • BMAC

Level III — Fair evidence
Moderate recommendation

HIGH procedural risk

EPIDURAL

PRP

Level III — Fair evidence
Moderate recommendation

MODERATE procedural risk

FACET / SI JOINT

PRP • MSCs

Level IV — Limited evidence
Moderate (facet) / Low (SIJ)

LOW procedural risk

CLINICAL CHECKLIST

Confirm the pain generator • Use after conservative care fails • Standardize product preparation and quality control • Obtain informed consent and discuss cost, risks and uncertainty • Integrate rehabilitation • Manage antithrombotics according to procedural risk

TAKE-HOME: Promising, selective options — not established cures. Match the biologic and route to a precise diagnosis, and do not overstate regeneration or disease modification.

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Manchikanti L, et al. Pain Physician. 2025;28(Suppl 7):S1–S119.

WHAT DO 13 RANDOMIZED TRIALS TELL US ABOUT SPINAL ORTHOBIOLOGICS?

A 2026 RCT-only systematic review (radiculopathy, facet pain, discogenic pain)

13 RCTs | PRP • BMAC • MSCs • MPCs

Search through 22 Sept 2025 | No pooled meta-analysis

LUMBAR RADICULOPATHY | 4 RCTs

Steroids faster (1–4 weeks); PRP better at 3–6 months.

FACETOGENIC PAIN | 2 RCTs

PRP helped some ODI responders; no significant difference.

INTRADISCAL PRP / AUTOLOGOUS CELLS

Mixed results; largest trial negative.

ALLOGENEIC MPCs | PROMISING, NOT ESTABLISHED

One RCT shows long-term benefit; still investigational.

KEY MESSAGE | **Efficacy is product- and indication-specific: strongest PRP signals in lumbar radiculopathy and facet pain.**

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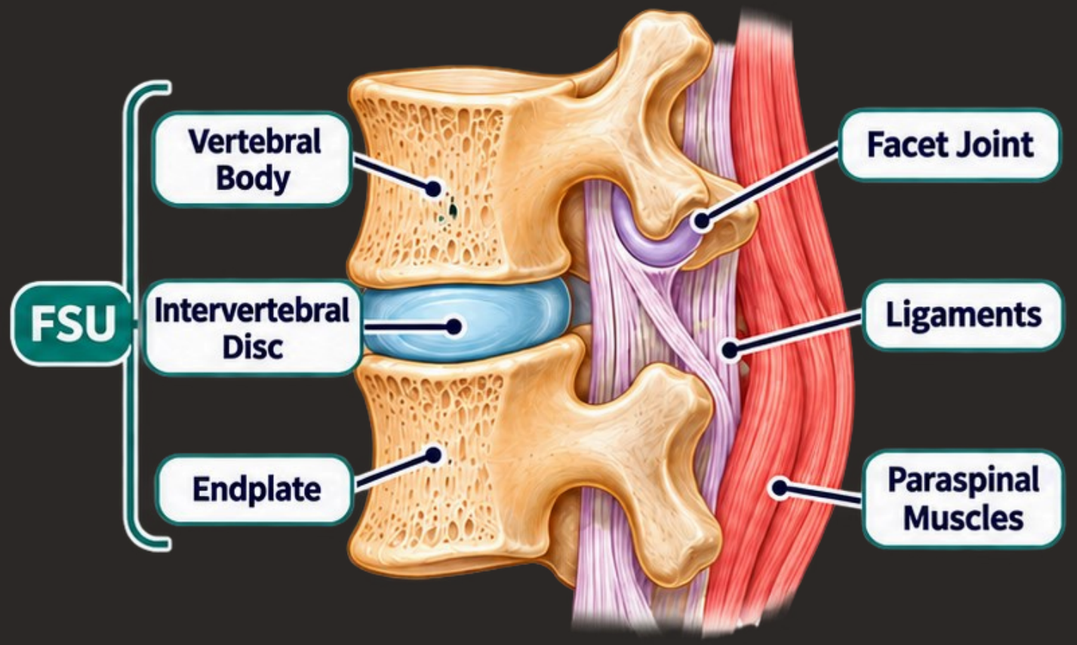
Zhang RE, Aurangzeb A, Sirisena D. Eur Spine J. 2026. doi:10.1007/s00586-026-09997-9

From a Single Pain Generator to a Whole-Unit Approach

Chronic low back pain is often a multifactorial condition, not a single pain source.



1. The **Functional Spinal Unit (FSU)** is an integrated unit comprising the disc, facet joints, endplates, ligaments, and muscles.
2. **Orthobiologics (PRP and MSCs)** can target multiple FSU components, modulating disease processes and promoting tissue repair.
3. Early studies show **promising** pain and functional improvement, but the current evidence is insufficient for a definitive recommendation.

Key Takeaway: Adopt a **multitarget, biomechanics-based approach** with high-quality clinical trials to validate and standardize treatment protocols.

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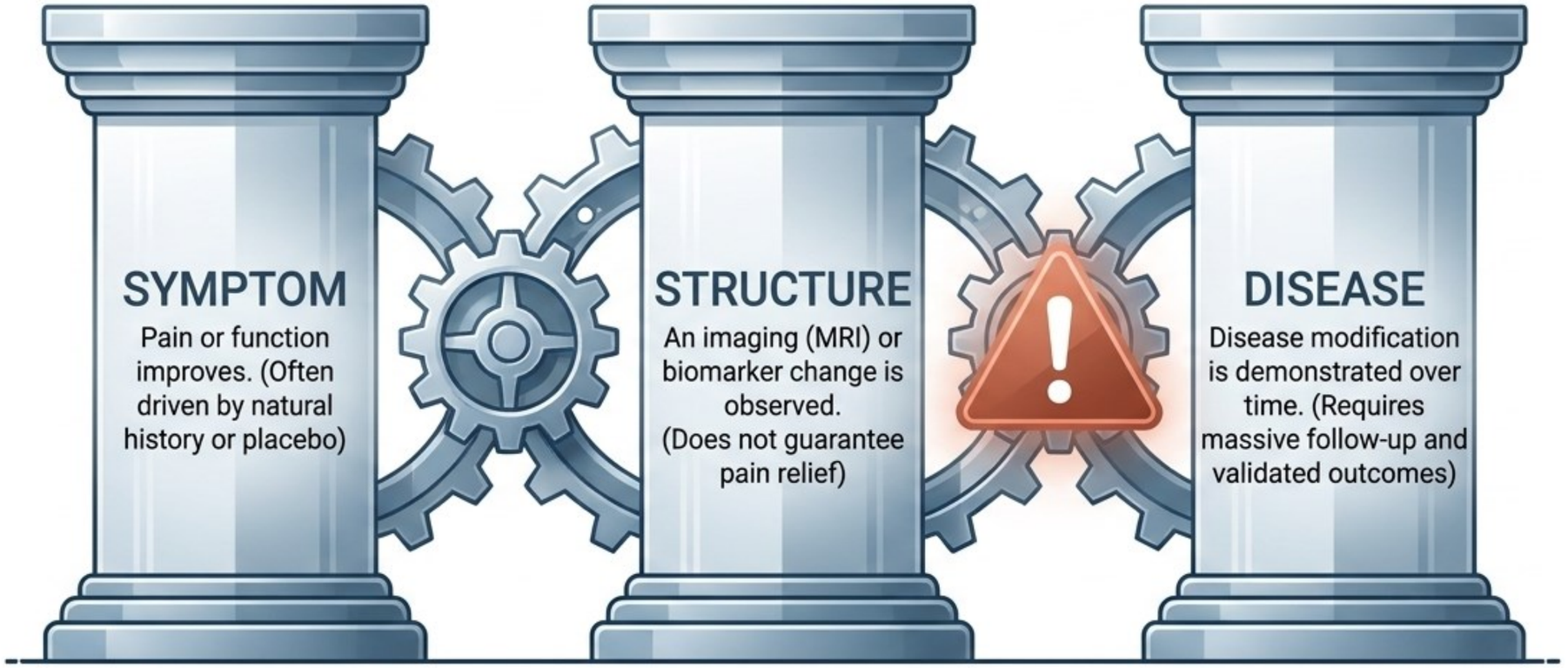
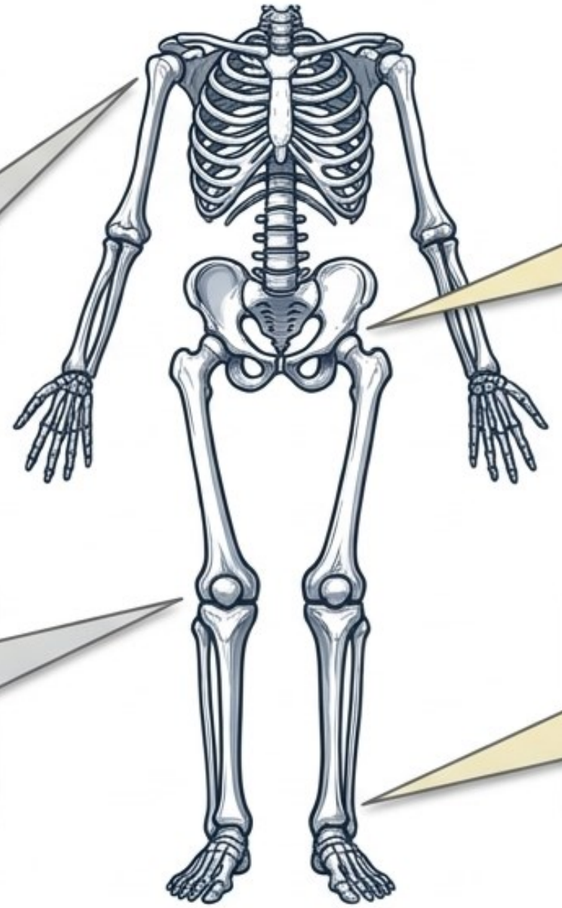
Navani A, et al. *Pain Physician*. 2025;28:S145–S156.

Interpreting the Disconnect: Three Distinct Claims



These are entirely distinct scientific claims.
Efficacy in one pillar does not prove efficacy in the others.

Peripheral Joints: The Anatomy of Evidence



Shoulder (Rotator Cuff)

Possible late benefit (6 months) over steroid; clinical importance limited.

Hip (PRP)

Inconsistent long-term results; highly heterogeneous protocols.

Knee (PRP/MSC)

Modest/Uncertain vs Saline. Some pain signal, but regeneration/disease modification remains unproven.

Achilles / Tendons

No routine support. Placebo-controlled data shows shows no meaningful improvement in VISA-A function.

A result in knee OA is not a class effect for all synovial joints. Do not extrapolate.

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RETHINKING THE GOAL OF ORTHOBIOLOGIC THERAPY

A patient- and phenotype-centered approach to knee osteoarthritis

THE GOAL IS NOT ALWAYS CARTILAGE REGENERATION

SYMPTOM RELIEF

Reduce pain and inflammation; improve function and quality of life.

JOINT ENVIRONMENT

Modulate the intra-articular biological milieu and support the patient's response to rehabilitation.

PATIENT & PHENOTYPE

Match treatment to disease stage, clinical phenotype, mechanical factors and patient goals.

CLINICAL TAKE-HOME

Symptom improvement ≠ proven structural regeneration.
Meaningful clinical benefit does not require demonstrable cartilage restoration.

The future of orthobiologics is not product-centered; it is patient- and phenotype-centered.

Aguayo-Pigeonutt et al. *Cureus*. 2026. doi:10.7759/cureus.114564

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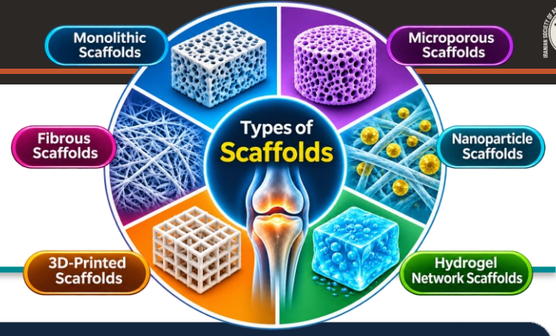
ARTICULAR CARTILAGE REPAIR

From symptom relief to biologically guided tissue restoration



THE FUTURE IS MULTIMODAL: CELLS + BIOACTIVE SIGNALS + BIOMATERIAL SCAFFOLDS

BIOLOGICAL

PRP • BMAC • MSCs • Exosomes

Potential roles: immunomodulation, paracrine signaling and support of matrix repair.

Clinical maturity varies; standardization and durable human outcomes remain key gaps.

STRUCTURAL

ACI / MACI • OATS • OCA

Established restorative options selected according to defect size, depth and subchondral bone involvement.

Greater procedural complexity, cost, graft availability and rehabilitation demands.

ENGINEERED

Hydrogels • Scaffolds • 3D bioprinting

Designed to mimic the extracellular matrix and deliver cells or bioactive cues.

Promising platforms, but many remain preclinical or at an early clinical stage.

CLINICAL TAKE-HOME

Improved pain or function ≠ proven hyaline-cartilage regeneration. Match treatment to the lesion, the patient and the evidence.

Lara-Bertrand AL, et al. J Funct Biomater. 2026;17:128. doi:10.3390/jfb17030128 | Narrative review

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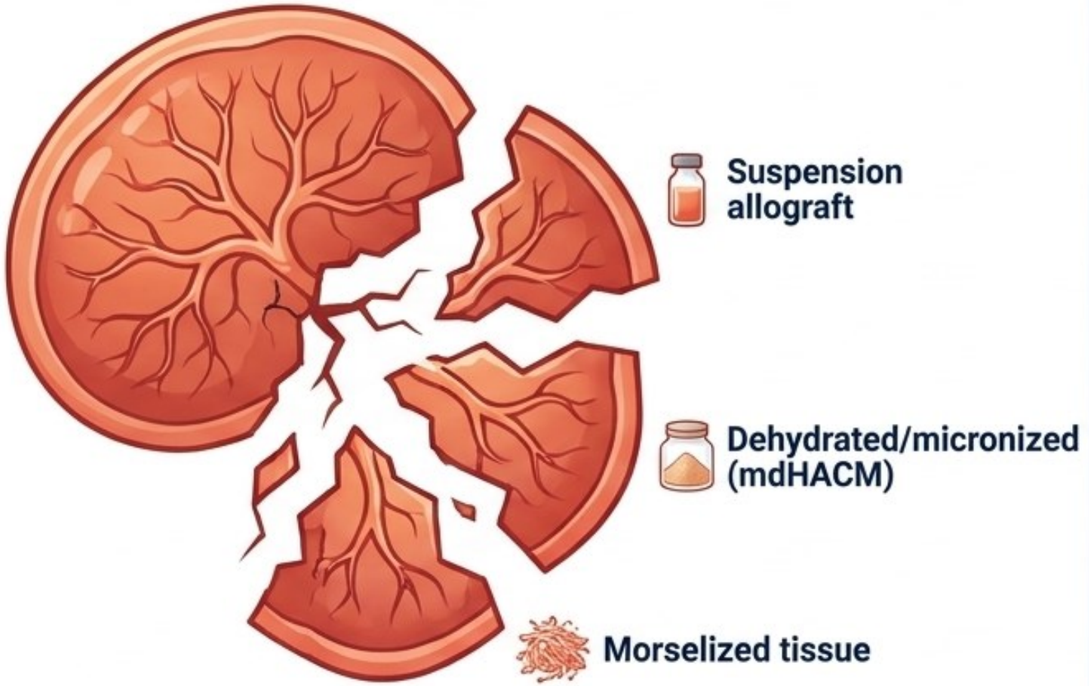
Safety, Ethics, and the Placental Wildcard

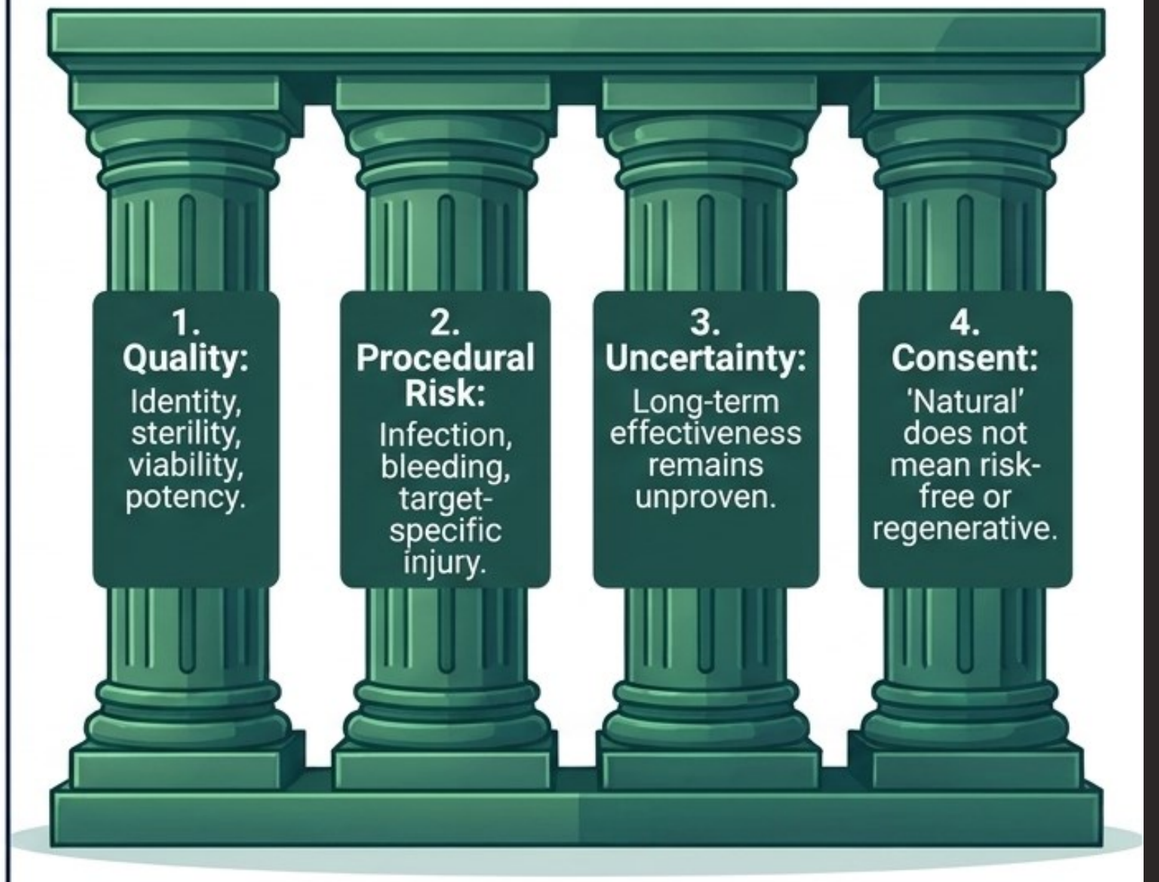


The Wildcard: Formulations

Suspension allograft vs. Dehydrated/micronized (mdHACM) vs. Morselized tissue.

Reality: Processing entirely changes cellular content. Prospective randomized knee-OA evidence for mdHACM is absent.

The 4 Pillars of Safety



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Refs: Chen KH (2026); FDA Consu

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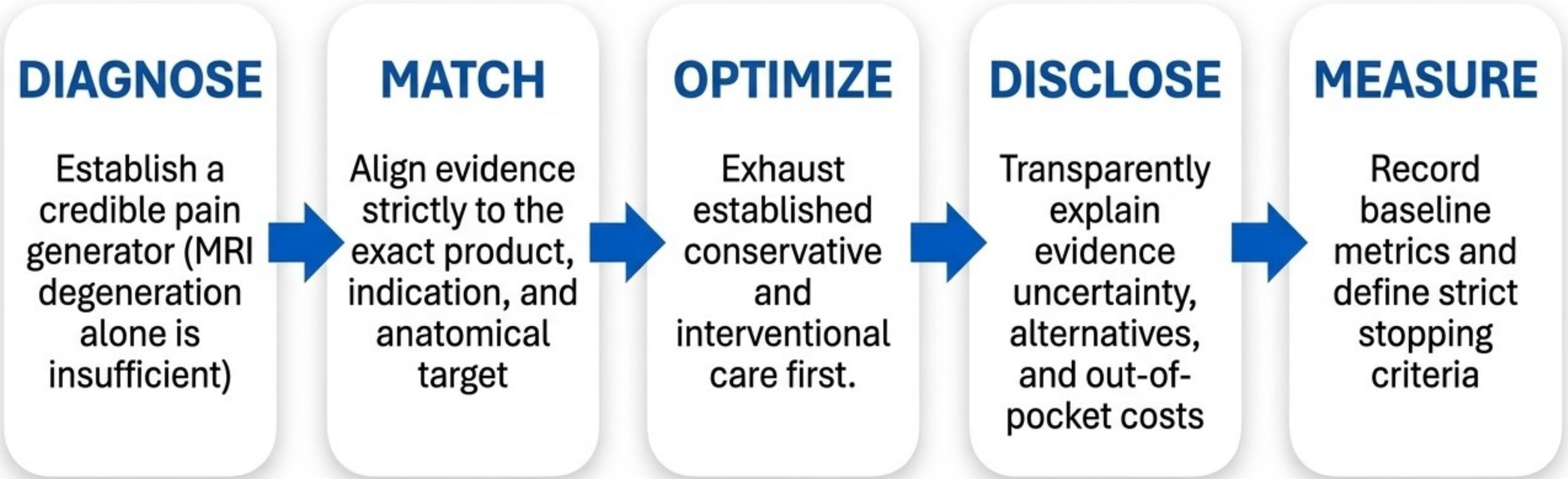
A Practical Decision Framework for the Pain Clinic

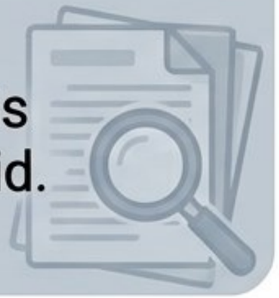


Orthobiologics: The Final Verdict

EVIDENCE

Limited, highly heterogeneous, and strictly product/target-specific.

Extrapolation is clinically invalid.



HYPE

The dangerous conflation of biological plausibility or short-term imaging signals with proven, disease-modifying clinical efficacy.



HOPE

Lies in rigorous sham-controlled trials, standardized product characterization, and prioritizing clinically meaningful patient outcomes.



"Hope should be guided by evidence, not driven by hype."

Dr. Reza Aminnejad

Ref: Orthobiologics 18th ISACC Congress Sum

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Master References & Core Evidence Base

Spine & Guidelines

Schepers et al. (2022) *Interv Pain Med.*

Levi et al. (2025) *Interv Pain Med.*

Vadalà et al. (2025) *JOR Spine.* (DREAM)

Pers et al. (2024) *Ann Rheum Dis.* (RESPINE)

Beall et al. (2025) *Spine J.*

Manchikanti L, et al. *ASIPP 2025 Guidelines.*

Peripheral & Reviews

Auroux M, et al. (2025) *Joint Bone Spine.*

Tabet CG, et al. (2024) *J Orthop Translat.*

Barreto ESR, et al. (2025) *Clin Orthop Relat Res.*

Chen KH, et al. (2026) *Biomedicines.*

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18th | International Congress of Anesthesiology, Critical Care and Pain

From Innovation to Resilience



Thank You & Q&A

"Hope should be guided by evidence, not driven by hype."



Access the Slides on LinkedIn

Tehran, Iran | 18th ISACC Congress

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