Advances in Clinical and Medical Research

Genesis-ACMR-7(4)-134
Volume 7 | Issue 4
Open Access
ISSN: 2583-2778

Photobiomodulation with the Proactive MR5 Platform in Regenerative Medicine: An Umbrella Study of Mechanisms, Orthobiologic Modulation, and Musculoskeletal Clinical Effects

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Citation: Kume MH, Furlan B, Boaventura CG, Probst MA, Peracchi E, et al. Photobiomodulation with the Proactive MR5 Platform in Regenerative Medicine: An Umbrella Study of Mechanisms, Orthobiologic Modulation, and Musculoskeletal Clinical Effects. Adv Clin Med Res. 7(4):1-17.

Received: August 29, 2026 | **Published:** September 29, 2026

Abstract

Background: Photobiomodulation (PBM) — the therapeutic use of red and near-infrared light — is one of the most widely studied non-pharmacological modalities in musculoskeletal and regenerative medicine, yet clinical adoption remains uneven because of protocol heterogeneity, imprecise dosimetry, and limited head-to-head comparison of devices. The Proactive MR5 family (ASA Laser, Vicenza, Italy) applies the proprietary Multiwave Locked System (MLS®) technology that synchronises an 808 nm continuous emission with a 905 nm super-pulsed emission and, in the LaserShower configuration, delivers this dual beam over a wider projected area with preset regimens including Tissue Repair. A structured, device-aware evidence synthesis has not been previously published.

Objectives: To (i) synthesise mechanistic, translational, and clinical evidence for PBM in regenerative medicine across mitochondrial signalling, orthobiologic priming (platelet-rich plasma [PRP], bone-marrow aspirate concentrate [BMAC], mesenchymal stem/stromal cells [MSCs], extracellular vesicles [EVs] / exosomes), and musculoskeletal indications; (ii) benchmark commonly reported dosimetric parameters against WALT 2010 recommendations; and (iii) position the Proactive MR5 / MLS platform inside this evidence landscape, distinguishing what is device-specific from what is generic to PBM.

Research Article | *Kume MH. Adv Clin Med Res*. 2026, 7(4)-134
DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

Methods: Overview of systematic reviews (SRs) and meta-analyses (MAs) using an adapted PRISMA 2020 / PRIOR workflow. PubMed, PMC, Cochrane, ScienceDirect, Springer, MDPI, Frontiers and WALT institutional sources were searched to August 2026. Eligible records were SRs / MAs of PBM in musculoskeletal or regenerative applications, mechanistic reviews on the mitochondrial and redox pathways, in-vitro/in-vivo studies of PBM combined with orthobiologics, and primary clinical evidence using the MLS platform. Data on wavelength, power, irradiance, fluence, energy per point, sessions, comparator, effect sizes with 95% confidence intervals (CIs), certainty of evidence (Cochrane RoB, GRADE, AMSTAR-2 when reported) and authors' conclusions were extracted in duplicate. A device-explicit narrative synthesis with structured tables complemented random-effects effect-size mapping (no re-pooling was performed).

Results: Across the ten thematic domains, PBM shows consistent, biologically coherent mechanistic evidence (photoactivation of cytochrome-c-oxidase in the 600–700 nm and 760–940 nm windows, nitric-oxide photodissociation, transient reactive-oxygen-species signalling, biphasic Arndt–Schulz dose response, and light-sensitive TRP/opsin channels). Clinical benefit is most robust when WALT-compliant dosing is used: in knee osteoarthritis, LLLT reduced pain by 14.23 mm VAS (95% CI 7.31–21.14) and with recommended doses by 18.71 mm VAS (95% CI 9.42–27.99); disability improved with SMD 0.59 (95% CI 0.33–0.86). Wavelength-specific pain effects were larger at 904–905 nm (SMD 1.42, 95% CI 0.31–2.53) than at 785–850 nm (SMD 0.82, 95% CI 0.11–1.50). Similar signal was seen for lateral elbow tendinopathy (short-term pain WMD 10.2 mm, 95% CI 3.0–17.5; 904 nm on the tendon WMD 17.2 mm, 8.5–25.9), plantar fasciitis, shoulder impingement, and temporomandibular disorders (VAS SMD −0.55, 95% CI −0.82 to −0.27). Signal was weaker for chronic non-specific low back pain and Achilles tendinopathy when PBM was added to eccentric exercise. Orthobiologic priming evidence is preclinical/translational: PBM 808 nm + PRP outperformed either alone in reducing intra-articular inflammation in Wistar rats; PBM 650/810 nm enhanced human ADSC viability ($p = 0.007–0.008$) and increased exosome protein yield with mean vesicle size ~86 nm; PBM at 3 J/cm² partially reversed senescence and restored proliferation in aged bone-marrow MSCs (SA-β-Gal-positive area 13.5% → 4.2%, $p<0.001$); 825 nm PBM promoted tenogenic differentiation of adipose-derived MSCs (Scleraxis 2.3-fold, Tenomodulin 2.3-fold). MLS-specific clinical evidence is small but positive across chronic low back pain, chronic neck pain, tendinopathy and osteoarthritis, with pain reductions from ~6.7 to ~1.9 on VAS in 12-session protocols. Certainty of evidence at meta-analytic level is generally low to very low (Cochrane RoB2, GRADE); no included SR reported AMSTAR-2 formally.

Conclusions: PBM has a coherent mechanistic base and reproducible short-term clinical benefit in several musculoskeletal indications when WALT-compliant, wavelength- and dose-transparent protocols are used. The Proactive MR5 / MLS platform is well positioned within this window (808 nm continuous + 905 nm super-pulsed), and its dual-emission architecture is biologically rational for orthobiologic priming, but device-specific randomised, sham-controlled trials — including ex-vivo photoactivation of PRP, BMAC, MSCs and EVs — are needed before adjuvant use can be considered evidence-based. Future work must standardise TIDieR-compliant dosimetry, adopt AMSTAR-2 appraisal, and separate PBM effects from orthobiologic effects using factorial designs.

Keywords

Photobiomodulation; low-level laser therapy; MLS Multiwave Locked System; Proactive MR5; platelet-rich plasma; mesenchymal stem cells; exosomes; osteoarthritis; tendinopathy; regenerative medicine; umbrella review.

Introduction

Photobiomodulation (PBM) therapy — historically referred to as low-level laser therapy (LLLT) — is defined by the World Association for Photobiomodulation Therapy (WALT) as the therapeutic application of non-ionising light in the visible red and near-infrared (NIR) ranges to elicit non-thermal biological effects. Contemporary mechanistic evidence converges on cytochrome-c-oxidase (unit IV of the mitochondrial respiratory chain) as the principal photoacceptor, whose photonic activation displaces inhibitory nitric oxide, restores mitochondrial membrane potential, increases oxygen consumption and ATP production, and triggers a brief burst of reactive oxygen species (ROS) that acts as a redox signal for anti-apoptotic, anti-inflammatory, and pro-regenerative transcriptional programs [9,10,11].

This mechanistic base has produced more than a thousand controlled experimental and clinical studies across musculoskeletal, dermatological, neurological, and stomatognathic indications. However, translation into routine care is impeded by three persistent problems: (i) dosimetric opacity — many trials report wavelength or nominal 'preset' but omit irradiance, fluence, energy per point, and total delivered dose; (ii) the biphasic Arndt–Schulz dose-response, which means that both underdosing and overdosing can abolish or reverse effect; and (iii) device heterogeneity — reviews pool RCTs using devices whose optical, spectral, and pulsing behaviour differ substantially, obscuring real between-device differences [12,13,14].

The Proactive MR5 family (ASA Laser, Vicenza, Italy) is one of the more distinctive devices in current musculoskeletal practice because it applies the proprietary Multiwave Locked System (MLS®) technology, which synchronises within a single impulse a 808 nm continuous-wave emission (typically associated with anti-inflammatory and anti-oedema effects) and a 905 nm super-pulsed emission (typically associated with analgesic effect and deeper penetration). The MR5 ACTIV PRO and MR5 LaserShower configurations further extend this dual-wavelength delivery over a larger projected area and offer clinician-facing presets such as Tissue Repair. This architecture is biologically rational both for direct tissue treatment and — an emerging line of investigation — for ex-vivo priming of orthobiologics (platelet-rich plasma [PRP], bone-marrow aspirate concentrate [BMAC], adipose-derived stem cells [ADSCs], extracellular vesicles [EVs] / exosomes) prior to intra-articular administration.

Despite this rationale, no structured evidence synthesis has previously (i) mapped the mechanistic, translational, and clinical PBM literature onto the same evidence grid, (ii) benchmarked reported doses against WALT recommendations, and (iii) positioned the Proactive MR5 / MLS platform explicitly inside this landscape. The present umbrella study addresses that gap. Its intended readership is clinicians and researchers in orthopaedics, sports and regenerative medicine planning device-aware clinical programmes and translational trials.

Objectives

- **Primary.** To synthesise the highest available level of evidence on PBM in regenerative medicine across three integrated domains — (i) mechanisms and photobiology, (ii) orthobiologic priming (PRP, BMAC, MSCs, EVs/exosomes), and (iii) musculoskeletal clinical indications — and to explicitly locate the Proactive MR5 / MLS platform in that landscape.
- **Secondary.** (a) To benchmark reported PBM parameters against WALT 2010 dose recommendations; (b) to identify indications where PBM is supported by ≥1 systematic review with meta-analysis showing a clinically relevant effect; (c) to map preclinical evidence on ex-vivo PBM priming of orthobiologics; and (d) to derive practical, device-explicit recommendations and a research agenda for the MR5 platform.

Methods

This overview of systematic reviews was conducted following the PRIOR (Preferred Reporting Items for Overviews of Reviews) statement and the PRISMA 2020 checklist adapted for overviews. No formal

PROSPERO registration was in place at the time of drafting; prospective registration is recommended before submission.

Eligibility criteria

Inclusion criteria — Population: humans (adults or children) with musculoskeletal, tendinous, cartilaginous, neural, or wound-healing conditions; or biological substrates relevant to regenerative medicine (PRP, BMAC, MSCs, chondrocytes, tenocytes, EVs/exosomes). Intervention: PBM delivered by laser or LED in the 400–1064 nm range, in vivo or ex vivo, including MLS-based devices. Comparator: sham/placebo PBM, alternative modality, or untreated control. Outcomes: pain (VAS/NRS), function (WOMAC, KOOS, PRTEE, DASH, NDI, ODI, VISA-A), range of motion, cell viability/proliferation/differentiation, growth factor/cytokine profiles, EV/exosome yield or size, and safety. Study design: systematic reviews with or without meta-analysis, umbrella reviews, mechanistic narrative reviews indexed in PubMed/PMC, and — for the MR5-specific and orthobiologic priming sections — primary controlled trials or high-quality preclinical studies. Language: English, Portuguese, or Spanish.

Exclusion criteria — Conference abstracts without full text, case reports, editorials without an evidence base, veterinary studies (unless they were the only evidence for a specific MLS parameter), and duplicate reports.

Information sources and search strategy

PubMed, PMC, Cochrane Library, ScienceDirect, SpringerLink, MDPI, Frontiers, Nature portfolio, and the World Association for Photobiomodulation Therapy (WALT) institutional site were searched to 28 August 2026. Search strings combined MeSH and free-text terms including (photobiomodulation OR PBM OR 'low-level laser therapy' OR LLLT OR 'photobiostimulation') AND (mechanisms OR cytochrome c oxidase OR 'nitric oxide' OR mitochondria OR 'biphasic dose response' OR wavelength) AND (osteoarthritis OR tendinopathy OR 'lateral epicondylitis' OR 'rotator cuff' OR 'plantar fasciitis' OR 'temporomandibular disorder' OR 'carpal tunnel' OR 'low back pain' OR 'muscle regeneration' OR 'bone healing' OR 'nerve regeneration' OR 'wound healing') AND ('systematic review' OR meta-analysis OR umbrella). Device-specific searches added ('Multiwave Locked System' OR MLS OR 'ASA Laser' OR 'MR5' OR 'LaserShower'). Orthobiologic searches combined PBM terms with ('platelet-rich plasma' OR PRP OR BMAC OR 'bone marrow aspirate' OR 'mesenchymal stem cells' OR MSC OR exosomes OR 'extracellular vesicles' OR ADSC).

Study selection, data extraction, and quality appraisal

Two reviewers screened titles and abstracts. Data on citation, design, population, PBM parameters (wavelength[s], output power, irradiance, fluence, energy per point, sessions, area, device brand), comparator, effect size with 95% CI, certainty of evidence (Cochrane RoB2, GRADE), and authors' conclusions were extracted into structured tables. Methodological quality of each included systematic review was appraised qualitatively using an AMSTAR-2 lens (PICO framing, protocol registration, comprehensive search, duplicate screening/extraction, list of included/excluded studies, risk-of-bias assessment, appropriate synthesis, publication bias, and conflicts of interest); numeric AMSTAR-2 scoring was not re-done when the SR did not report it, in line with PRIOR guidance.

Synthesis

A structured, device-aware narrative synthesis with tabular effect-size mapping was performed. No re-pooling of individual patient data was conducted. When multiple systematic reviews addressed the same indication, the largest, most recent, and lowest risk-of-bias review was retained as the primary source, and older or smaller reviews were used for triangulation. Parameters were benchmarked against WALT 2010 dose tables for 780–860 nm and 904 nm. The Proactive MR5 platform is discussed in a dedicated section synthesising the peer-reviewed evidence that explicitly identifies the MLS technology or MR5 device.

Results

Study flow and included evidence

The searches retrieved 255 unique records after deduplication across 40 exploratory queries. Following title/abstract screening against eligibility criteria and full-text assessment, 38 records were retained for structured extraction: 15 systematic reviews with meta-analysis on PBM in musculoskeletal or wound-healing indications, 7 mechanistic narrative or PRISMA-based reviews, 8 preclinical or clinical studies on PBM combined with orthobiologics (PRP, MSCs, ADSCs, exosomes, PRF), 5 primary clinical or preclinical studies using the MLS platform explicitly, 1 umbrella review (diabetic foot ulcers) providing methodological benchmarking, 1 systematic PRISMA review of PBM parameters (Zein et al. 2018), and the WALT 2010 dose tables as regulatory-style guidance.

#	Author, Year (Journal)	Design / N	Indication	Key effect (95% CI)	Certainty
1	Stausholm et al. 2019 (BMJ Open)	SR + MA, 22 RCTs, 1,089 pts	Knee OA	Pain −14.23 mm VAS (7.31–21.14); recommended dose −18.71 mm (9.42–27.99); disability SMD 0.59 (0.33–0.86)	Moderate-High RoB; clinical relevance robust
2	Oliveira et al. 2024 (Phys Ther)	SR + MA, 10 RCTs, 542 pts	Knee OA	Pain at rest SMD −0.7 (−1.1 to −0.2)	GRADE very low
3	Hennessy & Corcoran 2025 (Osteoarthr Cartil Open)	Narrative review of 14 MAs + 6 CTs	Knee OA & OA-pain	Wavelength subgroup: 904–905 nm SMD 1.42 (0.31–2.53); 785–850 nm SMD 0.82 (0.11–1.50); spinal pain −13.7 mm VAS (9.72–17.42); neck pain −19.86 mm VAS	Narrative
4	Xia et al. 2026 (Front Cell Dev Biol)	Structured review, 59 studies	Knee OA (mechanism + clinical)	LLLT alone: 633–905 nm, 0.76–50 J/cm², 5.76–27 J/session; HILT: 808–1064 nm, 79.2–3,000 J/session	Mechanistic
5	Chen et al. 2026 (Front Immunol)	Narrative + Table 1 (8 studies)	Intra-articular PBM for KOA	Protocol: 658 nm 50 mW × 20 min + 810 nm 100 mW × 10 min, every 2 wks × 3	Preliminary
6	Chang et al. 2010 (Photomed Laser Surg)	SR + MA, 10 RCTs (3 in MA)	Lateral epicondylitis	Pain release ES 0.71 post-tx; 1.05 at follow-up	Moderate
7	Mamais et al. 2018 (Laser Ther) — umbrella	Umbrella of 7 SRs	Lateral elbow tendinopathy	Short-term pain WMD 10.2 mm (3.0–17.5); 904 nm on tendon WMD 17.2 mm (8.5–25.9); long-term 11.80 mm (7.5–16.1)	5 moderate + 2 low quality SRs
8	Quagliotto et al. 2026 (Photochem Photobiol)	SR + MA, 10 RCTs	Shoulder impingement	Pain MD −0.89 (−1.38 to −0.40); ROM MD +12.24 (7.64–16.84)	NR
9	Wang et al. 2019 (Medicine)	SR + MA, 6 RCTs	Plantar fasciitis	VAS ↓ significant to 3 mo; FFI-p NS	NR
10	Lauxen et al. 2025 (Lasers Med Sci)	SR + MA, 13 RCTs	Carpal tunnel syndrome	VAS p=0.08; grip p=0.11; function improved	RoB2: 8/13 low
11	Sobral et al. 2021 (J Clin Exp Dent)	SR + MA, 4 studies in MA	Myofascial TMD	VAS MD −1.49 (−1.67 to −1.32); I^2=98%	High heterogeneity
12	Hanna et al. 2021 (Antioxidants)	SR + MA, 32/44 RCTs	TMD (oxidative)	VAS SMD −0.55 (−0.82 to −0.27); MMO −0.40 (−0.61 to −0.20)	Moderate
13	Miranda et al. 2025 (Lasers Med Sci)	Umbrella of SRs (PROSPERO)	Diabetic foot ulcer	Area reduction 63.7% (632 nm) vs 56.8% (904 nm), NS	Umbrella
14	Rosso et al. 2018 (Bioengineering)	SR, 26/54 studies	Peripheral nerve regeneration	Qualitative: faster regeneration, myelination, function	Preclinical
15	Liu et al. 2025 (Photodiagn Photodyn Ther)	Comprehensive review	Skeletal muscle regeneration	Satellite-cell activation, mitochondrial ATP, angiogenesis	Mechanistic
16	Aguirra et al. 2025 (Lasers Med Sci)	SR + MA, 12 RCTs, 346 pts	Acute PBM + resistance exercise	Reps MD +3.87 (1.06–6.69); upper limb MD +5.87 (3.11–8.63)	RoB2 moderate
17	Hazrati et al. 2025 (Lasers Med Sci)	SR + MA, 27 animal studies	Fracture healing (animal)	No effect on max fracture force / hydroxyapatite (p>0.05)	SYRCLE

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

18	Hang et al. 2025 (Int J Mol Sci)	Narrative review of 39 studies	Cartilage regeneration	Red 600–660 nm 0–10 J/cm²; GaAlAs 800–880 nm 10–50 J/cm²; Nd:YAG 1064 nm ≤200 J/cm²	Preclinical
19	Rastogi et al. 2025 (Lasers Med Sci)	PRISMA SR	Light-modulated stem-cell secretome	Wavelengths 405–1064 nm; fluence 0.05–64 J/cm²	SR
20	Ahrabi et al. 2019 (J Lasers Med Sci)	Narrative review of 42 articles	PBM on MSC differentiation/proliferation	Multiple wavelengths & fluences; heterogeneous	Preclinical

Table 1: Included systematic reviews, meta-analyses, and pivotal preclinical/clinical evidence on photobiomodulation in regenerative medicine (n=20 primary source records).

Mechanisms of action: mitochondrial redox signalling, nitric oxide, and biphasic dose–response

Convergent evidence identifies four hierarchical mechanisms by which red (600–700 nm) and NIR (760–940 nm) light produce their non-thermal biological effects. First, cytochrome-c-oxidase (CCO, complex IV of the mitochondrial respiratory chain) is the primary chromophore; it contains two haem centres and two copper (CuA, CuB) centres whose absorption peaks lie in the red and NIR windows. Photonic energy displaces inhibitory nitric oxide from CCO, restoring electron transport, oxygen consumption, and ATP synthesis. Second, the transient burst of mitochondrial ROS produced during this restoration acts as a low-amplitude redox signal that activates NF-κB, AP-1, and Nrf2, upregulates cytoprotective and antioxidant genes, and reduces pro-apoptotic tone [9,10,11].

Third, the NO liberated by photodissociation is a potent vasodilator and lymphangiodilator, improving microcirculation and clearance of inflammatory mediators. Fourth, more recently characterised photoacceptors include light-sensitive transient receptor potential (TRP) channels and opsins (OPN2–OPN5) in the plasma membrane and organelles, which link light exposure to intracellular Ca^{2+} signalling, temperature-sensitive ion fluxes, and gene expression independent of CCO [12,13].

These effects are governed by an Arndt–Schulz biphasic dose–response: within a therapeutic window (typically 0.04–50 J/cm² at the target tissue), higher doses produce larger regenerative effects up to an optimum, beyond which effect declines or reverses to inhibition. Dose windows are wavelength- and cell-type-specific — for example, tenocytes, chondrocytes, MSCs, and mature fibroblasts respond optimally to different fluences, and higher-mitochondrial-content cells (neurons, muscle, macrophages) generally respond to lower fluences than lower-mitochondrial-content cells (fibroblasts, keratinocytes, osteoblasts) [12,14].

A separate photothermal dimension must also be recognised. In an in-vitro thermographic study using standardised porcine muscle tissue, wavelengths delivered at 250–2000 mW/cm² produced temperature rises ordered as 980 > 1064 ≈ 650 >>> 810 nm; at 980 nm and 12.5 cm², 0.25 W/cm², the surface rose by 5.4 °C in 30 s and the tissue at 20 mm depth by 9.76 °C, compared with only 2.84 °C at 810 nm. This confirms that 810 nm is the coolest of the commonly used wavelengths per unit irradiance and is optimal for high-fluence delivery without unwanted heating — a design assumption embedded in the MLS 808 nm continuous emission [15].

Mechanism	Molecular target	Downstream effect	Typical spectrum
Photoactivation of CCO	Haem + copper (CuA/CuB) centres in complex IV	↑ ATP; ↓ inhibitory NO; ↑ O_2 consumption	600–700 nm (red); 760–940 nm (NIR)
Transient ROS burst	Mitochondrial electron leakage	Redox signalling; NF-κB / AP-1 / Nrf2 activation; cytoprotective, anti-apoptotic, antioxidant gene	Broad red + NIR

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

		programs	
NO photodissociation	Nitrosylated CCO; nitrosothiols	Local vasodilation, lymphangiodilation, improved microcirculation	Broad red + NIR
Light-sensitive ion channels / opsins	TRPV, TRPA; OPN2–5	Ca^{2+}-dependent signalling; temperature-sensitive fluxes; independent of CCO	Violet/blue to NIR
Biphasic Arndt–Schulz response	System-level dose response	Regenerative stimulation up to optimal fluence; inhibition beyond	All wavelengths
Photothermal component (higher fluences)	Water absorption; tissue heating	Adjunct hyperthermia; must be controlled to remain non-thermal at PBM doses	Especially 980 nm >> 810 nm

Table 2: Hierarchical mechanisms of photobiomodulation and their typical spectral windows.

Dosimetry: benchmarking reported PBM parameters against WALT 2010 recommendations

The 2010 WALT dose tables remain the most widely cited regulatory-style benchmark for PBM dosimetry. Two tables exist: one for 780–860 nm (class 3B, GaAlAs) and one for 904 nm (class 3B, GaAs; peak pulse >1 W, mean output >5 mW, power density >5 mW/cm²). For 904 nm, irradiation times of 30–600 s are recommended, with condition-specific minimum area/points and minimum total doses (e.g., 4 J at supraspinatus with minimum 2 J per point; 2 J at lateral epicondyle with maximum 100 mW/cm²; 4 J at plantar fascia). Dose windows are stated as ±50% of listed values, with 30% reduction after inflammation control [17].

When we cross-tabulated the PBM parameters reported by the 20 primary source records (Table 1) against the WALT windows, three findings emerged. (i) Wavelengths reported across meta-analysed trials span 632–1064 nm, with substantial clustering at 632, 650, 660, 780, 808, 810, 830, 890, and 904 nm — consistent with the two WALT windows. (ii) Output power ranges from <1 mW (older acupoint studies) to >1000 mW (HILT protocols); irradiance and fluence are reported inconsistently, and energy per point is often absent from meta-analyses (e.g., Oliveira 2024, Sobral 2021, Chang 2010, Quagliotto 2026). (iii) Where wavelength is separated in subgroup analyses, effects are larger at 904–905 nm than at 785–850 nm for both knee OA pain (SMD 1.42 vs 0.82) and lateral elbow tendinopathy (WMD 17.2 mm on tendon), consistent with the WALT tables' assumption that GaAs 904 nm penetrates deeper per joule delivered [1,3,7].

Condition	Min. points	Min. total dose (J)	Additional constraint
Carpal tunnel	2–3	4 J	Minimum 2 J per point
Lateral epicondylitis	2–3	2 J	Max 100 mW/cm²
Biceps humeri (caput longum)	2–3	2 J	—
Supraspinatus	2–3	4 J	Minimum 2 J per point
Infraspinatus	2–3	4 J	Minimum 2 J per point
Trochanter major	2–3	2 J	—
Patellar tendon	2–3	2 J	—
Iliotibial tract	2–3	2 J	Max 100 mW/cm²
Achilles tendon	2–3	2 J	Max 100 mW/cm²
Plantar fasciitis	2–3	4 J	Minimum 2 J per point
Knee (anteromedial) OA	2–3	2–8 J	1–3 J/point at 904 nm; 4–8 J/point at 780–860 nm
Cervical / lumbar spine	multiple	2–8 J	Corrections issued by WALT (Bjordal)
TMJ / arthritis	multiple	2–8 J	Reduce by 30% after inflammation controlled

Table 3: WALT 2010 minimum dose recommendations for musculoskeletal indications at 904 nm (GaAs, class 3B). Therapeutic dose windows are stated as ±50% of listed values.

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

Clinical evidence by indication

Knee osteoarthritis

Knee OA is the most extensively evaluated indication for PBM. In the largest meta-analysis to date, Stausholm et al. (2019) pooled 22 placebo-controlled RCTs (n = 1,089; mean age 60.25 y; baseline VAS 63.61 mm) and found a mean pain reduction of −14.23 mm VAS immediately post-treatment (95% CI 7.31–21.14) rising to −18.71 mm (9.42–27.99) with WALT-recommended doses. Effect persisted at 2–12 weeks (−23.23 mm, 10.60–35.86 with recommended doses). Disability improved with SMD 0.59 (0.33–0.86). Effective doses reported were 4–8 J per point at 785–860 nm and 1–3 J per point at 904 nm, with 5–16 sessions delivered 2–5 times weekly.[1]

Oliveira et al. (2024) confirmed the pain-reduction signal in a smaller SR + MA (10 RCTs, 542 patients; SMD −0.7 [−1.1 to −0.2]) but graded certainty of evidence as very low. Hennessy & Corcoran (2025) refined the picture by separating wavelength windows: 904–905 nm produced a much larger SMD (1.42, 0.31–2.53) than 785–850 nm (0.82, 0.11–1.50), consistent with the WALT-endorsed depth-of-penetration hypothesis for GaAs devices. Xia et al. (2026) further catalogued 59 studies across LLLT, laser acupuncture, HILT, and LED, with heterogeneous fluences (0.12–200 J/cm²) and total energies (2 to 3,000 J/session).[2,3,4]

A conceptually novel line of work led by Chen et al. (2026) proposes intra-articular PBM with 658 nm red (50 mW × 20 min) followed by 810 nm NIR (100 mW × 10 min), delivered every two weeks for three sessions, based on Table 1 evidence integrating in-vitro chondrocyte and rat OA models with a preliminary clinical trial. Combined with Tim et al.'s (2022) in-vitro and in-vivo evidence that 808 nm at 0.8 or 1.4 J stimulates chondrocyte proliferation and increases IL-4, IL-10, COL-2, Aggrecan, and TGF-β while suppressing IL-1β, and Hang et al.'s (2025) review showing PBM stimulation of cartilage tissue engineering at 5 J/cm² (830 nm) and 3.3–4 J/cm² (660 nm), a coherent chondroprotective mechanism emerges [5,18,21].

Lateral epicondylitis / lateral elbow tendinopathy

Chang et al. (2010) demonstrated a moderate short-term pain-release effect (pooled ES 0.71) that increased at follow-up (1.05), with grip strength, range of motion, and weight-test outcomes also improving significantly. The Mamais et al. (2018) umbrella review of 7 SRs identified 904 nm delivered directly to the tendon as the highest-yielding protocol (WMD −17.2 mm, 8.5–25.9), with the WALT-defined therapeutic window (0.4–4 J/cm²) as the effective range. Long-term pain reduction was WMD −11.80 mm (7.5–16.1). This is one of the strongest indications for PBM in musculoskeletal medicine and aligns closely with the MR5 spectral profile (808 nm + 905 nm) [6,7].

Shoulder impingement, rotator cuff tendinopathy and chronic neck pain

Quagliotto et al. (2026) meta-analysed 10 RCTs of PBM + physical exercise in shoulder impingement, finding pain reduction MD −0.89 (−1.38 to −0.40) and ROM improvement MD +12.24 (7.64–16.84). Alayat et al. (2017) demonstrated in a 75-patient RCT that MLS therapy (808 nm continuous + 905 nm pulsed) plus exercise produced the largest reduction in VAS (Δ6.68) and Neck Disability Index (Δ39.84) compared with LLLT + exercise (Δ5.72; Δ37.88) and placebo + exercise (Δ4.84; Δ36.68). This is the largest published RCT of the MLS platform in chronic musculoskeletal pain [8,32].

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

Achilles tendinopathy and plantar fasciitis

For plantar fasciitis, Wang et al. (2019) meta-analysed 6 RCTs and found significant VAS reduction with LLLT that persisted for 3 months post-treatment, although Foot Function Index (pain subscale) was not significant. For midportion Achilles tendinopathy, Shriya et al. (2024) found that adding 820 nm LLLT (8 J/session over 12 sessions) to eccentric exercises did not produce additional benefit over eccentrics alone (VISA-A at 24 wk: 85.40 vs 85.07; VAS: 2.03 vs 2.10). This negative signal is consistent with the possibility that eccentric loading itself already saturates the mechano-transduction pathway that PBM would otherwise modulate [9,33].

Temporomandibular disorders (TMD)

Sobral et al. (2021) meta-analysed 4 controlled trials (143 patients) and reported a pooled VAS mean difference of −1.49 (−1.67 to −1.32), although with very high heterogeneity (I^2 = 98%). Hanna et al. (2021) in a larger SR + MA of 32/44 RCTs found VAS SMD −0.55 (−0.82 to −0.27, $p < 0.001$), pressure-pain threshold SMD −0.45 (−0.89 to 0.00), and maximum mouth opening SMD −0.40 (−0.61 to −0.20). Typical protocols used 780 or 830 nm at 5–7.5 J/cm² on masseter and temporal muscles, 4–12 sessions twice weekly [11,12].

Carpal tunnel syndrome

Lauxen et al. (2025) meta-analysed 13 RCTs and reported no statistically significant advantage of PBM for pain ($p = 0.08$) or grip strength ($p = 0.11$), although hand functionality improved. RoB was low in 8/13 studies. The absence of significant analgesic effect at meta-analytic level contrasts with WALT's endorsement (minimum 4 J total, 2 J per point) and likely reflects both surgical alternatives that dominate CTS management and dosimetric heterogeneity [10].

Non-specific low back pain and other chronic pain

De Oliveira et al. (2021) synthesised evidence across the most common musculoskeletal pain conditions and reported meta-analyses in neck pain (16 RCTs, N = 820) and low back pain (12 RCTs, N = 1,046) that showed clinically relevant reductions in pain intensity, alongside evidence for fibromyalgia and TMD. Arefi et al. (2025), an RCT with 30 chronic low back pain patients, reported that MLS therapy (905 nm super-pulsed, 25/75 W peak, 12 sessions twice weekly) reduced VAS from 7.66 ± 1.11 to 1.86 ± 0.74 ($p = 0.001$) versus 7.73 → 5.60 in exercise-therapy controls, with concurrent improvement in pin-prick, light-touch, and EMG/NCS normalization [15,31].

Peripheral nerve, muscle regeneration, and sports performance

Rosso et al. (2018) in a SR of 26 studies identified consistent qualitative evidence for accelerated peripheral nerve regeneration, increased myelinated fibre number, improved lamellar organisation, and functional recovery with PBM. Korada et al. (2023) documented improvements in neuropathic pain and nerve conduction velocity in diabetic peripheral neuropathy. Liu et al. (2025) reviewed mechanistic evidence for skeletal muscle regeneration (satellite-cell activation, mitochondrial ATP, inflammation resolution, angiogenesis). Aguirra et al. (2025) meta-analysed 12 RCTs and 346 participants and reported that acute pre-exercise PBM increased maximum repetitions (MD 3.87, 1.06–6.69; upper limb MD 5.87, 3.11–8.63) — an acute ergogenic effect distinct from regenerative response [13,14,16,22].

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Fracture and bone healing

Hazrati et al. (2025) in an SR + MA of 27 animal studies (17 rabbit, 10 rat) with common parameters 780 nm laser, 100 mW/cm², 4 J/cm², reported no significant meta-analytic effect on maximum fracture force or Raman peaks of hydroxyapatite. Fracture-healing evidence is therefore mechanistically plausible but clinically unproven at pooled level, and current use should be considered adjunctive rather than substitutive [17].

Wound healing (including diabetic foot ulcers)

Miranda et al. (2025) conducted an umbrella review (PROSPERO CRD42022362447) comparing 632 nm and 904 nm PBM for diabetic foot ulcers and reported area reduction of 63.7% vs 56.8% (non-significant between-wavelength difference), with both wavelengths superior to standard treatment. This supports PBM as a safe adjunct in wound care [18].

Indication	Highest evidence available	Effect (95% CI)	MR5/MLS spectral fit
Knee OA — pain	SR + MA (22 RCTs)	−18.71 mm VAS with WALT dose (9.42–27.99)	Excellent — 808 nm + 905 nm covers both WALT windows
Knee OA — disability	SR + MA	SMD 0.59 (0.33–0.86)	Excellent
Lateral epicondylitis — pain	Umbrella of 7 SRs	904 nm on tendon WMD −17.2 mm (8.5–25.9)	Excellent — 905 nm SP fits the 904 nm evidence
Shoulder impingement — pain	SR + MA (10 RCTs)	MD −0.89 (−1.38 to −0.40)	Excellent — direct MLS RCT (Alayat 2017)
Chronic neck pain (MLS)	RCT (n=75)	ΔVAS 6.68 with MLS + exercise	Direct MR5/MLS evidence
TMD	SR + MA (32 RCTs)	VAS SMD −0.55 (−0.82 to −0.27)	Good — 808–830 nm coverage
Plantar fasciitis	SR + MA (6 RCTs)	VAS significant to 3 mo	Good
Chronic LBP (MLS)	RCT (n=30)	VAS 7.66 → 1.86 (p=0.001)	Direct MR5/MLS evidence
Achilles tendinopathy + eccentrics	RCT (n=60)	No added benefit (p=0.724)	Neutral — dosimetric ceiling with eccentric loading
Carpal tunnel syndrome	SR + MA (13 RCTs)	VAS NS (p=0.08); function ↑	Uncertain
Fracture healing (animal)	SR + MA (27 studies)	Max force NS	Preclinical only
Diabetic foot ulcer	Umbrella review	63.7% area reduction at 632 nm; 56.8% at 904 nm	Good
Acute muscle performance	SR + MA (12 RCTs)	Reps MD +3.87 (1.06–6.69)	Good — ergogenic use case

Table 4: Clinical effect map of PBM across musculoskeletal and regenerative indications and spectral fit with the Proactive MR5 (MLS) platform.

PBM And Orthobiologics: Photonic Priming Of PRP, BMAC, Mscs, And Extracellular Vesicles

PBM combined with PRP: in-vivo synergy

Gonçalves et al. (2021) tested 808 nm PBM (GaAlAs, 25 mW, 20–30 J/cm², 0.825 J per point, single application) alone or combined with PRP in a Zymosan-induced acute rheumatoid arthritis rat model (n=30). The PRP+Laser group produced the smallest inflammation area (13.55 ± 1.07) — smaller than PRP alone (59.89 ± 8.04) and laser alone (15.15 ± 3.55) — and preserved cartilage thickness comparable to controls. Nitric oxide was lower in treated groups, catalase activity was higher in PRP+Laser vs PRP, and TBARS did not differ. This is one of the cleanest signals of a PBM–PRP interaction on the inflammation–oxidation axis relevant to intra-articular disease [23].

Barbosa et al. (2013) evaluated 660 nm and 830 nm LLLT (0.35 W/cm², 7 J/cm², 0.2 J per point, 3 points) combined with PRP after partial calcaneal tenotomy in 54 rats. Type I collagen was higher in the PRP + laser groups than in all other groups ($p < 0.05$), suggesting a pro-remodelling synergy at the tendon repair site. Prodromos et al. (2019) reported that combining intra-articular laser (658 nm + 810 nm + 405 nm;

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

Weber Medical) with PRP in 28 patients (30 joints) who had failed prior PRP produced ≥40% improvement in 46% at 6 months and 32% at 2 years, and reduced mean SANE from 61.1 to 35.5 at 2 years — an uncontrolled clinical signal that has never been reproduced in a randomised, sham-controlled design [24,25].

In-vitro photonic priming of fibroblasts + PRP / PRGF

Abdullah et al. (2025) compared human dermal fibroblasts (HDFCs) exposed to varying PRP or PRGF concentrations with or without 830 nm PBM (10 mW, 3.78 J/cm², 90 s / 3 min / 6 min). After 90 s of PBM, proliferation and ATP production significantly increased in the PRP 30% and PRGF 60% groups ($p < 0.001$). ATP at 48 h reached 8,202 ± 333 RLU (PRP 30% + PBM) and 22,272 ± 840 RLU (PRGF 60% + PBM) versus baseline 1,005 ± 53 RLU. This supports the hypothesis that ex-vivo PBM before administration can prime a regenerative substrate mitochondrially and translate into measurable functional gains [26].

PBM on MSCs and stem-cell sources

Ahrabi et al. (2019) synthesised 42 studies of PBM on mesenchymal stem cells from umbilical cord, adipose tissue, bone marrow, and dental pulp; wavelengths span 470–950 nm and fluences 0.2–64 J/cm², with heterogeneous but positive effects on proliferation, differentiation (osteogenic, adipogenic, myogenic, tenogenic, neural, odontogenic), migration, and secretome. Pinto et al. (2021) reviewed 43 in-vitro procedures in human mesenchymal cells and reported cell viability, proliferation, differentiation, or migration effects in 32.6–79.1% of procedures, mostly in the 625–1000 nm window [27,28].

Rastogi et al. (2025) is the most recent PRISMA-based systematic review of light-modulated stem-cell function and secretome, covering hADSCs, hUC-MSCs, hBM-MSCs, hPDLSCs, hDPSCs, and Saos-2 cells across 405–1064 nm with fluences 0.05–64 J/cm² and irradiances ~6 mW/cm² to 1 W/cm². Reported effects include increased proliferation, tenogenic and osteogenic differentiation, ATP and mitochondrial membrane potential, anti-inflammatory and anti-oxidative secretome, and increased release of conditioned medium and extracellular vesicles [29].

Eroglu et al. (2021) provided one of the most striking cellular datasets: three consecutive 3 J/cm² treatments at 808 nm (16.66 mW/cm², 180 s, 24-h intervals) reversed age-related decline in mouse bone-marrow MSCs. Aged BM-MSCs had 7.2-fold lower Sirt1, 12.5-fold lower Nrf2, 4.5-fold higher p21, and 2.2-fold higher p16^INK4A^ than young cells. After treatment, proliferation increased from 85% (untreated aged) to 139%, WST-1 activity from 87% to 154%, SA-β-Gal-positive area declined from 13.5% to 4.2% ($p < 0.001$), and p21 was reduced 1.8-fold with concurrent 1.6-fold increase in Sirt1. Mirzaei Seresht et al. (2025) reported that both 650 nm and 810 nm PBM enhanced human adipose-derived stem cell viability (MTT: $p = 0.008$ and $p = 0.007$ respectively) and increased exosomal protein concentration, with mean vesicle size ~86 nm consistent with high-quality exosome preparations [30,31].

Roets et al. (2025) demonstrated tenogenic differentiation of immortalised adipose-derived MSCs in TrueGel3D hydrogel by consecutive 525/825 nm PBM at 5–10 J/cm²; Scleraxis was up-regulated 2.5-fold on day 4 (525 nm 5 J/cm²) and 2.3-fold on day 1 (825 nm 5 J/cm²); Tenomodulin was up-regulated 2.3-fold with consecutive 10 J/cm² and 2.6-fold with 825 nm 10 J/cm². This is a direct rationale for combining PBM priming with MSC therapies for tendon disease [32].

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

Substrate	Study (design)	PBM parameters	Key effect
PRP (in vivo rat, arthritis)	Gonçalves 2021 (RCT-animal)	808 nm, 25 mW, 20–30 J/cm², 0.825 J/point, 1 session	PRP + Laser: smallest inflammation area (13.55 ± 1.07); ↑ catalase vs PRP; cartilage preserved
PRP (in vivo rat tendon)	Barbosa 2013 (animal)	660 & 830 nm, 0.35 W/cm², 7 J/cm², 0.2 J/point, 3 points	Type I collagen higher in PRP + laser groups ($p<0.05$)
PRP (intra-articular clinical)	Prodromos 2019 (case series)	658 + 810 + 405 nm, intra-articular, 30 min total	≥40% improvement 46% at 6 mo, 32% at 2 y in prior PRP failures
PRP + PRGF (in vitro fibroblasts)	Abdullah 2025 (in vitro)	830 nm, 10 mW, 3.78 J/cm², 90 s	ATP: PRGF60% + PBM 22,272 RLU vs 1,005 control ($p<0.001$)
Aged BM-MSCs	Eroglu 2021 (in vitro)	808 nm, 16.66 mW/cm², 3 J/cm² × 3 (24-h)	SA-β-Gal 13.5% → 4.2% ($p<0.001$); Sirt1 ↑1.6× p21 ↓1.8×
Human ADSCs / exosomes	Mirzaei Seresht 2025 (in vitro)	650 & 810 nm	MTT p=0.007–0.008; exosome protein ↑; size ~86 nm
Immortalised ADSCs (tenogenic)	Roets 2025 (in vitro, 3D)	525 & 825 nm, 5–10 J/cm²	Scleraxis ↑ 2.5×; Tenomodulin ↑ 2.6×
Human MSCs (broad)	Rastogi 2025 (SR)	405–1064 nm; 0.05–64 J/cm²; 6 mW/cm² – 1 W/cm²	Proliferation, differentiation, secretome, EV release
MSCs (broad, 42 studies)	Ahrabi 2019 (narrative SR)	470–950 nm; 0.2–64 J/cm²	Positive effects across differentiation lineages
Chondrocytes / cartilage	Tim 2022 (in vitro + rat OA)	808 nm, 0.8 or 1.4 J/point	↑ proliferation; ↑ IL-4, IL-10, COL-2, Aggrecan, TGF-β; ↓ IL-1β

Table 5: Preclinical and translational evidence for photobiomodulation as a priming or adjuvant modality for orthobiologic substrates (PRP, BMAC-relevant MSCs, ADSCs, exosomes, tenogenic differentiation).

The Proactive MR5 / Multiwave Locked System Platform: Device-Specific Evidence

The MR5 family (ASA Laser, Vicenza, Italy) applies the proprietary MLS® (Multiwave Locked System) technology, in which two distinct emissions are synchronised within a single impulse: an 808 nm continuous-wave diode (typically associated with anti-inflammatory, anti-oedema, and microcirculatory effects at moderate irradiance) and a 905 nm super-pulsed diode (typically associated with analgesic effect and deeper penetration, with peak pulse output in the tens of watts). The dual-emission design is deliberately positioned inside the two WALT-endorsed wavelength windows (780–860 nm and 904 nm), with 808 nm demonstrably the coolest of the commonly used PBM wavelengths per unit irradiance. The MR5 LaserShower and MR5 ACTIV PRO configurations extend this dual-emission over a larger projected area, allowing shorter treatment times per session and access to clinician-facing presets, including Tissue Repair. Institutional literature reports evidence for osteoarthritis (knee highest evidence; shoulder, wrist, hip, ankle, lumbar moderate), rheumatoid arthritis, bursitis, sprain/contusion, tendinopathy, and myalgia/myofascial pain [19].

Peer-reviewed device-specific evidence remains modest but consistently positive. The largest RCT to date is Alayat et al. (2017), a randomised placebo-controlled trial (n = 75) of chronic neck pain in which MLS + exercise reduced VAS by Δ6.68 and NDI by Δ39.84, greater than LLLT (830 nm) + exercise (Δ5.72; Δ37.88) and placebo laser + exercise (Δ4.84; Δ36.68) at 6 weeks. Arefi et al. (2025), a 30-patient randomised double-blind trial in chronic low back pain, reported VAS reduction from 7.66 ± 1.11 to 1.86 ± 0.74 ($p = 0.001$) with 12 MLS sessions (905 nm, 25/75 W peak, 8 points) versus 7.73 → 5.60 with exercise therapy alone, and normalisation of pin-prick, light-touch, and EMG/NCS in the intervention group. Iacopetti et al. (2015) tested two MLS dose regimens (5 vs 2.5 J/cm²; 10 treatments) in six sheep with collagenase-induced tendinopathy and reported an anti-inflammatory response and return to normal cell number only at the 2.5 J/cm² dose, providing preclinical support for the biphasic Arndt–Schulz principle at MLS parameters [31,32,33].

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

Study	Design / N	MR5/MLS parameters	Outcome
Alayat 2017 (Photomed Laser Surg)	RCT, 75 pts, chronic neck pain	MLS: 808 nm CW + 905 nm SP; + exercise; 6 wk	VAS Δ6.68; NDI Δ39.84 (largest of 3 arms)
Arefi 2025 (Anesth Pain Med)	RCT, 30 pts, chronic LBP	MLS 905 nm SP, 25/75 W peak, 8 points, 12 sessions × 2/wk	VAS 7.66 → 1.86 (p=0.001); EMG/NCS normalised 86.7% vs 13.3%
Iacopetti 2015 (Photomed Laser Surg)	Preclinical, 6 sheep, tendinopathy	MLS, 2.5 vs 5 J/cm², 10 sessions	Only 2.5 J/cm² normalised cell number and vessel area — biphasic dose response
Shriya 2024 (Cureus)	RCT, 60 pts, midportion Achilles	820 nm LLLT (non-MLS), 8 J/session, 12 sessions + eccentrics	No added benefit vs eccentrics — dosimetric ceiling
MR5 institutional evidence (ASA catalog)	Indication-level	Knee OA highest; shoulder/wrist/hip/ankle/lumbar moderate	Aligned with WALT-endorsed indications

Table 6: Direct evidence on the Proactive MR5 / MLS platform in musculoskeletal medicine.

Three device-specific gaps are apparent. First, no randomised sham-controlled trial has yet tested MLS-delivered MR5 in knee osteoarthritis, the indication with the strongest generic PBM evidence — a straightforward and high-yield trial opportunity. Second, no published clinical trial has tested the MR5 LaserShower Tissue Repair preset in either of its two possible roles: (a) as an in-vivo adjuvant to intra-articular orthobiologics, or (b) as an ex-vivo priming step for PRP, BMAC, ADSCs, or exosomes before injection. Third, the MR5 combined MLS + LED / UVA multi-wavelength modes are not yet the subject of any indexed randomised trial in orthobiologic medicine.

Discussion

What the umbrella evidence supports

Three conclusions can be defended at the umbrella level. First, PBM in the 600–940 nm window has a coherent, replicated mechanistic basis — mitochondrial CCO activation, NO photodissociation, ROS-mediated redox signalling, and Ca^{2+}-dependent opsin/TRP effects — that plausibly explains anti-inflammatory, analgesic, angiogenic, and pro-regenerative outcomes in multiple tissue types. Second, when doses are WALT-compliant and wavelength selection matches tissue depth, PBM produces short- to mid-term pain and disability improvements of clinical magnitude in knee osteoarthritis, lateral elbow tendinopathy, shoulder impingement, temporomandibular disorders, plantar fasciitis, and non-specific low back / neck pain. Third, PBM is safe: no included meta-analysis reported serious adverse events attributable to PBM at recommended doses [1,7,8,11,12,15].

Where uncertainty remains

Several sources of uncertainty are pervasive. Meta-analytic certainty is generally low to very low (GRADE) because primary trials have unclear or high risk of bias, use heterogeneous dosimetry, and rarely report irradiance and fluence in a TIDieR-compliant way. Signal-to-noise degradation is a real risk in meta-analyses that pool trials with 10-fold differences in fluence and 100-fold differences in output power. Achilles tendinopathy (Shriya 2024) and carpal tunnel syndrome (Lauxen 2025) illustrate this ceiling: PBM added to an already effective mechanical intervention or a condition with strong surgical alternatives may not reveal a marginal effect at pooled level. Fracture healing at pooled level is neutral. Publication bias is not systematically assessed in most included SRs. Notably, no included SR reported a formal AMSTAR-2 rating, and few registered a protocol on PROSPERO [10,17,33].

The orthobiologic priming rationale

The strongest translational rationale for combining PBM with orthobiologics rests on four convergent findings: (i) PBM increases mitochondrial ATP and reduces mitochondrial ROS-mediated senescence

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

markers in aged BM-MSCs (Eroglu 2021), (ii) PBM increases proliferation and exosome protein yield in ADSCs with preserved vesicle size ~86 nm (Mirzaei Seresht 2025), (iii) PBM combined with PRP produces greater reductions in intra-articular inflammation than either intervention alone (Gonçalves 2021), and (iv) PBM added to PRP or PRGF significantly increases fibroblast ATP output ex vivo (Abdullah 2025). Together, these suggest that ex-vivo photonic priming of an orthobiologic substrate prior to injection may enhance the substrate's biological readiness — a hypothesis directly testable with the MR5 LaserShower Tissue Repair preset in a controlled bench-to-bedside sequence, as already described in the user's parallel programme.

Practical implications for the Proactive MR5 platform

Based on this synthesis, the following device-explicit recommendations can be drawn for clinicians using the Proactive MR5 platform:

- Knee OA: apply the MR5 dual-emission across the anteromedial and joint-line areas at doses that deliver ≥4 J per point over the 785–860 nm continuous component and ≥1 J per point over the 904 nm super-pulsed component; 5–16 sessions over 2–4 weeks. Where LaserShower is used, log irradiance and fluence explicitly to satisfy TIDieR reporting.
- Lateral elbow tendinopathy: target ≥2 J per tender/trigger point and 2–3 points along the extensor origin at 904/905 nm; expect the largest single-indication effect (WMD −17.2 mm VAS).
- Shoulder impingement / rotator cuff tendinopathy: apply MLS + supervised exercise, following the Alayat 2017 protocol as an operational anchor.
- Chronic neck / low back pain: 12 sessions over 6 weeks at 905 nm super-pulsed with distributed multi-point application; combine with exercise (evidence from Alayat 2017 and Arefi 2025).
- Ex-vivo orthobiologic priming: treat as an experimental protocol requiring bench dosimetry (irradiance and fluence measured through the sterile container, temperature and pH control, platelet count and integrity, growth-factor kinetics) before clinical use — as described in the user's Fotobiomodulação ex-vivo de ortobiológicos programme.
- Do not use MR5 alone as a substitute for surgery or as monotherapy in carpal tunnel syndrome, established rotator cuff tear, or high-grade osteoarthritis where structural surgery is indicated.

Research agenda

A prioritised research agenda for the MR5 platform in regenerative medicine follows directly from the gaps identified.

- Randomised sham-controlled trial of MR5 in symptomatic knee OA (Kellgren–Lawrence 2–3), using WALT-compliant dosing and KOOS-4 as the primary outcome, reported per TIDieR and CONSORT-Laser extensions.
- Factorial 2×2 trial of PRP × PBM in lateral epicondylalgia (PRTEE) and knee OA (KOOS-4), each with concurrent sham arms — isolating PBM effect from PRP effect and from any PBM × PRP interaction.

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

- Bench dosimetry programme quantifying irradiance and fluence through the actual PRP container walls, verifying platelet integrity, pH, osmolarity, growth-factor kinetics (PDGF, TGF-β, VEGF), and any change in EV/exosome yield or size.
- Ex-vivo photonic priming of BMAC, ADSCs, and MSC-derived EVs at defined MR5 doses, with functional assays on target cells (chondrocytes, tenocytes, myoblasts).
- Head-to-head evaluation of MR5 (MLS dual-emission) vs matched single-wavelength LLLT devices for the same indication, controlling for delivered energy — the only design that can support device-specific labelling claims.
- Formal AMSTAR-2 appraisal and PROSPERO registration for future PBM systematic reviews, per PRIOR guidance.

Limitations

Three limitations of the present umbrella study should be recognised. First, no re-pooling of individual-patient data was performed; effect sizes reported are those extracted from the primary source reviews, which themselves carry pooling assumptions. Second, formal AMSTAR-2 numerical scoring was not repeated for each included systematic review; instead, qualitative appraisal of the seven AMSTAR-2 critical domains was applied. Third, our dedicated MR5 / MLS evidence base is small (three peer-reviewed clinical/preclinical studies plus institutional literature), reflecting an authentic evidence gap that is itself one of our findings. Publication bias in PBM literature is plausible given the volume of positive small trials and warrants funnel-plot analysis in any future device-specific meta-analysis.

Conclusions

Photobiomodulation in the 600–940 nm window has a coherent mitochondrial and redox-signalling mechanism, a WALT-endorsed dosimetric framework, and reproducible short- to mid-term clinical benefit in several musculoskeletal indications — most robustly in knee osteoarthritis, lateral epicondylitis, shoulder impingement, temporomandibular disorders, and chronic neck / low back pain — when wavelength-appropriate and dose-transparent protocols are used. The Proactive MR5 platform, with its synchronised 808 nm continuous and 905 nm super-pulsed MLS® emissions, is spectrally well-positioned inside this evidence window. Its dual-emission architecture is biologically rational for combined use with orthobiologics, and translational preclinical evidence supports ex-vivo photonic priming of PRP, ADSCs, and exosomes. However, device-specific randomised sham-controlled trials of MR5 in knee OA and orthobiologic priming remain the essential next step before adjuvant use can be considered evidence-based. A properly designed factorial trial and a bench-dosimetry programme are, at this moment, the two most valuable investments the field can make.

Declarations

Ethics approval and consent to participate: Not applicable (overview of published evidence).

Availability of data and materials: Full extraction tables and search logs are available from the corresponding author upon reasonable request.

DOI: https://doi.org/10.52793/ACMR.2026.7(4)-134

Competing interests: The authors declare no financial relationship with ASA Laser or any manufacturer of photobiomodulation equipment. Any future updates will disclose any change in this status.

Funding: No external funding was received for this work.

Author contributions: All authors: conception, evidence retrieval, extraction, synthesis, drafting, and final approval.

Acknowledgements: The author acknowledges the WALT and ASAcampus initiatives for maintaining publicly accessible dose recommendations and mechanistic photobiology literature.

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