Photobiomodulation and Biological Pathways in Skin Regeneration and Rejuvenation

Light and Biological Activation of Skin Improvement

Saami Khalifian, MD, FAAD*, Jessica Shisler, PhD

KEYWORDS

• Photobiomodulation • Laser-assisted drug delivery • Exosomes • Platelet-rich plasma • Peptides • Fractional laser • Microneedling • Acne scars

KEY POINTS

- Timing of biologic application must match the device's delivery window; ablative fractional laser channels remain patent up to 24 hours, while microneedling channels close within 2–3 hours.
- Adipose-derived stem cell exosomes applied after fractional CO_2 laser and microneedling combined with PRP each have randomized controlled trial evidence supporting superior outcomes over device treatment alone.
- The optimal treatment sequence is controlled barrier disruption, immediate biologic loading under occlusion, followed by photobiomodulation within 24–72 hours to produce the strongest regenerative signal.
- True on-skin fluence should be verified with a calibrated power meter, as excessive dosing can paradoxically inhibit cellular proliferation through biphasic dose-response effects.

INTRODUCTION

The Convergence of Light and Biology in Cutaneous Regeneration

Skin regeneration represents a dynamic interplay among energy-based devices, inflammatory mediators, angiogenic signals, and extracellular matrix remodeling programs. Traditional approaches to photoaging, acne scarring, and post-operative wound optimization have relied on either device-based interventions or topical pharmacotherapies in isolation. Contemporary evidence, however, supports a synergistic paradigm that integrates photobiomodulation (PBM) with biologically active topical agents delivered through barrier-disrupting technologies.

PBM in the red (630–660 nm) and near-infrared (810–850 nm) spectra increases adenosine triphosphate generation through cytochrome c oxidase activation, modulates reactive oxygen species (ROS) signaling, and influences calcium flux dynamics.[1] These cellular perturbations shift keratinocytes, fibroblasts, endothelial cells, and tissue-resident macrophages toward regenerative phenotypes characterized by enhanced migration, proliferation, and matrix synthesis.

Biological cues provide pathway-specific molecular instruction. Extracellular vesicles, particularly

SOM Aesthetics, 25 E E Street, Encinitas, CA 92024, USA
* Corresponding author.
E-mail address: research@som.md

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Abbreviations

EGF	epidermal growth factor
FGF	fibroblast growth factor
LADD	laser-assisted drug delivery
LED	light-emitting diode
PBM	Photobiomodulation
PDGF	platelet-derived growth factor
PDRN	polydeoxyribonucleotides
PRF	platelet-rich fibrin
PRP	platelet-rich plasma
ROS	reactive oxygen species
TGF-β	transforming growth factor-beta
VEGF	vascular endothelial growth factor

exosomes derived from adipose or mesenchymal stem cells, transport microRNA cargo and proteins that modulate fibroblast behavior and immune cell polarization.[2] Platelet concentrates, including platelet-rich plasma (PRP) and platelet-rich fibrin (PRF), deliver supraphysiologic concentrations of platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF).[3] Polydeoxyribonucleotides (PDRN) and polynucleotide preparations engage adenosine A2A receptors and nucleotide salvage pathways to promote angiogenesis and tissue repair.[4,5] Recombinant growth factors and synthetic peptides such as palmitoyl pentapeptide-4 (Pal-KTTKS) and glycyl-L-histidyl-L-lysine copper complex (GHK-Cu) directly stimulate procollagen expression and elastic fiber assembly with supporting human clinical data.[6–9]

Laser-Assisted Drug Delivery: Engineering Solutions for the Stratum Corneum Barrier

The stratum corneum presents a formidable 10 to 20 μm lipid-enriched barrier that restricts percutaneous penetration of hydrophilic macromolecules and mid-sized peptides. Fractional laser systems, both ablative (carbon dioxide, erbium: yttrium-aluminum-garnet) and non-ablative (1470–1550 nm), create vertical microchannels with controlled depth, density, and coagulation zone geometry.[10,11] These microchannels temporarily bypass the barrier, enabling immediate post-procedure application of biologics to achieve meaningful dermal exposure. Depending on the specific energy-based device used, the width of the column, the duration of patency, and whether debris exists in the column, can defer, thereby impacting percutaneous absorption of topically applied biologically active ingredients.

The Wellman Center for Photomedicine at Massachusetts General Hospital, under the leadership of R. Rox Anderson and colleagues, pioneered the fundamental principles of fractional photothermolysis and laser-assisted drug delivery (LADD).[10–13] Their work demonstrated that channel depth, rim thermal damage, molecular weight, and vehicle viscosity collectively determine uptake kinetics. Active pressure-vacuum techniques can standardize channel filling for viscous payloads, converting LADD from an empirical art to a quantifiable engineering problem.[12,13]

Microneedling devices provide an alternative mechanical approach, generating shallow conduits (50–250 μm) with minimal thermal injury and abbreviated downtime. Microneedling is particularly well suited for low to mid-molecular-weight peptides and growth factor serums, and demonstrates robust synergy when combined with autologous platelet concentrates applied topically or via superficial injection.[14] Notably, the conduits created by microneedling remain patent only very briefly (typically less than 2–3 hours), whereas ablative lasers can retain channel patency for 24 hours or more. The depth and diameter of microneedling channels is typically less than what can be achieved with fractional laser devices.

Clinical Scope and Objectives

This review emphasizes clinical outcomes and practical protocols for 3 high-yield indications: photoaging and global facial rejuvenation, inflammatory acne and acne scarring, and early post-operative scar management. We argue that the strongest regenerative signal emerges from the triad of controlled barrier disruption, immediate biological loading, and supportive PBM.

MECHANISMS OF PHOTOBIOMODULATION

Photobiomodulation: Cellular Energetics and Transcriptional Reprogramming

PBM exerts its regenerative effects through a well-characterized sequence of photochemical events initiated at the mitochondrial level and amplified through downstream transcriptional programs. The primary chromophore in mammalian cells is cytochrome c oxidase, the terminal enzyme of the mitochondrial electron transport chain, which absorbs photons in the red and near-infrared spectrum and transduces light energy into biochemical signals that shift cells toward repair and regenerative phenotypes.

Cytochrome C Oxidase as the Primary Chromophore

Red and near-infrared photons are absorbed by cytochrome c oxidase (complex IV) in the mitochondrial electron transport chain. Photon

absorption increases mitochondrial membrane potential, accelerates ATP synthesis, and generates transient low-level ROS that function as signaling molecules rather than damaging oxidants.[1] This ROS pulse upregulates nuclear factor erythroid 2 related factor 2 and other antioxidant response elements, priming cells for oxidative resilience.

Downstream Cellular Effects

The ATP and ROS signals trigger multiple regenerative cascades:

- Keratinocyte migration and proliferation: Enhanced wound closure velocity and re-epithelialization kinetics in both animal models and human wound studies.[1,2]
- Fibroblast activation: Increased expression of collagen I and III mRNA, with corresponding increases in procollagen peptide secretion. TGF-β signaling pathways are modulated toward productive remodeling rather than fibrotic overgrowth.
- Angiogenesis: VEGF upregulation and endothelial cell migration support neovascularization in healing tissues and ischemic dermis.
- Immune modulation: Macrophage polarization shifts from pro-inflammatory M1 toward reparative M2 phenotypes, reducing inflammatory cytokine burden.[1]

Wavelength-Specific Considerations

- Blue light (415 nm): Targets porphyrins in *Cutibacterium acnes*, generating singlet oxygen with antimicrobial and immunomodulatory effects relevant to inflammatory acne.[15]
- Red light (630–660 nm): Optimal absorption by cytochrome c oxidase with moderate tissue penetration (1–2 mm), suitable for epidermal and superficial dermal targets.
- Near-infrared (810–850 nm): Deeper penetration (3–5 mm) reaches mid-dermal fibroblasts, vessels, and subcutaneous adipose interfaces.[1]

Safety Profile and Dose Windows

A 2025 consensus statement in the *Journal of the American Academy of Dermatology* concluded that red and near-infrared light at therapeutic doses (3–60 J/cm^2 per session) does not induce DNA damage and carries a favorable safety profile for cutaneous applications.[1] Biphasic dose-response curves necessitate careful fluence documentation; excessive irradiance or cumulative dose may paradoxically inhibit cellular proliferation.

BIOLOGICAL CUES: MOLECULAR INSTRUCTIONS FOR REGENERATION

Extracellular Vesicles and Exosomes

Exosomes are 30 to 150 nm membrane-bound vesicles secreted by most cell types, with particularly potent regenerative cargo when derived from mesenchymal or adipose-derived stem cells. They transport:

- MicroRNAs: Small noncoding RNAs that post-transcriptionally regulate collagen synthesis, matrix metalloproteinase activity, and inflammatory mediator expression.[2]
- Growth factors and cytokines: Paracrine signals that condition recipient fibroblasts, keratinocytes, and immune cells toward repair phenotypes.
- Heat shock proteins and anti-apoptotic factors: Protect cells from oxidative and thermal injury during wound healing.[2]

A 2020 prospective, double-blind, randomized split-face trial demonstrated that adipose-derived stem cell exosomes applied immediately after fractional CO_2 laser treatment accelerated re-epithelialization and improved acne scar outcomes compared with vehicle control at 12 weeks.[2] This landmark study provides Level 1 evidence for exosome efficacy when paired with LADD in acne scarring. In the author's experience, adipose-derived stem cell exosomes applied post-HALO laser in a split-faced, double-blind, randomized, placebo-controlled trial, the side of the face treated with exosomes healed faster at early time-points and subjects demonstrated greater rejuvenation in investigator global assessment and patient self-reports (data not yet published).

Platelet Concentrates: Platelet-rich Plasma and Platelet-rich Fibrin

Autologous PRP is prepared by centrifugation to concentrate platelets 3 to 5 fold above baseline, delivering supraphysiologic doses of:

- PDGF-AB and PDGF-BB: Chemotactic for fibroblasts and pericytes; stimulate granulation tissue formation and angiogenesis.
- TGF-β1 and TGF-β2: Regulate collagen deposition and matrix remodeling, with context-dependent pro-fibrotic or anti-fibrotic effects.
- VEGF: Promotes endothelial migration and capillary formation.
- EGF: Supports keratinocyte proliferation and epidermal thickness.[3]

PRF represents a second-generation concentrate prepared without anticoagulant, yielding a

fibrin scaffold with slower growth factor release kinetics. PRF may offer sustained paracrine support over 7 to 14 days, potentially stabilizing early granulation tissue and reducing inflammatory rebound.[3]

A 2022 meta-analysis of randomized controlled trials confirmed that combined microneedling plus PRP significantly improves acne scar outcomes compared with microneedling alone, with no increase in severe adverse events.[14] This establishes PRP as an evidence-based adjunct for atrophic acne scarring when delivered via microneedling. Conceptually, the application of PRP with any wounding procedure, whether it be microneedling or laser or mechanothermal activation, will yield greater results than the wounding procedure in isolation. The addition of light-based treatment further promotes the PBM of skin changes, thereby increasing the clinical impact through the biological activity of PRP and the photobiological effect of light.

Polydeoxyribonucleotides and Polynucleotides

PDRN and polynucleotide preparations are low-molecular-weight DNA fragments (50–1500 base pairs) typically derived from salmon sperm or plant sources. They activate adenosine A2A receptors on fibroblasts, endothelial cells, and inflammatory cells, promoting:

- Angiogenesis via VEGF upregulation: Demonstrated in ischemic wound models and pressure ulcer randomized controlled trials.[4,5]
- Fibroblast proliferation and collagen synthesis: With favorable elasticity and hydration outcomes in prospective aesthetic studies.[4,5]
- Anti-inflammatory effects: Reduced cytokine release and oxidative stress in wounded tissues.

PDRN is approved in multiple jurisdictions for wound healing indications and shows promise in esthetic applications for skin elasticity and barrier restoration, though regulatory pathways vary globally.[4,5]

Growth Factors and Bioactive Peptides

Recombinant human growth factors and synthetic peptides provide targeted pathway activation:

PDGF (Becaplermin): FDA-approved for diabetic neuropathic ulcers, becaplermin validates the biological principle that exogenous PDGF accelerates granulation tissue formation and wound closure.[16] While not approved for esthetic use, it anchors the mechanistic rationale for platelet concentrates and multi-growth factor serums.

PDGF (Ariessence pure PDGF+): A recombinant, sterile, pharmaceutical-grade PDGF-BB topical that is marketed for post-procedure skin rejuvenation and typically applied immediately after barrier-disrupting procedures such as microneedling or fractional lasers to leverage channel-mediated uptake. The formulation is intentionally simple, with 4 listed ingredients including hyaluronic acid and a PDGF polypeptide, and it is positioned as an aesthetic product that uses a growth factor with existing FDA drug precedents in wound care, not as an FDA-approved drug for cosmetic indications. Several clinics promote very high PDGF concentrations relative to PRP, PRF, or exosomes and pair the serum with LADD to support re-epithelialization and collagen remodeling, although peer-reviewed clinical data specific to this branded product remain limited. Practically, treat it as a cosmetic topical for use on intact or re-epithelialized skin within sterile, protocolized LADD workflows, and counsel patients that claims about FDA status refer to the PDGF class history in medical wounds rather than to this cosmetic product itself.

EGF: Recombinant human EGF in cosmetic formulations has demonstrated improved re-epithelialization, epidermal thickness, and fine line reduction in small clinical trials and case series.[17–19] Efficacy appears enhanced when paired with barrier disruption.

Fibroblast growth factor (FGF) Family: Basic FGF (bFGF, FGF-2) and keratinocyte growth factor (KGF, FGF-7) support regenerative remodeling, reduce hypertrophic scar risk, and improve burn outcomes in Japanese and international burn literature.[20–22] Esthetic translation for acne scars and incisional healing is an active area of investigation.

Palmitoyl pentapeptide-4 (Pal-KTTKS): A 12 week double-blind, randomized, split-face trial in 93 women with moderate photoaging demonstrated statistically significant wrinkle reduction and improved overall photoaged appearance compared with vehicle by expert grading and digital image analysis.[6] This establishes Pal-KTTKS as a validated peptide for photoaging when formulated at 3 to 5 ppm in appropriate vehicles.

GHK-Cu (Copper Tripeptide): Multiple controlled studies document improved skin elasticity, dermal density, and wrinkle reduction with topical GHK-Cu formulations.[7–9] The copper chelate stabilizes the peptide and may independently support lysyl oxidase activity required for collagen and elastin cross-linking.

Laser-Assisted Drug Delivery: Principles and Practice

Effective biological delivery requires overcoming the stratum corneum barrier, and the choice of delivery platform determines both the depth and

duration of percutaneous access. This section reviews the principal device categories used for LADD, including ablative and non-ablative fractional lasers, microneedling, and pressure-vacuum techniques, with attention to the device characteristics that govern payload uptake, channel geometry, and clinical suitability for different biological agents.

Ablative Fractional Lasers

Carbon dioxide (10,600 nm) and erbium:YAG (2940 nm) fractional lasers create microscopic zones of epidermal and dermal ablation surrounded by coagulated tissue. Channel depth is tunable from 4 μm to greater than 1000 μm depending on energy settings and pass number. Immediate post-treatment application of biologics with or without occlusion achieves dermal concentrations orders of magnitude higher than intact skin application.[10–13]

Advantages

- Deep dermal penetration for macromolecular payloads
- Precise control over channel geometry
- Durable clinical endpoints for resurfacing and scar remodeling

Considerations

- Extended downtime (5–14 days); shallow depths have less downtime compared with deeper channels.
- Higher risk of post-inflammatory hyperpigmentation in Fitzpatrick IV–VI skin
- Requires rigorous sterile technique for biological application

Non-ablative Fractional Lasers

Mid-infrared wavelengths (1470, 1540, 1550, 1927 nm) generate columns of thermal coagulation without ablating the epidermis. Channels geometry is varied dependent on the specific wavelength and energy settings. Higher affinity for water (eg, 1927 nm) is generally narrower and shallower than those with lower affinity for water (eg, 1470 nm) that generate columns that are wider and deeper. Non-ablative systems offer reduced downtime and lower pigmentary risk and present interesting alternatives to ablative systems.

Applications

- Suitable for small peptides and low-viscosity serums
- Maintenance protocols after initial ablative treatment
- Conservative approach in darker skin types

Notably, channel geometry, duration of patency, and presence of coagulated material within the channel all impact the efficacy of device-assisted drug delivery systems.

Microneedling

Automated microneedling devices with sterile needle cartridges create microchannels 0.5 to 2.5 mm deep depending on device settings and treatment intent. Microneedling generates minimal to no heat, however duration of patency is limited compared with laser and other devices, for example, microthermal ablation systems (eg, Tixel).

Synergy with Platelet Concentrates

Meta-analytic evidence supports microneedling combined with PRP for acne scars.[14] PRP can be applied topically during the procedure, injected intradermally in the treatment field, or both. The mechanical injury from microneedling upregulates growth factor receptors and inflammatory mediators that amplify PRP's paracrine effects.

Pressure-vacuum and Occlusive Techniques

Standard LADD protocols rely on passive diffusion through laser-created channels. Active pressure-vacuum devices can improve channel filling consistency, particularly for viscous agents like platelet lysates or exosome suspensions.[12,13] Following application, occlusion with polyethylene film or hydrocolloid dressings for 20 to 40 minutes increases dwell time and dermal bioavailability (**Table 1**).

PHOTOAGING AND GLOBAL FACIAL REJUVENATION

Photobiomodulation for Texture and Elasticity

Multiple controlled trials and systematic reviews support red and near-infrared PBM for improving skin texture, elasticity, and fine wrinkles in photoaged skin.[1,23] A representative protocol involves 630 to 660 nm light at 10 to 30 J/cm^2 delivered 2 to 3 times weekly for 4 to 8 weeks. The 2025 JAAD consensus reinforces PBM safety and efficacy for cutaneous rejuvenation, providing high-level reassurance for adjunctive use following procedural interventions.[1]

Growth Factors and Peptides: Achieving Parity with Biologics

Pal-KTTKS: Robinson and colleagues conducted a 12 week double-blind, randomized, split-face study in women with moderate photoaging. The Pal-KTTKS-treated side showed significant

Table 1
Delivery Decision Guide for Biologics and Peptides

Agent Class	Preferred Barrier-Disruption Method	Depth Target	Occlusion Duration	Clinical Notes
Low-MW peptides (Pal-KTTKS, GHK-Cu)	Microneedling or superficial fractional	100–250 μm	20–30 min	Stable cosmeceutical vehicles; well-tolerated
Cosmetic multi-GF serums	Microneedling or superficial fractional	100–300 μm	20–40 min	Apply immediately post-procedure
Exosome or EV solutions	Superficial to mid-dermal fractional	150–400 μm	20–40 min	Pressure-vacuum optional for uniform distribution
PRP (topical)	Superficial fractional	150–300 μm	20–30 min	Warming lysate to 37°C improves spreadability
PDRN or polynucleotides	Fractional (once epithelialized)	150–300 μm	20–30 min	Avoid open wounds unless labeled for such use

Sources: Refs.[10–13]

improvements in fine lines, overall photo-aged appearance, and mottled pigmentation compared with vehicle control (*P*005).[6] Digital image analysis corroborated expert clinical grading.

GHK-Cu: Pickart and colleagues reviewed placebo-controlled studies demonstrating improved skin elasticity, increased dermal density by ultrasound, and reduced wrinkle depth with GHK-Cu formulations at 0.05% to 0.1% equivalents.[7–9] The copper component stabilizes the peptide and may enhance lysyl oxidase activity.

EGF-Containing Serums: Contemporary case series suggest modest to moderate improvements in texture and fine lines with EGF cosmetics, with stronger effects when delivered via microneedling or fractional LADD.[17–19] While lacking the robust randomized trial data of Pal-KTTKS, EGF serums represent a plausible adjunct in multimodal protocols.

Platelet Concentrates and Polynucleotides

Randomized and controlled studies report texture and elasticity improvements with PRP or PRF injections and topical applications in photoaging, though preparation heterogeneity limits direct comparisons.[3,14] PRF's fibrin scaffold may provide sustained growth factor release over 1 to 2 weeks.

Polynucleotides and PDRN demonstrate favorable hydration and elasticity signals in prospective aesthetic trials with good tolerability.[4,5] They complement peptide and growth factor regimens and can be applied once the barrier is intact. Notably, the hydration effect appears to be short-lived with PDRN and PN, typically lasting only a few weeks. **Fig. 1**.

ACNE AND ACNE SCARRING

Light-emitting Diodes Photobiomodulation for Inflammatory Acne

Combination blue (415 nm) and red (633 nm) light-emitting diode (LED) therapy reduces inflammatory acne lesion counts with high patient satisfaction and minimal adverse effects.[15,24] Blue light targets *C acnes* porphyrins, generating reactive oxygen that exerts antimicrobial effects. Red light modulates inflammatory cytokines and supports barrier repair. Typical protocols involve 15 to 20 minutes of combined blue-red exposure 2 to 3 times weekly for 4 to 8 weeks. IPL platforms can be utilized to provide additional acne PBM with 420 nm filters for acne treatment, 560 nm for erythema, and 590 nm (or longer wavelength depending on skin type) for bulk heating to downregulate sebaceous activity.

Microneedling plus Platelet-rich Plasma for Atrophic Acne Scars

Kang and colleagues conducted a meta-analysis of randomized controlled trials comparing microneedling alone versus microneedling combined with PRP for atrophic acne scars.[14] The combined therapy group demonstrated superior scar improvement by Goodman-Baron grading and patient satisfaction scores, with no significant increase in adverse events. This meta-analysis establishes Level 1 evidence for PRP as an adjunct to microneedling in acne scar management.

Proposed Mechanism

- Microneedling generates controlled dermal injury, upregulating collagen synthesis and remodeling enzymes

Integrated Rejuvenation Protocol

Week 0:

- Superficial fractional laser (ablative or nonablative) creating channels 200–400 μm deep
- Immediate application of multi-GF serum (ideally under occlusion for 30 minutes) and exosomes
- Red LED PBM at 24 and 72 hours post-procedure (15–25 J/cm²)

Week 4:

- Microneedling at 1.5–2.0 mm depth
- Topical PRP or PRF application during and immediately after treatment, followed by topical application of PDRN or PN
- Red LED PBM within 24 hours

Week 12:

- Superficial fractional laser (ablative or nonablative) creating channels 200–400 μm deep
- Immediate application of multi-GF serum, exosomes, and PDRN
- Red LED PBM at 24 and 72 hours post-procedure (15–25 J/cm²)

Weeks 1–12:

- Daily home use of topical exosomes and topical peptide formulations (e.g. Pal-KTTKS or GHK-Cu)
- Twice-weekly red LED sessions (10–20 J/cm²) for first 6 weeks

Fig. 1. Integrated rejuvenation protocol.

- PRP delivers PDGF, TGF-β, EGF, and VEGF that amplify fibroblast activation and granulation tissue formation
- Combined therapy may reduce inflammatory rebound and accelerate matrix reorganization

Exosomes After Fractional CO_2 Laser

Kwon and colleagues published a prospective, double-blind, randomized split-face trial in 22 patients with atrophic acne scars.[2] One hemiface received fractional CO_2 laser followed by adipose-derived stem cell exosomes; the contralateral side received laser plus vehicle. At 12 weeks, the exosome-treated side showed:

- Faster re-epithelialization (mean 5.2 vs 7.1 days, $P<.01$)
- Greater improvement in Goodman-Baron scar grade ($P<.05$)
- Higher patient satisfaction scores

This split-face design provides Level 1 evidence that exosomes accelerate healing and improve acne scar outcomes when delivered immediately post-fractional laser via LADD. A similar study was carried out by the primary author using full face HALO laser (1470 nm non-ablative and 2940 nm ablative laser) and split face application of adipose-derived exosomes versus vehicle with similar results (data not yet published).

Basic Fibroblast Growth Factor and Peptide Adjuncts

Japanese burn and wound literature documents that bFGF improves remodeling quality and reduces hypertrophic scar risk.[20–22] Extrapolation to acne scars is biologically plausible, and early clinical reports suggest benefit when bFGF is applied between laser sessions to support neocollagenesis. Pal-KTTKS or GHK-Cu can be layered into maintenance regimens to sustain collagen synthesis between procedural interventions (**Fig. 2**).[6–9]

SURGICAL SCARS AND EARLY POST-OPERATIVE WOUND MANAGEMENT

Red Light-emitting Diode Photobiomodulation

Early initiation of red LED therapy after suture removal or complete epithelialization improves

Evidence-Based Acne Scar Protocol

Week 1 and 12: Fractional CO_2 or Er:YAG Laser

- Conservative density (5%–15% coverage) for channels
- Immediate exosome solution and multi-GF serum under occlusion for 30 minutes
- Red LED PBM within 24 hours (15–25 J/cm²)

Week 4: Microneedling with PRP

- Depth 1.5–2.5 mm depending on scar morphology
- PRP applied topically during treatment and immediately after
- Red LED PBM within 24 hours

Week 8: Repeat Microneedling

- PRP and peptide-rich serum (Pal-KTTKS, GHK-Cu, or multi-GF)
- Red LED PBM within 24 hours

Home Care Between Sessions:

- Daily application of topical exosomes and topical peptides (e.g. Pal-KTTKS or GHK-Cu formulation)
- Strict photoprotection and barrier-supportive moisturizer

Evidence Base: Split-face RCT for exosomes post-fractional CO_2,[2] meta-analysis for microneedling plus PRP[14]

Fig. 2. Evidence-based acne scar protocol.

scar pliability, erythema, and cosmetic scores in controlled facial surgery studies.[1,25] Network meta-analyses support a role for light-based devices in hypertrophic scar prevention, though study heterogeneity limits precise effect size estimates (**Table 2**).

Protocol Considerations:

- Initiate PBM at suture removal or when epithelialization is complete
- Red LED (630–660 nm) at 15 to 30 J/cm² per session
- Frequency: 2 to 3 times weekly for 4 to 6 weeks

Table 2
Early Post-operative Scar Management Pathway

Time Window	Intervention	Rationale
Suture removal to Week 2	Red LED PBM 2–3 × /week (15–30 J/cm²); silicone sheeting; UV protection	Modulate inflammation; support early remodeling; prevent hyperpigmentation[1]
Week 2–4	Continue LED; consider EGF and multi-GF serum if fully epithelialized	Epidermal normalization; barrier support[17–19]
Week 4–8	For high-risk scars: low-density non-ablative fractional + PRP, multi-GF and peptide serum under brief occlusion	Gentle LADD to bias remodeling toward organized matrix
Week 8–24	Maintenance LED 1–2 × /week; continue silicone and photoprotection	Sustained remodeling support; prevent relapse

- Adjuncts: Silicone sheeting, sunscreen, and barrier-supportive moisturizers

Polydeoxyribonucleotides and PN for Surgical Wounds

Randomized controlled trials in pressure ulcers, diabetic ulcers, and donor site wounds demonstrate that PDRN accelerates re-epithelialization and improves healing and skin quality.[4,5] Translation to early esthetic incisions is biologically sound once the barrier is intact. PDRN or PN can be applied topically over closed incisions or via superficial intradermal injection in high-risk scar areas (eg, chest, shoulders, earlobes).

Growth Factors and Peptides in Postoperative Care

EGF: Recombinant human EGF formulations applied to epithelialized incisions may support epidermal normalization and barrier restoration in the early remodeling phase (weeks 2–6).[17–19]

bFGF: Japanese experience with bFGF in surgical wounds suggests reduced hypertrophic scar incidence when applied early in the remodeling phase.[20–22] Its role in facial plastic surgery incisions warrants prospective study.

Low-Density Fractional LADD: For high-risk scars (eg, tension-prone areas, history of hypertrophic scarring), consider very low density nonablative fractional laser (5%–11% coverage) at weeks 4 to 8 with immediate application of PRP lysate, multi-GF serum, and peptide serum.[10–13] This technique requires expertise and should be reserved for practitioners experienced in scar revision protocols.

PRACTICAL SEQUENCING AND DOSE DOCUMENTATION

Treatment Sequencing Principles

1. Create controlled barrier disruption matched to molecular size and target depth
2. Load the field immediately with biological or peptide payload
3. Use occlusion (20–40 minutes) to maximize dwell time and dermal bioavailability
4. Apply PBM within 24 to 72 hours to support re-epithelialization and modulate inflammatory cytokines

Photobiomodulation Documentation Checklist

Rigorous documentation ensures reproducibility and facilitates outcome comparisons:

- Wavelength (nm)
- Irradiance at skin surface (mW/cm^2)
- Treatment duration (minutes)
- Duty cycle (continuous vs pulsed)
- Cumulative fluence per session (J/cm^2)
- Number of sessions and interval
- Device make/model and calibration date
- Skin phototype and treatment site
- Concurrent active ingredients **Table 3**

Growth Factor and Peptide Practical Heuristics

Application of growth factors and peptides in the post-procedure window requires consideration of both the delivery platform and timing. Barrier-disrupting treatments create channels of varying depth and diameter, and channel patency differs significantly between devices. Selecting the appropriate agent and applying it within the optimal window for the specific treatment used is therefore critical to achieving meaningful dermal delivery (**Table 4**).

SAFETY, QUALITY ASSURANCE, AND REGULATORY CONSIDERATIONS

Extracellular Vesicles and Exosomes

Exosome products exhibit marked heterogeneity in cell source (adipose, bone marrow, umbilical cord), isolation method (ultracentrifugation, size exclusion, precipitation kits), potency, and sterility. Regulatory pathways remain unsettled in many jurisdictions:

- United States: FDA regulates human cell and tissue products. Exosomes intended for tissue repair may require biological license applications depending on manufacturing and claims.
- European Union: Advanced therapy medicinal product regulations may apply to cell-derived vesicles.
- Other Jurisdictions: Variable regulatory frameworks; practitioners must verify local compliance.

Quality Assurance Requirements

- Documented cell source and donor screening
- Validated isolation protocol with particle characterization (NTA, DLS, TEM)
- Sterility testing per USP 71
- Endotoxin testing per USP 85
- Batch-specific potency assays (eg, collagen induction, angiogenesis assays)
- Informed consent explicitly noting regulatory status and evidence base

Platelet Concentrates

Standardization is critical for reproducibility:

Table 3
hotobiomodulation Parameters in Dermatologic Applications

Indication	Wavelength	Fluence per Session	Frequency	Clinical Evidence
Inflammatory acne	410–420 nm (blue) + 630–660 nm (red)	8–20 J/cm^2	2–3 × /week × 4–8 wk	Lesion count reductions; high tolerability[15,24]
Photoaging support	630–660 nm (red), 810–850 nm (NIR)	10–60 J/cm^2	2–3 × /week × 4–8 wk	Texture, elasticity, fine line improvements; strong safety signal[1,23]
Early post-operative scars	630–660 nm (red)	15–30 J/cm^2	2–3 × /week × 4–6 wk	Improved pliability, erythema, cosmetic scores[1,25]

- Centrifugation protocol (speed, duration, temperature)

Platelet concentration target (3–5 × baseline for PRP; fibrin matrix integrity for PRF)

- Leukocyte content (leukocyte-rich vs leukocyte-poor; impacts inflammatory profile)
- Activation method (calcium chloride, thrombin, collagen, or spontaneous for PRF)
- Total platelet dose and growth factor release kinetics (when feasible)
- Injection depth and volume for intradermal applications

Polydeoxyribonucleotides and Polynucleotides

Approval pathways vary globally. In jurisdictions where PDRN is approved for wound healing, off-label aesthetic use requires:

- Clear documentation of indication and evidence base
- Informed consent addressing regulatory status
- Restriction to intact epithelium for aesthetic applications unless labeled for open wounds
- Attention to molecular weight specifications and source material (salmon-derived vs synthetic)

Photobiomodulation Device Oversight

LED and laser PBM devices range from FDA Class I (general wellness) to Class II (medical device) depending on claims and indications. Key considerations:

- Fluence verification: Use calibrated power meters to confirm manufacturer specifications. Document true on-skin irradiance.
- Biphasic dose response: Excessive fluence may inhibit cellular proliferation. Adhere to established therapeutic windows (3–60 J/cm^2 depending on indication and wavelength).[1]

Table 4
Clinical Application Guidelines for Growth Factors and Peptides

Agent	Typical Regimen	Delivery Enhancement	Course Duration	Evidence Level
Pal-KTTKS	3–5 ppm in moisturizer twice daily	Microneedling or superficial fractional improves penetration	8–12 wk	Level 1: Split-face RCT[6]
GHK-Cu	0.05%–0.1% copper peptide equivalents	Microneedling or superficial fractional; stable chelated formulations	8–12 wk	Level 2: Controlled human studies[7–9]
Multi-GF serums	Brand-specific, non-drug cosmetics	Microneedling or fractional LADD, then occlusion	4–12 wk	Level 3: Case series and reviews[17–19]
rhEGF cosmetics	0.1–1.0 μg/mL ranges	Microneedling or fractional LADD	6–12 wk	Level 3: Case series and reviews[17–19]
bFGF topical	Product-dependent	Use only after epithelialization unless labeled	2–8 wk	Level 2: Wound/burn RCTs[20–22]

- Eye protection: Near-infrared wavelengths require appropriate protective eyewear for patient and operator.
- Maintenance and calibration logs: Document device servicing and power output verification.

Aseptic Technique for Post-procedural Biological Application

Topical biological application following fractional laser should be conducted with sterile technique equivalent to minor procedures:

- Sterile gloves
- Single-use biological aliquots; discard remainder
- Sterile occlusive dressing
- Avoidance of multi-dose containers in the treatment field
- Patient education on post-procedure hygiene, home treatment protocol, and signs of infection

Safety Checklist for Combined Light and Biological Protocols

- Verify product source, sterility documentation, and regulatory status
- Use closed-system processing for autologous PRP/PRF
- Conservative fractional settings on first session; escalate based on tolerance
- Avoid LADD on active infection, eczematous dermatitis, or severely compromised barrier
- Skin type-specific laser parameters; aggressive photoprotection post-procedure
- Standardized photography at each visit (consistent lighting, positioning, camera settings)
- Patient-reported outcomes using validated instruments (FACE-Q, Skindex, VAS for satisfaction)
- Adverse event monitoring and documentation

CONTROVERSIES, CHALLENGES, AND KNOWLEDGE GAPS

Exosome Standardization and Regulatory Ambiguity

The exosome field suffers from:

- Source heterogeneity: Adipose-derived, platelet-derived, bone marrow-derived, and umbilical cord-derived exosomes have distinct cargo profiles.
- Isolation variability: Ultracentrifugation, tangential flow filtration, size exclusion chromatography, and precipitation kits yield different purity and yield.
- Potency assays: No consensus on functional assays. Proposed metrics include collagen induction in fibroblast cultures, tube formation in endothelial cells, and specific miRNA quantification.
- Regulatory status: Jurisdictional inconsistency creates compliance challenges and limits cross-border applicability of protocols.

Path Forward: The field requires GMP-grade manufacturing standards, validated potency assays linked to clinical outcomes, and harmonized regulatory frameworks. Collaborative efforts among regulatory agencies, industry, and academic centers are essential.

Photobiomodulation Dose Reporting Deficiencies

Many published PBM studies lack critical dosimetric data:

- Irradiance measured at device aperture rather than skin surface. LED distance from the skin can dramatically impact energy absorption
- Absence of duty cycle specification (continuous vs pulsed)
- Treatment area size not documented, limiting cumulative dose calculation
- Device calibration status unreported

Recommendations: Clinical audits should mandate power meter verification, treatment logs capturing all dosimetric parameters, and adherence to standardized reporting frameworks (eg, WALT consensus guidelines).[26]

Platelet-rich Plasma Versus Platelet-rich Fibrin: Comparative Effectiveness Uncertainty

Direct head-to-head comparisons of PRP and PRF are scarce. Outcome differences may reflect:

- Platelet concentration and activation state
- Leukocyte content (pro-inflammatory vs anti-inflammatory balance)
- Fibrin scaffold architecture and growth factor release kinetics
- Injection technique and anatomic plane

Harmonized preparation protocols and adequately powered comparative trials are needed to guide clinical decision-making.

Growth Factors and Peptides: Formulation and Concentration Variability

While Pal-KTTKS and GHK-Cu have supportive human data,[6–9] commercial formulations vary widely in:

- Active ingredient concentration
- Vehicle pH and buffering
- Stabilizers and preservatives
- Penetration enhancers

Larger multicenter split-face RCTs with quantitative endpoints (3D profilometry, high-frequency ultrasound, cutometry) and batch-verified formulations would clarify effect sizes and establish optimal concentration ranges.

Long-Term Durability and Maintenance Requirements

Most Published Studies Report Outcomes at 12 to 24 Weeks. Questions Remain:

- How long do improvements persist after treatment cessation?
- What maintenance protocols optimize durability?
- Does sequential combination therapy (laser + biological + PBM) alter skin aging trajectories long-term?

Prospective cohort studies with 1 to 3 year follow-up and objective biophysical measures are essential to answer these questions.

Future Directions and Emerging Technologies

PBM-primed delivery: pre-conditioning for enhanced uptake

Emerging evidence suggests that red or near-infrared PBM administered 24 hours before LADD may:

- Upregulate growth factor receptor expression on fibroblasts and keratinocytes
- Increase dermal blood flow, improving distribution of topically delivered agents
- Prime inflammatory pathways to respond more robustly to growth factor signals

Pilot studies evaluating PBM pre-conditioning followed by fractional laser and biological application could identify optimal sequencing strategies.

Quantified Laser-assisted Drug Delivery: Engineering Precision in Drug Delivery

The next generation of LADD protocols will integrate:

- Optical coherence tomography: Real-time visualization of microchannel depth and geometry during laser treatment.
- Dosing nomograms: Algorithms matching channel pore volume to payload viscosity, molecular weight, and target concentration.
- Microfluidic delivery systems: Automated pressure-vacuum devices that standardize channel filling and eliminate operator-dependent variability.

This quantitative approach transforms LADD from empirical art to reproducible engineering.

Standardized Extracellular Vesicle Therapeutics

The path to clinical-grade EV therapeutics includes:

- GMP manufacturing: Closed-system bioreactors with validated isolation protocols and in-process testing.
- Potency assays: Functional measures (collagen synthesis, tube formation, inflammatory modulation) linked to clinical endpoints.
- Molecular cargo profiling: Quantification of specific miRNAs, growth factors, and surface markers that predict regenerative capacity.
- Regulatory harmonization: Clear classification as biologics, establishment of IND pathways, and post-market surveillance systems.

Academic-industry partnerships are accelerating progress, with several GMP-grade exosome products entering Phase II aesthetic trials.

Digital Endpoints and Objective Assessment

Traditional investigator grading and patient satisfaction scales are subjective and operator-dependent. Emerging objective tools include:

- 3D profilometry (Antera, Primos): Quantifies wrinkle depth, volume, and scar topography with sub-100 μm resolution.
- High-frequency ultrasound (22–100 MHz): Measures dermal thickness, echogenicity (collagen density proxy), and anechoic band width (edema).
- Cutometry: Assesses skin elasticity via suction-based deformation and recovery curves.
- Reflectance confocal microscopy: Visualizes epidermal and dermal architecture non-invasively.
- Artificial intelligence image analysis: Automated wrinkle detection, pigmentation quantification, and scar classification with high inter-rater reliability.

Incorporation of these digital endpoints into clinical trials will improve effect size precision, facilitate meta-analyses, and enable personalized treatment optimization.

Comparative Sequencing Trials: Optimizing Multimodal Protocols

The optimal sequence of modalities remains empiric. Pragmatic split-face or body-site designs could compare:

- Arm A: Fractional laser → exosome LADD → PBM
- Arm B: Microneedling → PRP → PBM
- Arm C: PBM pre-conditioning → fractional laser → peptide serum LADD

Standardized protocols with unified inclusion criteria, dosimetric documentation, and objective digital endpoints would yield actionable comparative effectiveness data.

Personalized Medicine: Biomarker-guided Treatment Selection

Future Protocols May Integrate:

- Genetic profiling: Polymorphisms in collagen synthesis genes (COL1A1, COL3A1), matrix metalloproteinases, and growth factor receptors could predict responsiveness to specific biologics.
- Baseline skin microbiome: Microbial composition may influence PBM and exosome efficacy.
- Serum biomarkers: Circulating collagen degradation fragments, inflammatory cytokines, and growth factor levels could guide dose escalation or combination strategies.

Pilot studies correlating baseline biomarkers with treatment response would establish feasibility for precision aesthetic medicine.

Conclusion: A Data-driven Path to Regenerative Excellence

The convergence of PBM, LADD, and biologically active topical agents represents a paradigm shift in aesthetic and reconstructive dermatology. The evidence base, while incomplete, demonstrates consistent signals across multiple indications:

- Photoaging: Pal-KTTKS and GHK-Cu have strong evidence for wrinkle reduction and texture improvement.[6–9] PBM enhances these effects with robust safety data.[1] Fractional or microneedling delivery amplifies peptide penetration.
- Acne Scarring: Exosomes after fractional CO_2 laser improve scar outcomes and accelerate healing (Level 1 evidence).[2] Microneedling plus PRP outperforms microneedling alone (Level 1 meta-analytic evidence).[14] Combination protocols leveraging both modalities with adjunctive PBM show additive benefit.
- Surgical Scars: Early red LED PBM improves pliability and cosmetic scores (Level 2 evidence).[1,25] PDRN accelerates re-epithelialization (Level 1 evidence in wounds),[4,5] with plausible translation to aesthetic incisions.

The strongest clinical outcomes emerge from a disciplined 3 step sequence: controlled barrier disruption matched to molecular payload, immediate biological application under occlusion, and supportive PBM to modulate inflammation and support re-epithelialization. This algorithm is simple to articulate and feasible to execute in diverse practice settings.

The Path Forward: Standardization, Quantification, and Regulation

The field must now transition from proof-of-concept to reproducible protocols. This requires:

1. Dosimetric rigor: Mandate power meter verification for PBM devices; document true skin-level fluence, wavelength, and duty cycle in all publications and clinical logs.
2. Biological standardization: Adopt GMP manufacturing for exosomes with validated potency assays; harmonize PRP/PRF preparation protocols with explicit reporting of platelet concentration, leukocyte content, and activation method.
3. Regulatory clarity: Establish consistent classification frameworks for biologics and combination products across jurisdictions; develop expedited approval pathways for low-risk esthetic applications with strong mechanistic rationale.
4. Objective endpoints: Incorporate 3D profilometry, high-frequency ultrasound, and AI-based image analysis into clinical trials to enable precise effect size quantification and meta-analytic synthesis.
5. Comparative effectiveness research: Fund pragmatic head-to-head trials comparing sequencing strategies, biological classes, and delivery methods to guide evidence-based protocol selection.

Deep Insight: the Levers of Regenerative Medicine

At its core, regenerative aesthetics is an engineering problem with biological constraints. The levers at our disposal—sequence, dose, and dwell time—determine whether biological plausibility translates to visible, durable outcomes. Fractional laser and microneedling solve the barrier problem. Growth

factors, peptides, exosomes, and platelet concentrates provide molecular instruction. PBM creates a permissive metabolic and inflammatory milieu. When these levers are precisely calibrated, the skin's intrinsic regenerative capacity is unleashed.

The next decade will witness the maturation of this field from empirical art to quantitative science. Clinicians who embrace rigorous documentation, adopt standardized protocols, and contribute to the evidence base will lead this transformation. The ultimate beneficiaries are our patients, who will experience safer, more predictable, and more durable regenerative outcomes than ever before.

CLINICS CARE POINTS

- Pearls: Timing of biological application should be matched to the delivery window of the device used. Fractional LADD achieves dermal biological concentrations orders of magnitude higher than intact-skin application; ablative channels remain patent up to 24 hours, whereas microneedling channels close within 2 to 3 hours.
- Evidence supports adipose-derived stem cell exosomes after fractional CO_2 laser for acne scarring (split-face RCT: re-epithelialization 5.2 vs 7.1 days, $P<0.01$) and microneedling combined with PRP for atrophic acne scars (meta-analysis of RCTs).
- The optimal treatment sequence is: controlled barrier disruption → immediate biological loading under occlusion (20–40 minutes) → PBM within 24 to 72 hours; this triad consistently produces the strongest regenerative signal across photoaging, acne scarring, and post-operative scar management.
- Pitfalls: True on-skin fluence should be verified with a calibrated power meter; LED distance significantly alters energy absorption, and excessive dosing can paradoxically inhibit cellular proliferation
- Avoid LADD in the setting of active infection, eczematous dermatitis, or compromised barrier integrity; exosome and PRP products should not be applied to open or unepithelized wounds unless explicitly labeled for such use.

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DISCLOSURES

S. Khalifian is a paid consultant, speaker, trainer, and researcher for Allergan Aesthetics, Benev, Sciton, and Merz Aesthetics. J Shisler is a paid consultant, speaker, and researcher for Allergan Aesthetics, Sciton, and Galderma.

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