Chapter

Regenerative Dermatology Through Energy-Based Channels: Transdermal Delivery and Biological Synergy with Topical Biomaterials

Carl K.L. Cheng

Abstract

Recent developments in fractional energy-based devices (EBDs) and percutaneous technologies have transformed the concept of cutaneous rejuvenation from simple resurfacing to true tissue regeneration. Modern dermatologic interventions increasingly rely on the creation of controlled microscopic treatment zones that function as temporary therapeutic channels within the skin. These channels can be generated using several technologies, including ablative fractional lasers, nonablative fractional lasers, microneedling systems, and microneedling radiofrequency devices. The microchannels produced by these devices transiently disrupt the integrity of the stratum corneum, the primary barrier of the skin, thereby enabling enhanced penetration of topical biologically active substances. When such device-generated channels are combined with modern regenerative biomaterials – such as platelet-rich plasma (PRP), exosomes, polydeoxyribonucleotide (PDRN), and natural or synthetic scaffolds – the efficiency of transdermal delivery can be markedly improved. This combination strategy enhances both the penetration depth and local retention of therapeutic agents, allowing them to exert greater biological activity within the dermis.

Keywords: LADD, MN, MNRF, PRP, PDRN, exosome, scaffold

1. Introduction

This chapter reviews the biological basis and clinical significance of therapeutic channels created by fractional technologies. Particular emphasis is placed on device–specific channel characteristics, mechanisms that enhance transdermal drug delivery, and the regenerative outcomes and cellular evidence observed when these technologies are combined with biomaterials. Together, these developments

highlight channel-assisted biomaterial delivery as a promising frontier in regenerative dermatology.

2. Channel-assisted delivery of biomaterials in skin regeneration

2.1 Skin barrier and topical drug delivery

The skin is the largest organ of the human body, covering approximately 1.7 m^2 of surface area, and represents one of the most accessible routes for drug administration. Despite this accessibility, effective transdermal drug delivery remains challenging because of the highly efficient barrier function of the *stratum corneum* (SC), the outermost layer of the epidermis.

The SC is composed of densely packed, terminally differentiated keratinocytes known as corneocytes, which have lost their intracellular organelles and consist primarily of keratin-rich cellular envelopes. These corneocytes are embedded within an intercellular lipid matrix containing ceramides, cholesterol, and free fatty acids. This highly organized lipid–protein structure forms a compact barrier that restricts the passage of most molecules.

Due to this barrier function, only a limited range of substances are able to penetrate the skin effectively. In general, molecules capable of passive diffusion through the SC are small (typically < 500 Da) and lipophilic, such as nicotine, fentanyl, and certain steroid hormones. Consequently, only a relatively small number of transdermal therapeutic systems have been approved for clinical use. Most large molecules, hydrophilic compounds, and biologic agents exhibit very limited permeability through intact skin [1].

2.2 Pathways for permeation across the SC

Drug molecules can traverse the SC through three primary pathways [2].

2.2.1 Intercellular pathway

The most common route is intercellular diffusion, in which molecules migrate through the lipid lamellae located between adjacent corneocytes. Because this pathway is dominated by lipid structures, it primarily favors lipophilic compounds, which can partition into the lipid matrix and diffuse along these intercellular channels.

2.2.2 Transcellular pathway

The transcellular pathway involves the direct transport across the corneocytes themselves. In this route, molecules must repeatedly cross alternating hydrophilic and lipophilic domains as they move through both intracellular and lipid environments. Disruption of intercellular junctions, such as corneodesmosomes, may facilitate this pathway. Certain physical enhancement techniques – including occlusion, ultrasound, and iontophoresis – have been shown to increase transcellular permeability.

2.3 Appendageal pathway

A third route involves transport through skin appendages, including hair follicles and sweat glands. Although these structures occupy only a small fraction of the total skin surface area, they may serve as localized reservoirs for drug deposition. The efficiency of this pathway depends on the physicochemical properties of the drug formulation and the density of hair follicles or sebaceous glands in a given anatomical region [3].

3. Laser-assisted drug delivery and vertical channel technologies

3.1 Laser-assisted drug delivery

Laser-assisted drug delivery (LADD) has gained increasing attention as a strategy to enhance the dermal uptake of topically applied therapeutic agents. Since the concept was first introduced in 1987 [4], this approach has evolved from an experimental technique to an increasingly investigated platform for improving transdermal delivery of a wide range of pharmacologic and biologic agents. Early investigations focused primarily on applications in oncology and various pathological skin disorders, while more recent studies have explored its role in esthetic dermatology, including facial rejuvenation and regenerative skin therapies.

The fundamental principle of LADD involves the use of laser energy to transiently disrupt the skin barrier, thereby facilitating the penetration of therapeutic molecules that would otherwise be unable to cross the intact SC. Laser-mediated enhancement of drug delivery can be broadly categorized into complete ablation technologies, which create open microchannels through tissue vaporization, and partial or nonablative approaches, which increase permeability through controlled thermal or mechanical disruption of tissue structures.

Beyond purely ablative mechanisms, several laser-induced biological processes can enhance transdermal drug transport. These include photothermal effects, photomechanical disruption, and photochemical activation, each of which contributes to changes in cellular membrane permeability or the formation of microscopic transport pathways. By adjusting parameters such as wavelength, energy density, pulse duration, and exposure time, laser systems can be optimized to enable the delivery of larger molecules, nanoparticles, and biomaterials that normally cannot penetrate biological barriers.

3.2 Photothermal mechanisms in laser-induced drug delivery

One of the primary mechanisms underlying laser-enhanced drug delivery is the photothermal effect. When laser energy is absorbed by chromophores within the tissue, light energy is converted into heat, producing localized temperature elevations [5]. This thermal response can disrupt the lipid bilayers of cellular membranes, resulting in transient structural alterations that increase tissue permeability [6].

Localized heating may induce the formation of temporary membrane pores, a phenomenon often referred to as laser-induced thermal pore formation. When higher energy levels are applied, rapid thermal expansion can generate microscopic

vaporization within cellular or extracellular structures, producing microthermal zones (MTZs) or vertical microchannels within the tissue.

3.3 Photomechanical disruption

In addition to thermal effects, photomechanical mechanisms play an important role in laser-facilitated drug delivery. High-energy lasers operating with extremely short pulse durations – typically in the picosecond or femtosecond range – can generate rapid pressure waves when their energy is absorbed by tissue [7].

These pressure waves produce mechanical stresses capable of temporarily disrupting the integrity of cellular membranes. This process, sometimes referred to as optoporation or laser-induced membrane stretching, results in the formation of transient nanopores within the lipid bilayer [8]. Through these openings, therapeutic agents can diffuse directly into the cytoplasm.

In certain conditions, photomechanical energy may also lead to microcavitation phenomena, where rapid pressure fluctuations create microscopic bubbles within tissue. This mechanical disturbance further weakens the barrier function of the skin and enhances the transport of topical agents into deeper tissue compartments.

3.4 Ablative fractional laser systems

Among ablative laser technologies, three principal wavelengths have been investigated for topical drug delivery [9]: 2,910 nm erbium fiber laser, 2,940 nm Er:YAG laser, and 10,600 nm CO_2 laser. These systems rely primarily on water absorption as the dominant chromophore interaction. When water within tissue absorbs laser energy, rapid heating leads to vaporization of intracellular and extracellular fluid, resulting in tissue ablation and the formation of vertical microchannels.

The Er:YAG laser (2940 nm) exhibits a very high absorption coefficient in water, allowing precise removal of superficial tissue layers with minimal residual thermal damage. In contrast, the CO_2 laser (10,600 nm) produces deeper thermal effects and generally forms larger MTZs due to greater heat diffusion into surrounding tissues.

More recently, lasers operating at approximately 2,910 nm have been developed to target the peak water absorption range between 2,940 nm and 10,600 nm. This wavelength allows efficient tissue ablation while maintaining relatively limited residual thermal injury. A small amount of residual thermal damage – often in the range of 20–40 μm – may be beneficial, as it can act as a temporary channel reservoir that facilitates sustained release and diffusion of topical agents.

Certain systems employ microbeam arrays, in which multiple microbeams are arranged within a treatment spot. For example, a microbeam diameter of approximately 170 μm can be organized into a circular pattern consisting of dozens of individual beams. When applied in a superficial treatment mode, this configuration enables efficient removal of the SC with relatively high coverage while preserving deeper tissue integrity. As a result, the primary barrier to topical drug delivery is selectively disrupted, allowing enhanced penetration of larger therapeutic molecules [10].

3.5 Nonablative fractional laser systems

In addition to ablative devices, nonablative fractional lasers (NAFL) can also facilitate drug delivery by generating controlled microthermal injury without

removing tissue. Common NAFL wavelengths include 1,440 nm, 1,550 nm, and 1,565 nm, as well as wavelengths in the midinfrared spectrum, such as 1927 nm.

These lasers create microscopic treatment zones similar to ablative systems but do so through thermal coagulation rather than tissue vaporization. As a result, the epidermis remains largely intact, although localized columns of microscopic epidermal necrosis and dermal collagen denaturation may occur.

Because nonablative systems produce less direct tissue removal, they generally result in reduced epidermal injury and lower residual thermal damage compared with ablative fractional lasers. However, the localized disruption of skin architecture and temporary impairment of the barrier function can still enhance the permeability of the treated region, allowing topical agents to diffuse more effectively into the dermis [1].

4. Factors influencing channel-assisted topical drug delivery

Successful laser- or device-assisted drug delivery depends not only on the characteristics of the delivery device but also on multiple biological and physicochemical factors that influence diffusion and tissue uptake. Important determinants include channel density, channel depth, coagulation zone characteristics, molecular properties of the drug, formulation type, drug concentration, and the timing of application. Understanding how these variables interact is essential for optimizing therapeutic outcomes and ensuring safe and effective delivery of topical agents [11].

4.1 Channel density

Channel density refers to the proportion of the skin surface area that is disrupted during treatment and can be adjusted by modifying the laser spot size or the number of channels generated within a defined scanning pattern [12]. The density of microchannels directly influences both the rate and the extent of drug permeation.

Experimental studies using fractional ablative lasers have investigated the relationship between channel density and drug uptake [13]. For example, Bachhav and colleagues evaluated the effect of channel density on topical lidocaine permeation using an in vitro porcine skin model treated with an Er:YAG fractional laser. Surprisingly, increasing the channel density beyond a certain threshold did not significantly improve cumulative drug permeation. No statistically significant differences were observed between 450 and 900 channels at 6 hours, nor among 300, 450, and 900 channels after 24 hours [14].

In clinical practice, fractional laser parameters are often selected conservatively to balance efficacy and safety. A commonly used starting configuration involves channel depths of approximately 100–150 μm with treatment densities of 5–10%, which can provide adequate permeability while minimizing adverse effects [14].

4.2 Channel depth

Early investigations evaluating lidocaine penetration suggested that deeper channels might enhance dermal drug uptake by reducing the diffusion distance required for molecules to reach target tissues. However, results from subsequent studies have been inconsistent. While some reports indicate improved delivery with

deeper channels, others suggest that beyond a certain depth, the benefit may plateau due to additional diffusion barriers within the dermal extracellular matrix (ECM) [12].

Therefore, the optimal channel depth may depend on several variables, including the physicochemical characteristics of the drug, the targeted skin layer, and the specific treatment indication.

4.3 Coagulation zone

In fractional ablative laser treatments, each ablation column is typically surrounded by a coagulation zone, which represents thermally denatured tissue adjacent to the ablated channel. The presence of coagulated tissue can influence drug diffusion because its diffusion coefficient is generally lower than that of normal tissue. Consequently, a thick coagulation zone may function as a secondary barrier to drug transport.

However, the coagulation zone may also serve a beneficial role by acting as a localized drug reservoir within the microchannels. This reservoir effect may allow therapeutic compounds to remain within the treated tissue for prolonged periods, promoting sustained local delivery while limiting systemic absorption [15].

Experimental observations suggest that the characteristics of the coagulation zone may significantly influence drug uptake. Studies have demonstrated that both minimal coagulation (0 μm) and excessive coagulation (approximately 80 μm) can reduce topical drug absorption, whereas an intermediate coagulation zone – approximately 20 μm in thickness – may significantly enhance drug uptake in CO_2 fractional laser-treated skin.

Another factor affecting channel persistence is the mechanism of channel formation [15]. Nonthermal channels typically close within several hours as fibrin plugs develop, whereas thermally induced channels may behave more like a subepidermal sponge-like structure, remaining permeable for longer durations.

4.4 Molecular properties of the drug

The physicochemical properties of the therapeutic agent also play a critical role in determining delivery efficiency. Important variables include molecular weight, lipophilicity, diffusion coefficient, and solubility.

Using a fractional ablative CO_2 laser, Haak and colleagues evaluated the influence of both channel density and molecular weight on the penetration of polyethylene glycol (PEG) molecules with molecular weights ranging from 250 to 4,000 Da [16]. The study demonstrated that increasing channel density improved drug delivery up to approximately 100 microscopic treatment zones (MTZs) per cm^2, after which additional channels produced no significant increase in permeability. Furthermore, molecules with lower molecular weights showed greater penetration compared to larger molecules.

While the SC represents the primary barrier in conventional topical drug delivery, device–assisted delivery alters the environment encountered by the drug. When the lipophilic SC barrier is disrupted by fractional lasers or microneedling (MN), topically applied agents are exposed to the underlying hydrophilic ECM. Consequently, this environment may present greater resistance to lipophilic molecules, whereas hydrophilic compounds may diffuse more readily [17].

Consistent with this concept, several studies have reported that deeper ablation zones improve tissue deposition of hydrophilic molecules [16, 17].

4.5 Drug concentration and sustained delivery

Drug concentration is another important factor influencing therapeutic outcomes in device-assisted delivery. Unlike systemic administration, where higher doses may be required to achieve therapeutic tissue concentrations, localized delivery through microchannels may allow lower drug concentrations to achieve similar or superior effects. This approach could potentially reduce treatment costs and minimize systemic adverse effects associated with higher drug doses.

An emerging strategy in channel-assisted drug delivery is the development of sustained-release formulations. Controlled drug release may reduce the frequency of application, improve patient compliance, and enhance therapeutic efficacy while limiting toxicity [18].

4.6 Drug formulation and vehicle type

The formulation or vehicle used for topical administration can significantly affect drug distribution within laser-generated microchannels. In experimental studies using ex vivo porcine skin treated with ablative fractional lasers, Olesen and colleagues compared the delivery efficiency of liquid, gel, and cream formulations. Their findings indicated that liquid and gel formulations achieved greater filling of laser-generated microchannels compared with cream–based preparations, regardless of channel depth [19].

These observations suggest that formulations with lower viscosity may more effectively penetrate microchannels and distribute throughout the treated tissue.

4.7 Timing of drug application

The timing of drug administration relative to device treatment is another critical factor influencing delivery efficiency. Following ablative fractional laser treatment, the skin barrier remains disrupted until reepithelialization occurs, typically two to four days [18].

However, microchannels begin to close progressively as tissue fluids, fibrin, plasma proteins, and inflammatory cells accumulate within them. Optical coherence tomography studies have demonstrated that laser channels remain fully open for approximately 30 minutes after treatment, with partial closure occurring over time. Approximately 75% of channels remain open at 6 hours, whereas only a small fraction remains patent after 24–48 hours.

Clinical investigations have shown that the highest drug uptake occurs when topical agents are applied immediately or within 30 minutes after laser exposure. These findings emphasize the importance of early drug application in order to take full advantage of the depth channel and permeability [18].

5. MN and MN radiofrequency

Microneedling, often referred to as collagen induction therapy, is a minimally invasive dermatologic technique that uses fine needles to create controlled microinjuries within the skin. These microinjuries activate the natural wound-healing cascade, stimulating fibroblast activity and increasing the synthesis of

collagen and elastin, two key structural components responsible for maintaining skin integrity and elasticity [20].

In addition to stimulating dermal remodeling, the microchannels created during MN significantly enhance the transdermal absorption of topical agents [21]. When combined with topical therapies such as vitamin C, retinoids, or other biologically active compounds, MN facilitates deeper penetration and improved therapeutic outcomes, particularly in the treatment of pigmentation disorders and skin rejuvenation.

5.1 MN radiofrequency

More recently, MN technology has been further advanced through the integration of radiofrequency (RF) energy. Microneedling radiofrequency (MNRF) devices deliver thermal energy through insulated or noninsulated needles, producing controlled dermal heating while simultaneously creating mechanical microchannels [22].

This thermal stimulation enhances the wound-healing cascade and promotes collagen remodeling and tissue tightening, leading to improved skin texture and firmness compared with conventional MN alone. Histologic studies have demonstrated that RF-induced dermal injury can stimulate mixed cellular infiltration, angiogenesis, and granulation tissue formation within several days following treatment [23].

Compared with many laser systems, insulated RF MN can produce localized dermal injury while largely sparing the epidermis, thereby reducing the risk of undesirable side effects such as persistent erythema, postinflammatory pigmentation changes, or scarring.

6. Biomaterials in skin regeneration and rejuvenation

6.1 Regenerative medicine in dermatology

Regenerative medicine is an evolving field aimed at restoring the structure and function of damaged tissues through biological repair, replacement, or regeneration [24]. In dermatology, regenerative strategies focus on repairing injured or aging skin, promoting tissue remodeling, and restoring normal physiological function [25]. Because the skin is the body's largest organ and serves as the primary barrier against environmental insults, maintaining its structural integrity is essential for overall health [26].

Skin damage may occur as a result of trauma, chronic disease, aging, or environmental stressors such as ultraviolet radiation and pollution. Traditional dermatologic therapies often focus primarily on symptom management or superficial correction of cosmetic concerns. In contrast, regenerative approaches aim to address the underlying structural damage by stimulating cellular repair, ECM reconstruction, and tissue regeneration [27].

Recent advances in regenerative dermatology have introduced several biological therapies capable of promoting skin repair and rejuvenation. These include stem cell-based therapies, platelet-rich plasma (PRP), extracellular vesicles such as exosomes, polydeoxyribonucleotide (PDRN), and scaffold-based biomaterials. Such therapies

have demonstrated promising potential in accelerating wound healing, improving skin quality, and restoring normal tissue architecture [28].

7. Biomaterial-based strategies for skin regeneration

Within regenerative dermatology, several biomaterials have emerged as key therapeutic tools. These materials can either deliver biological signals that stimulate cellular activity or provide structural frameworks that guide tissue regeneration. Among the most widely investigated biomaterials are PRP, exosomes, PDRN, and scaffold-based biomaterials [28].

7.1 PRP

Platelet-rich plasma is an autologous blood-derived product obtained through centrifugation of whole blood, resulting in a concentrated suspension of platelets. PRP contains numerous growth factors and cytokines, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) [29].

These bioactive molecules stimulate several regenerative processes, including fibroblast proliferation, angiogenesis, and collagen synthesis, all of which are essential for effective wound healing and tissue remodeling. Clinically, PRP has been applied in the management of chronic wounds, acne scars, and photoaging, where it may enhance dermal regeneration and improve skin quality.

Despite these benefits, variability in PRP preparation methods – including differences in platelet concentration, leukocyte content, and activation protocols – can influence therapeutic outcomes. As a result, further standardization of preparation techniques remains an important area of research.

7.2 Exosomes

Exosomes are nanoscale extracellular vesicles secreted by various cell types, including mesenchymal stem cells. These vesicles typically range from 30 to 150 nanometers in diameter and contain a variety of biologically active molecules, such as micro-RNA, messenger RNA, proteins, and lipids [30].

Through these molecular cargos, exosomes serve as important mediators of intercellular communication, influencing cellular proliferation, inflammation, and ECM remodeling. In the context of skin regeneration, exosomes have been shown to regulate fibroblast activity, collagen synthesis, angiogenesis, and immune modulation [31].

Clinically, exosome-based therapies have been investigated for skin rejuvenation, wound healing, and pigmentation disorders. Compared with cell-based therapies, exosomes offer several potential advantages, including lower immunogenicity, improved safety profiles, and easier storage and standardization [32].

Emerging evidence also suggests that exosomes may contribute to pigmentation regulation. In conditions such as vitiligo, exosome-derived signaling molecules may promote melanocyte activation and melanogenesis, thereby supporting repigmentation processes [33].

7.3 PDRN

Polydeoxyribonucleotide is a DNA-derived biomaterial typically obtained from salmon sperm DNA fragments. PDRN exerts its biological effects primarily through the activation of the adenosine A2A receptor and the stimulation of the nucleotide salvage pathway [34].

These mechanisms promote several regenerative processes, including angiogenesis, fibroblast proliferation, collagen synthesis, and antiinflammatory activity. PDRN has, therefore, been investigated in various clinical applications involving tissue repair, including wound healing, skin rejuvenation, and the treatment of chronic ulcers.

By enhancing cellular metabolism and improving microvascular circulation, PDRN may help restore tissue homeostasis and accelerate the repair of damaged skin structures.

7.4 Scaffold-based biomaterials

Scaffolds represent another important category of regenerative biomaterials. These materials may be derived from natural or synthetic sources and are designed to provide three-dimensional frameworks that mimic the architecture of the ECM.

Scaffold structures support cell adhesion, migration, proliferation, and differentiation, thereby guiding organized tissue regeneration. In addition to providing mechanical support, scaffolds can also function as delivery platforms for biologically active substances such as PRP, exosomes, or PDRN.

Experimental studies have demonstrated the regenerative potential of scaffold–based biomaterials. For instance, Hsieh and colleagues investigated hair regeneration using a supercritical carbon dioxide-processed porcine acellular dermal matrix scaffold in a murine model. In this study, C57BL/6 mice received injections of the acellular dermal matrix scaffold either alone or in combination with PRP. The results demonstrated increased hair follicle formation and hair density in animals treated with the scaffold. Furthermore, the combination of scaffold and PRP produced synergistic regenerative effects, suggesting that scaffold structures may enhance the biological activity of growth factor-based therapies [35].

8. Clinical evidence for regenerative synergy: Channels and biomaterials

In recent years, the integration of energy-based devices (EBDs) with regenerative biomaterials has become increasingly popular in esthetic and regenerative dermatology. Fractional lasers, MN, and RF devices can create controlled microchannels within the skin, enhancing the delivery of topically applied biomaterials while simultaneously inducing controlled microinjury that stimulates collagen remodeling [28].

Although this combined approach has gained widespread clinical use, the number of published studies evaluating these synergistic effects remains relatively limited.

8.1 Energy-assisted delivery of PRP

Several clinical studies have investigated the combination of PRP with fractional laser treatments. Gala and colleagues compared fractional laser treatment alone with combined fractional laser and PRP therapy for the treatment of acne scars using a split-face study design. Both treatment modalities produced improvements in scar depth; however, the side treated with combined PRP and fractional CO_2 laser demonstrated significantly greater improvement [36].

Similarly, Abdel–Hamid and colleagues evaluated the effects of Er:YAG fractional laser-assisted delivery of PRP compared with MN combined with PRP for the treatment of localized stable vitiligo. Both treatment methods induced repigmentation, but the fractional Er:YAG laser combined with PRP produced superior outcomes [37].

Another study conducted by Kadry and colleagues assessed the efficacy of fractional CO_2 laser combined with PRP versus intradermal PRP injection in patients with stable nonsegmental vitiligo. The results demonstrated that laser-assisted PRP delivery achieved greater repigmentation, whereas fractional CO_2 laser treatment alone produced minimal improvement [38].

8.2 Energy-assisted delivery of exosomes

Exosomes have also been investigated as adjunctive therapies in energy-assisted regenerative treatments. Park and colleagues conducted a randomized clinical study comparing laser-assisted delivery of exosomes with laser treatment alone for facial scars and skin rejuvenation. Patients receiving adjunctive exosome therapy demonstrated greater short-term improvements in scar appearance, as well as improvements in pigmentation uniformity, erythema, pore size, and fine wrinkles [39].

Histologic evidence supporting the regenerative effects of exosome-assisted treatments has also been reported. In a case study involving MN followed by topical exosome application, histological analysis performed eight weeks after treatment revealed substantial remodeling of the dermo-epidermal junction (DEJ). Significant increases were observed in rete ridge formation, epidermal thickness, basal keratinocyte density, and dermal collagen density, indicating enhanced regenerative activity without evidence of inflammation or fibrosis [40].

8.3 Histologic evidence from laser-assisted exosome studies

Additional histological investigations (Study I) (**Figure 1**) conducted in our clinic have evaluated regenerative responses following treatment with a 2,910-nm erbium laser, both with and without adjunctive exosome (Exocake, Bionet Therapeutics Corp., Taiwan) application. Tissue sections stained with Masson's trichrome (**Figure 2**) and Verhoeff–Van Gieson (**Figure 3**) demonstrated enhanced deposition of collagen and elastin in areas receiving the combined therapy compared with sites treated with the laser alone. Quantitative assessment further showed a 50% increase in type III collagen production in regions treated with the 2,910-nm laser alone, whereas areas receiving laser treatment followed by exosome delivery exhibited an approximately 12-fold increase in type III collagen at six weeks posttreatment (**Figure 4**).

Figure 1.
Histological assessment of regenerative responses following 2,910-nm erbium laser treatment, with and without adjunctive exosome application.

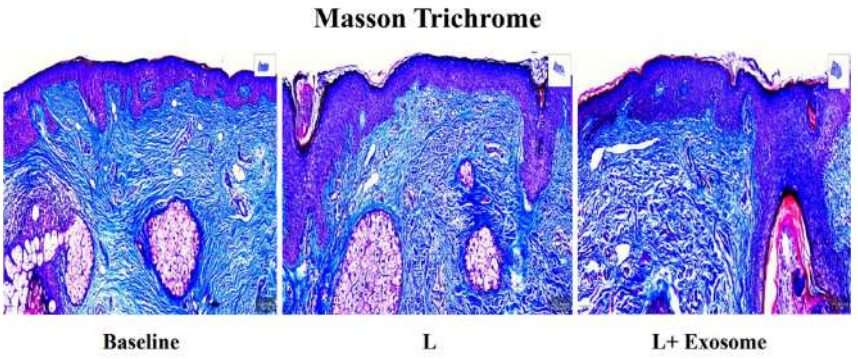

Figure 2.
Masson's trichrome staining across baseline, laser (L), and laser combined with exosome (L + exosome) groups. Compared to baseline, treatment L increases collagen density, while L + exosome shows the most significant accumulation and organization.

Additional histologic observations (Study I) (**Figure 5**) were obtained from melasma cases treated using the Reepot laser platform**.** Immunohistochemical staining with S-100 revealed a reduction in melanocyte dendritic structures after laser therapy, with a more pronounced decrease observed when exosomes (Exocake, Bionet Therapeutics Corp., Taiwan) were applied in conjunction with laser treatment (**Figure 6**). Moreover, type IV collagen expression at the basement membrane increased, suggesting partial regeneration of DEJ integrity (**Figures 7** and **8**).

Early histologic evaluation (Study II) performed two weeks after treatment also demonstrated accelerated wound healing in sites treated with 2,910-nm erbium laser therapy combined with exosomes (ExoCoBio Inc., Korea) and natural collagen scaffolds (Collagen ADM Scaffold, Acro Biomedical Co., Ltd., Taiwan). These specimens showed enhanced epidermal regeneration, increased neocollagenesis, and

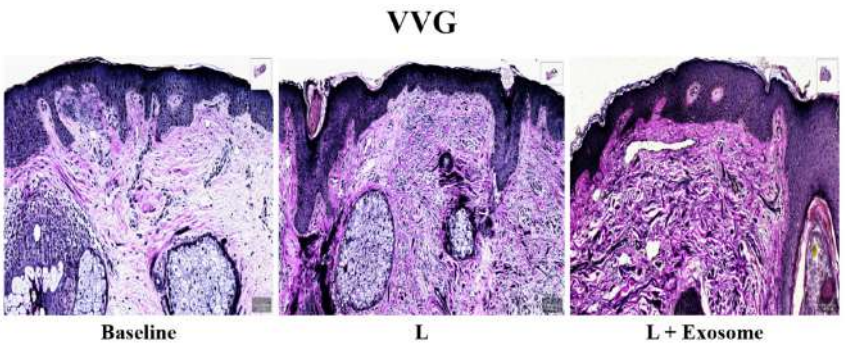

Figure 3.
Verhoeff–Van Gieson (VVG) staining for elastic fiber distribution across baseline, laser (L), and laser + exosome groups. Compared to baseline, treatment L shows an increase in elastic fiber staining. The L + exosome group exhibits a more significant increase in fiber density and structural organization.

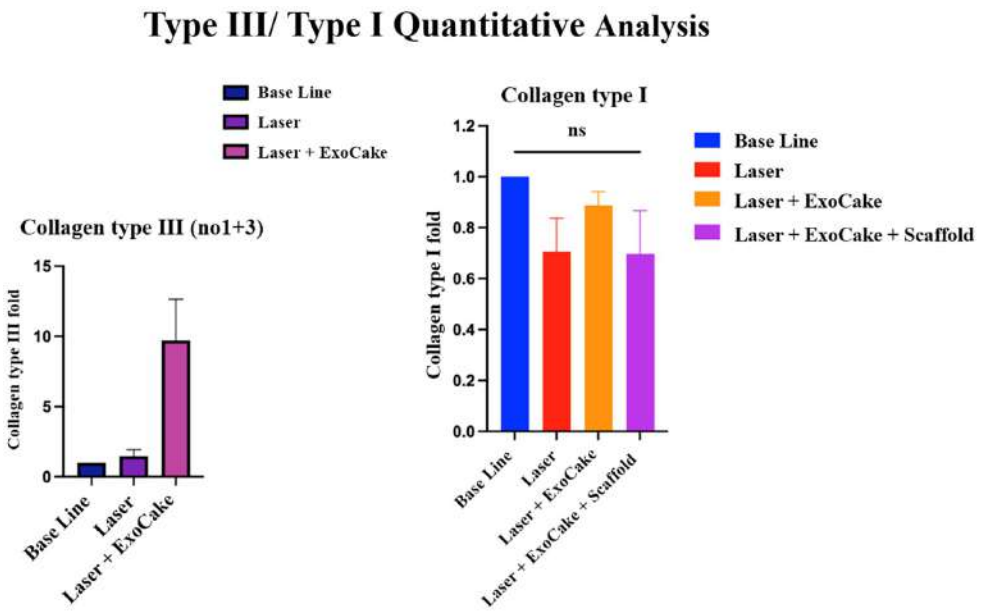

Figure 4.
Quantitative analysis of collagen type III and collagen type I expression levels across different treatment groups. Bar graphs showing collagen expression at 6 weeks. (Left) A 50% increase in type III collagen at six weeks was measured after laser treatment alone, while a 12-fold increase in type III when exosome is combined. (Right) compared to baseline, type I collagen showed reduction (ns) across all groups. Results indicate the treatment specifically promotes type III collagen upregulation.

the development of newly organized medium-sized vascular structures when the scaffold was combined (**Figure 9**), indicating active tissue remodeling and vascular regeneration.

Based on these observations, we propose that the vascular regeneration observed at two weeks (Study II) and the reversal of the type III/I collagen ratio at six weeks (Study I) represent regenerative phenomena that have not been previously described

Figure 5.
Histological observations from melasma cases treated with the Reepot laser platform.

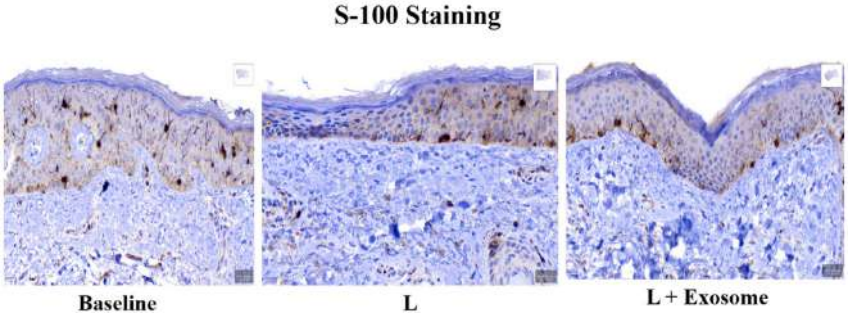

Figure 6.
Immunohistochemical staining of S-100 across different treatment groups: BASE LINE, laser only (L), and laser combined with exosome (L + exosome). Compared to BASELINE, treatment L shows a significant decrease in melanocytic dendrites at six weeks. The L + exosome group exhibits an even more pronounced reduction, suggesting a stronger inhibitory effect.

in studies examining microinjury induced by fractional ablative lasers. These effects may result from the formation of optimal therapeutic channels, characterized by a controlled coagulation zone of approximately 20–40 μm and laser–induced membrane stretching generated by the high-frequency 5,000 Hz delivery of the 2,910-nm laser. Such parameters may facilitate efficient penetration and retention of a large quantity of exosomes and/or scaffold materials, thereby providing both potent biological signaling and an appropriate ECM environment to recruit stem cells with subsequent partial tissue engineering.

Collectively, these findings suggest that precisely engineered therapeutic channels, when combined with targeted biomaterial delivery, may enhance stem cell recruitment, ECM remodeling, and vascular regeneration, ultimately supporting advanced strategies for regenerative tissue engineering in dermatological applications.

8.4 Energy-assisted delivery of polynucleotides

Polynucleotide-based biomaterials have also been explored in combination with EBDs. Gulfan and colleagues evaluated the efficacy of MN radio frequency combined

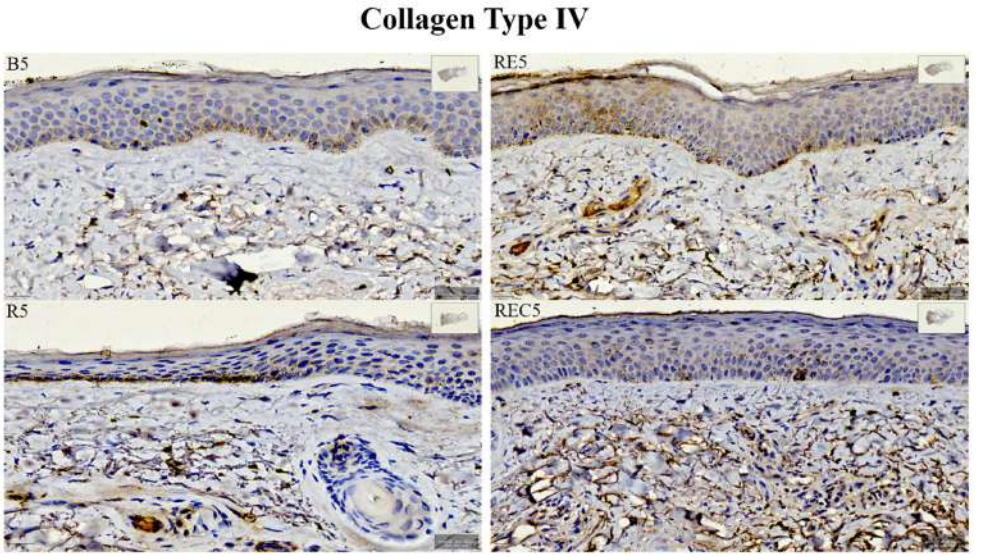

Figure 7.
Immunohistochemical staining of collagen type IV in skin tissues. Representative micrographs across experimental groups: B5 (baseline), R5 (laser only), RE5 (laser + exosome), and REC5 (laser + exosome + scaffold).

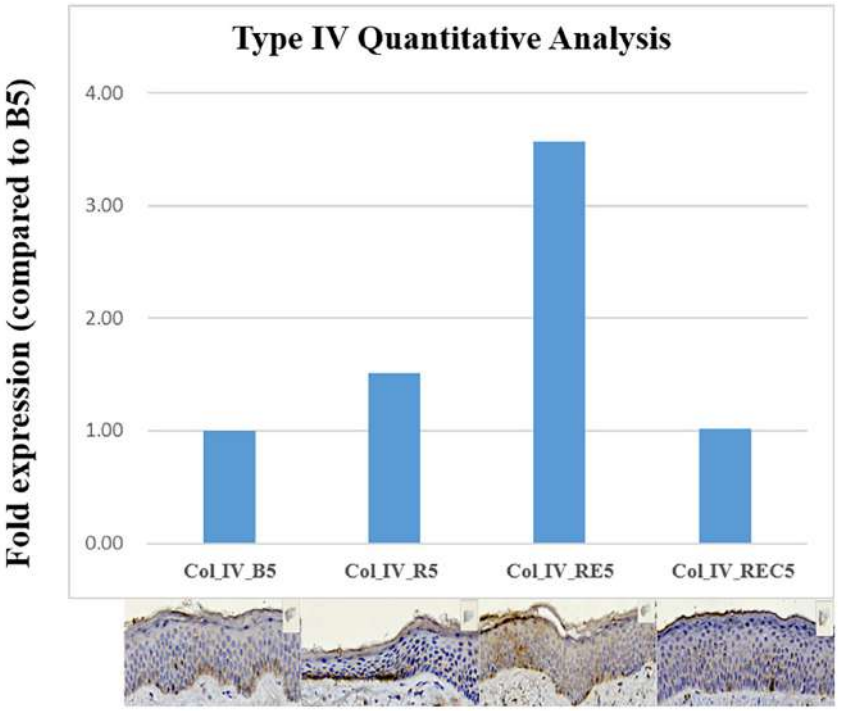

Figure 8.
Quantitative analysis and IHC staining of collagen type IV. Compared to baseline, laser-only treatment increases expression, while laser + exosome shows the most significant 3.5-fold increase. The addition of the scaffold (laser + exosome + scaffold) does not show a significant increase in expression.

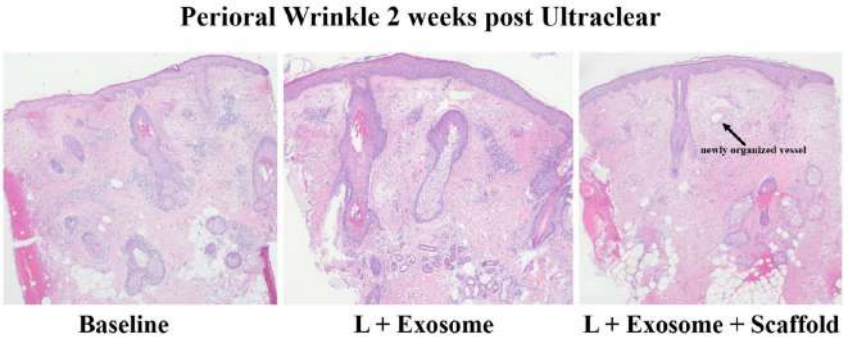

Figure 9.
Histological evaluation of wound healing in perioral wrinkles. Representative H&E staining images at two weeks post – ultraclear treatment across baseline, l + exosome, and l + exosome + scaffold groups. Compared to baseline, the l + exosome group shows significantly faster wound healing. The l + exosome + scaffold group exhibits even further accelerated healing with enhanced epidermal maturation, decreased dermal inflammation, and new medium sized vessel formation.

with polynucleotides for the treatment of melasma. Their results indicated that the combined therapy was not significantly superior to MNRF alone, suggesting that further research is required to clarify the potential benefits of this combination [41].

8.5 Energy-assisted delivery of scaffold materials

Energy-assisted delivery technologies have also been applied to the administration of scaffold-related biomaterials. Choi and colleagues investigated a pneumatic-mechanical microneedle system ("fusion tip") designed to facilitate transcutaneous delivery of fibroblast-stimulating substances such as small-particle hyaluronic acid, large-particle hyaluronic acid, calcium hydroxylapatite, and poly-L-lactic acid (PLLA) [42].

The study demonstrated the successful delivery of most biomaterials, particularly with deeper needle penetration. The pneumatic-mechanical microneedle system enhanced the delivery of small-particle hyaluronic acid and PLLA, both immediately after treatment and during follow-up evaluation.

Another clinical study conducted by Cheng and colleagues evaluated the synergistic effects of microneedle-delivered ECM compounds combined with RF for the treatment of periorbital wrinkles. Participants receiving the combined treatment showed greater improvements in wrinkle reduction, skin elasticity, and dermal thickness compared with MN alone, further supporting the concept of synergistic regenerative effects between biomaterials and EBDs [43].

9. Conclusion

With the rapid advancement of biomaterial science, esthetic medicine is transitioning from conventional remodeling approaches toward regenerative esthetics. The integration of biomaterials with energy-based transdermal delivery systems represents a promising strategy for enhancing skin regeneration. However, the success of energy-based transdermal delivery of topical biomaterials depends on

the creation of effective therapeutic channels that permit the delivery of adequate biomaterial concentrations at therapeutic levels.

Scientific evidence indicates that ablative fractional lasers generate deeper and more sustained microchannels, particularly when channel properties are optimized to enhance transchannel delivery. Beyond the structural characteristics of these channels induced by ablative thermal effects, the mode of energy emission also plays a critical role in influencing the mechanisms by which topically applied agents are delivered.

Furthermore, successful clinical application relies not only on the precise selection of energy parameters tailored to specific channel properties but also on the accurate dosing of biomaterials, guided by robust cellular and histological evidence. Such an evidence-based approach is essential for optimizing therapeutic outcomes and advancing the predictability of regenerative esthetic treatments.

Acknowledgements

The author acknowledges the use of ChatGPT for language polishing of the manuscript.

Author details

Carl K.L. Cheng
Haute Beauté Skin Clinic, Taipei, Taiwan

*Address all correspondence to: dermacarl@gmail.com

References

[1] Zaleski-Larsen LA, Fabi SG. Laser-assisted drug delivery. Dermatologic Surgery. 2016;**42**(8):919–931. DOI: 10.1097/DSS.0000000000000556

[2] Danish Environmental Protection Agency. Dermal absorption of pesticides—evaluation of variability and prevention. Pesticides Research No. 124, Version 1.0. Copenhagen: Danish EPA; 2009. Available from: https://mst.dk/publikationer/2009/oktober/dermal–absorption–of–pesticides–evaluation–of–variability–and–prevention [Accessed: 2015–October–30]

[3] Liu X, Grice JE, Lademann J, et al. Hair follicles contribute significantly to penetration through human skin only at times soon after application as a solvent-deposited solid in man. British Journal of Clinical Pharmacology. 2011;**72**(5):768–774. DOI: 10.1111/j.1365-2125.2011.04022.x

[4] Wu CH, Gittleman JI. Laser-induced surface diffusion. Journal of Applied Physics. 1984;**55**:2928–2934

[5] Liu C, Gong P, Liang Y, et al. The application of gold nanorods for photothermal therapy of ovarian cancer. Medžiagotyra. 2020; **26**:243–248

[6] Li Z, Shao J, Luo Q, et al. Cell-borne 2D nanomaterials for efficient cancer targeting and photothermal therapy. Biomaterials. 2017;**133**:37–48

[7] Bäuerle D, Luk'yanchuk B, Piglmayer K. On the reaction kinetics in laser-induced pyrolytic chemical processing. Applied Physics A. 1990;**50**:385–396

[8] Bezemer R, Heger M, van den Wijngaard JVD, et al. Laser-induced (endo)vascular photothermal effects studied by combined brightfield and fluorescence microscopy in hamster dorsal skin fold venules. Optics Express. 2007;**15**:8493–8506

[9] Brisson P. Percutaneous absorption. Canadian Medical Association Journal. 1974;**110**(10):1182–1185

[10] Ali FR, Al Niaimi F. Laser-assisted drug delivery in dermatology: From animal models to clinical practice. Lasers in Medical Science. 2016;**31** (2):373–381

[11] Zhao Y, Voyer J, Li Y, et al. Laser microporation facilitates topical drug delivery: A comprehensive review about preclinical development and clinical application. Expert Opinion on Drug Delivery. 2022;**20**:31–54

[12] Oni G, Brown SA, Kenkel JM. Can fractional lasers enhance transdermal absorption of topical lidocaine in an in vivo animal model? Lasers in Surgery and Medicine. 2012;**44**(2):168–174

[13] Lippert J, Smucler R, Vlk M. Fractional carbon dioxide laser improves nodular basal cell carcinoma treatment with photodynamic therapy with methyl 5-aminolevulinate. Dermatologic Surgery. 2013;**39** (8):1202–1208

[14] Haak CS, Bhayana B, Farinelli WA, et al. The impact of treatment density and molecular weight for fractional laser-assisted drug delivery. Journal of Controlled Release 2012; **163**:335–341

[15] Haedersdal M, Sakamoto FH, Farinelli WA, et al. Pretreatment with ablative fractional laser changes kinetics and biodistribution of topical 5-aminolevulinic acid (ALA) and methyl aminolevulinate (MAL). Lasers in Surgery and Medicine. 2014;**46**: 462–469

[16] Erlendsson AM, Doukas AG, Farinelli WA, et al. Fractional laser-assisted drug delivery: Active filling of laser channels with pressure and vacuum alteration. Lasers in Surgery and Medicine. 2016;**48**:116–124

[17] Haak CS, Christiansen K, Erlendsson AM, et al. Ablative fractional laser enhances MAL-induced PpIX accumulation: Impact of laser channel density, incubation time and drug concentration. Journal of Photochemistry and Photobiology B: Biology. 2016;**159**:42–48

[18] Banzhaf CA, Thaysen-Petersen D, Bay C, et al. Fractional laser-assisted drug uptake: Impact of time-related topical application to achieve enhanced delivery. Lasers in Surgery and Medicine. 2017;**49**:348–354

[19] Olesen UH, Mogensen M, Haedersdal M. Vehicle type affects filling of fractional laser-ablated channels imaged by optical coherence tomography. Lasers in Medical Science. 2017;**32**(3):679–684

[20] Shauly O, Marxen T, Menon A, et al. Radiofrequency microneedling: Technology, devices, and indications in modern plastic surgery practice. Aesthetic Surgery Journal Open Forum. 2023;**5**:ojad100

[21] Hantash BM, Renton B, Berkowitz RL, et al. Pilot clinical study of a novel minimally invasive bipolar microneedle radiofrequency device. Lasers in Surgery and Medicine. 2009;**41**:87–95

[22] Zheng Z, Goo B, Kim DY, et al. Histometric analysis of skin-radiofrequency interaction using a fractionated microneedle delivery system. Dermatologic Surgery 2014;**40**:134–141

[23] Ramaut L, Hoeksema H, Pirayesh A, et al. Microneedling: Where do we stand now? A systematic review. Journal of Plastic, Reconstructive & Aesthetic Surgery. 2018;**71**:1–14

[24] Mao AS, Mooney DJ. Regenerative medicine: Current therapies and future directions. Proceedings of the National Academy of Sciences of the United States of America. 2015;**112**(47):14452–14459

[25] Shimizu Y, Ntege EH, Sunami H, et al. Current regenerative medicine-based approaches for skin regeneration: A review of literature and clinical applications in Japan. Regenerative Therapy. 2022;**21**:73–80

[26] Parrado C, Mercado Saenz S, Perez Davo A, et al. Environmental stressors on skin aging: Mechanistic insights. Frontiers in Pharmacology. 2019;**10**:759

[27] Fadilah NI, Mohd Abdul Kader Jailani MS, Badrul Hisham MAI, et al. Cell secretomes for wound healing and tissue regeneration: Next-generation acellular-based tissue-engineered products. Journal of Tissue Engineering. 2022;**13**:20417314221114273. DOI: 10.1177/20417314221114273

[28] Alves NSD, Reigado GR, Santos M, et al. Advances in regenerative medicine-based approaches for skin regeneration and rejuvenation.

Frontiers in Bioengineering and Biotechnology. 2025;**13**:1527854

[29] Wu WS, Chen LR, Chen KH, et al. Platelet-rich plasma (PRP): Molecular mechanisms, actions and clinical applications in human body. International Journal of Molecular Sciences. 2025;**26**(21):10804

[30] Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. Science. 2020;**367**:6478

[31] Fang W, Wang G, Lin L, Ajoolabady A, Ren J. Extracellular vesicles in skin health and diseases. Life Sciences. 2025;123813. DOI: 10.1016/j.lfs.2025.123813

[32] Tan F, Li X, Wang Z, et al. Clinical applications of stem cell-derived exosomes. Signal Transduction and Targeted Therapy. 2024;**9**:17

[33] Flemming JP, Wermuth PJ, Mahoney MG. Extracellular vesicles in the skin microenvironment: Emerging roles as biomarkers and therapeutic tools in dermatologic health and disease. Journal of Investigative Dermatology. 2024;**144**(2):225–233. DOI: 10.1016/j.jid.2023.08.024

[34] Akaberi SM, Sharma K, Ahmadi-Ashtiani HR, et al. Polydeoxyribonucleotide in skincare and cosmetics: Mechanisms, therapeutic applications, and advancements beyond wound healing and anti-aging. Journal of Skin Stem Cell. 2025;**12**:e159728

[35] Gu C, Feng J, Waqas A, et al. Technological advances of 3D scaffold-based stem cell/exosome therapy in tissues and organs. Frontiers in Cell and Developmental Biology. 2021;**9**:709204. DOI: 10.3389/fcell.2021.709204

[36] Galal O, Tawfik AA, Abdalla N, Soliman M. Fractional CO2 laser versus combined platelet-rich plasma and fractional CO2 laser in treatment of acne scars: Image analysis system evaluation. Journal of Cosmetic Dermatology. 2019;**18**(6):1665–1671

[37] Abdel-Hamid S, Ibrahim HM, Hameed AM, Hegazy EM. Effectiveness of fractional erbium-YAG laser, microneedling, and platelet-rich plasma in localized stable vitiligo: Randomized clinical trial. Archives of Dermatological Research. 2024;**316**(7):399. DOI: 10.1007/s00403-024-03035-8

[38] Kadry M, Tawfik A, Abdallah N, Badawi A, Shokeir H. Platelet-rich plasma versus combined fractional carbon dioxide laser with platelet-rich plasma in the treatment of vitiligo: A comparative study. Clinical, Cosmetic and Investigational Dermatology. 2018;**11**:551–559. DOI: 10.2147/CCID.S178817

[39] Park JY, Park JH. Randomized clinical study of laser-assisted delivery of exosome boosters for postoperative facial scars and facial rejuvenation. Life (Basel). 2026;**16**(2):217. DOI: 10.3390/life16020217

[40] Lee YS. Preliminary histological evidence of epidermal and DEJ remodeling with microneedling-assisted topical exosome therapy: A single-subject case report. Clinical, Cosmetic and Investigational Dermatology. 2025;**18**:2377–2385. DOI: 10.2147/CCID.S542022

[41] Gulfan MCB, Wanitphakdeedecha R, Wongdama S, et al. Efficacy and safety of using noninsulated microneedle radiofrequency alone versus in

combination with polynucleotides for the treatment of melasma: A pilot study. Dermatologic Therapy. 2022;**12**(6). DOI: 10.1007/s13555-022-00728-8

[42] Choi S, Parmar J, Abrishami P, Mosher M, Wu DC. A histological study of a novel pneumatic-mechanical microneedle-assisted topical cutaneous delivery system. Dermatologic Surgery. 2025;**51**(9S):S44–S48

[43] Cheng H, Zhang R, Zhuo F. Synergistic effect of microneedle-delivered extracellular matrix compound and radiofrequency on periorbital wrinkles. Frontiers in Medicine. 2022;**9**:900784. DOI: 10.3389/fmed.2022.900784