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MADE SCIENTIFIC

A MADE SCIENTIFIC RESEARCH REPORT · PREPARED IN THE CONTEXT OF ARIZONA AESTHETICS

# MSC-Derived Secretome & Exosomes in Aesthetic and Regenerative Medicine

A scientific evidence review of mesenchymal stromal cell secretome for hair restoration, skin rejuvenation, and regenerative wellness applications.

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Prepared by Made Scientific · July 8, 2026

# Contents

# Executive Summary

Mesenchymal stromal cells (MSCs) have emerged as a cornerstone of regenerative medicine, initially investigated for their potential to differentiate into specialized tissue types. Over the past two decades, a fundamental shift in understanding has occurred: the therapeutic benefit of MSCs derives not from cellular engraftment but from the rich mixture of bioactive factors they secrete into their surrounding environment. This secreted material, collectively termed the MSC secretome, comprises soluble proteins (growth factors, cytokines, chemokines, and extracellular matrix components) and membrane-bound extracellular vesicles (EVs), including exosomes and microvesicles. These secreted molecules orchestrate tissue repair through multiple convergent mechanisms, including immunomodulation, angiogenesis, reduction of fibrosis, anti-apoptotic signaling, and activation of resident progenitor cells. For aesthetic medicine and regenerative wellness, the secretome offers a cell-free, acellular approach that circumvents key safety concerns associated with live-cell therapies while providing an off-the-shelf product platform suitable for topical, intradermal, or injectable administration.

Extracellular vesicles, particularly exosomes (30–150 nm diameter vesicles of endosomal origin), represent a specialized component of the broader secretome. These vesicles carry a protected cargo of proteins, lipids, messenger RNAs, microRNAs, and other regulatory molecules that can be transferred between cells, modulating recipient cell behavior. Preclinical studies demonstrate that MSC-derived EVs promote dermal papilla cell proliferation in hair follicles, enhance collagen synthesis and matrix remodeling in photoaged skin, and suppress inflammatory pathways in multiple tissue contexts. The molecular mechanisms involve activation of Wnt/β-catenin and vascular endothelial growth factor (VEGF) signaling, delivery of pro-regenerative microRNAs, and polarization of macrophages toward anti-inflammatory phenotypes.

For hair restoration, preclinical evidence from rodent models shows that MSC-secretome and EV preparations can prolong the anagen (growth) phase of follicular cycling, increase hair density and shaft thickness, and enhance vascularization of the follicular niche. Early-stage human case series and small clinical trials, primarily from South Korea and China, report increases in hair density ranging from 14 to 29 percent and improvements in hair thickness of 6 to 28 micrometers following topical or intradermal administration of MSC-conditioned medium over 12 to 16 weeks, with no serious adverse events documented. In skin rejuvenation, preclinical models of ultraviolet-induced photoaging demonstrate that MSC-secretome reduces wrinkle depth, increases dermal thickness, and elevates type I collagen expression while suppressing matrix metalloproteinase-1 activity. Human studies remain limited to case series and uncontrolled observations, but collectively suggest improvements in skin elasticity, hydration, and subjective appearance scores.

The tissue source of MSCs profoundly influences secretome composition and functional potency. Wharton's jelly, the gelatinous connective tissue of the neonatal umbilical cord, provides MSCs with intrinsic advantages over adult-tissue sources such as bone marrow or adipose tissue. Neonatal umbilical-cord MSCs exhibit higher proliferative capacity, longer telomeres, and lower senescence

rates, enabling robust expansion to the cell numbers required for industrial-scale secretome production. Comparative studies indicate that Wharton's jelly MSCs produce secretomes enriched in pro-angiogenic, anti-inflammatory, and pro-regenerative factors. The neonatal origin also minimizes donor-to-donor variability and environmental exposure, supporting batch-to-batch consistency in manufacturing.

All MSC-derived secretome and EV products currently available in the United States are classified by the Food and Drug Administration as biological products and drugs requiring licensure through a Biologics License Application. No secretome or exosome product is FDA-approved for cosmetic or therapeutic use in aesthetic medicine. Products marketed as cosmetic ingredients or research-use-only (RUO) materials may not bear disease-treatment claims. Aesthetic practitioners must operate within this regulatory framework, clearly distinguishing investigational applications from approved therapies.

**What this report covers:** This Made Scientific report provides a rigorous, evidence-grounded overview of MSC-derived secretome and extracellular vesicles for aesthetic, cosmetic, and regenerative-wellness applications. It describes the biological rationale for secretome use, the scientific advantages of the Wharton's jelly cell source, preclinical and early clinical evidence in hair restoration and skin rejuvenation, adjacent regenerative-wellness applications, the regulatory and safety landscape, and the general industry framework for cGMP manufacturing and quality control.

CHAPTER 0

# What Is the MSC Secretome? Biology, Cargo, and Mechanisms

Mesenchymal stromal cells (MSCs) have been studied intensively for their regenerative potential, initially with the assumption that their benefit derived from direct cell engraftment and differentiation into specialized tissue lineages. Over the past two decades, however, the field has reached a consensus that MSCs exert their therapeutic effects primarily through paracrine signaling rather than cell replacement. Upon tissue damage, endogenous MSCs migrate from perivascular niches and create a regenerative microenvironment by secreting bioactive factors and modulating local immune responses. This paracrine activity, collectively termed the "MSC secretome," drives tissue repair through immunomodulation, angiogenesis, reduction of fibrosis, anti-apoptotic signaling, and stimulation of resident progenitor cells. For aesthetic, cosmetic, and regenerative-wellness applications in hair restoration, skin rejuvenation, and wound healing, the secretome offers a cell-free, off-the-shelf alternative to live-cell therapies, with fewer safety concerns such as microvascular occlusion or unintended tumorigenicity.

## Defining the Secretome: Soluble Factors and Extracellular Vesicles

The MSC secretome, also referred to as conditioned medium (CM), comprises two major compartments: (1) soluble proteins, including growth factors, cytokines, and chemokines, and (2) extracellular vesicles (EVs) that encapsulate and transfer proteins, lipids, and genetic material between cells. Soluble factors in the secretome include vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF-β), and numerous interleukins and chemokines. These molecules participate directly in processes such as angiogenesis, fibroblast activation, and matrix remodeling. Extracellular vesicles, a heterogeneous population of membrane-bound nanoparticles, have emerged as particularly important mediators of intercellular communication. EVs transport functional cargo—including messenger RNAs (mRNAs), microRNAs (miRNAs), peptides, cytokines, and bioactive lipids—from donor MSCs to recipient cells, where they modulate gene expression and cellular behavior.

EVs are commonly categorized by size and biogenesis pathway. Exosomes, typically 50 to 200 nanometers in diameter, originate from the endosomal system. Early endosomes mature into late endosomes, which undergo inward budding of the limiting membrane to form multivesicular bodies (MVBs) containing intraluminal vesicles (ILVs). When MVBs fuse with the plasma membrane, ILVs are released into the extracellular space as exosomes. This process is coordinated by the endosomal sorting complex required for transport (ESCRT), a multiprotein machinery composed of ESCRT-0 through ESCRT-III subunits and the Vps4 ATPase. The ESCRT machinery recognizes ubiquitinated cargo on the endosomal membrane, recruits downstream complexes, and drives membrane scission to generate ILVs. MVBs ultimately undergo exocytosis, releasing exosomes. Larger EVs, sometimes termed microvesicles, bud directly from the plasma membrane through outward blistering and are generally 100 to 1,000 nanometers in size. Both populations carry surface markers reflective of their parent cells and cargo reflective of their cellular origin and activation state.

## Cargo Content and Functional Diversity

The cargo within MSC-derived EVs is diverse and tissue-type dependent. Analysis of exosomal RNA from MSCs reveals an abundance of small RNA species, typically less than 300 nucleotides in length, including both mature microRNAs and precursor forms (pri-miRNA and pre-miRNA). Notably, ribosomal RNA species such as 18S and 28S are absent or minimal in MSC exosomes, distinguishing them from whole-cell lysates. The microRNA content is not random; rather, MSCs appear to selectively package miRNAs into exosomes through a regulated sorting process. More than 150 distinct miRNAs have been cataloged in MSC exosomes, and these miRNAs regulate pathways involved in angiogenesis, inflammation, and neurogenesis. Proteomic analysis has identified over 800 gene products in exosomal fractions, encompassing tetraspanins (CD9, CD63, CD81), heat-shock proteins, cytoskeletal proteins, and enzymes involved in metabolism and signaling. Lipidomic studies reveal enrichment of cholesterol, sphingomyelin, and glycerophospholipids in EV membranes, which influence vesicle stability and fusion with recipient cells. Importantly, exosomal cargo composition varies with MSC tissue source (bone marrow, adipose, umbilical cord), culture conditions (oxygen tension, three-dimensional spheroid versus monolayer culture), passage number, and preconditioning stimuli (cytokine priming, mechanical strain). For instance, exosomes from adipose-derived MSCs differ in protein expression and

functional activity compared to those from bone marrow or umbilical cord MSCs, underscoring the importance of source-specific characterization.

## The Paracrine Hypothesis and Mechanisms Relevant to Aesthetics

The paracrine hypothesis posits that the therapeutic benefits of MSCs, including those relevant to aesthetic and regenerative-wellness medicine, are largely mediated by secreted factors rather than by cellular engraftment. Preclinical models have demonstrated that MSC-derived conditioned medium and isolated exosomes recapitulate many of the beneficial effects of live MSCs, including enhanced wound healing, reduced scarring, improved angiogenesis, and mitigation of inflammatory damage. In cutaneous injury models, both MSC-CM and exosomes accelerate re-epithelialization, increase collagen deposition, and modulate fibroblast activity. In models of limb ischemia, exosomal delivery promotes neovascularization and tissue perfusion. These observations support the use of cell-free secretome products in aesthetic applications such as hair follicle regeneration, dermal rejuvenation, and scar revision.

Four core mechanisms underpin the aesthetic and regenerative potential of the MSC secretome:

1. **Angiogenesis**: Secreted VEGF, HGF, and bFGF stimulate endothelial cell proliferation, migration, and tube formation, promoting new capillary growth. Enhanced vascularization improves nutrient delivery and waste removal in aging or damaged skin and supports hair follicle cycling.

2. **Fibroblast Activation and Matrix Remodeling**: Growth factors and exosomal cargo activate dermal fibroblasts to synthesize collagen, elastin, and glycosaminoglycans, thereby restoring dermal thickness and elasticity. Secretome components also modulate matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), balancing matrix degradation and deposition to reduce fibrosis and improve tissue architecture.

3. **Immunomodulation**: MSC-secreted cytokines, including interleukin-10 (IL-10) and TGF-β, shift the local immune environment from pro-inflammatory (M1 macrophages, Th1 responses) toward an anti-inflammatory, pro-regenerative state (M2 macrophages, regulatory T cells). This immunomodulation attenuates chronic inflammation, a driver of skin aging and hair loss.

4. **Anti-Oxidative and Anti-Apoptotic Effects**: The secretome contains enzymes and signaling molecules that reduce oxidative stress and inhibit apoptosis in stressed cells, protecting keratinocytes, fibroblasts, and hair follicle stem cells from damage induced by ultraviolet radiation, reactive oxygen species, or nutrient deprivation.

## Standardization and Characterization: The MISEV Framework

Given the compositional complexity and batch-to-batch variability of EV products, the International Society for Extracellular Vesicles (ISEV) has developed the Minimal Information for Studies of Extracellular Vesicles (MISEV) guidelines to standardize reporting and ensure rigor. MISEV recommends characterizing EVs by multiple orthogonal methods: quantification by at least two techniques (e.g., protein concentration, particle number via nanoparticle tracking analysis, lipid content), global characterization of size and morphology (electron microscopy, dynamic light

scattering), identification of positive markers (CD9, CD63, CD81, heat-shock proteins) by flow cytometry or Western blot, and assessment of expected contaminants (non-vesicular proteins such as albumin, lipoproteins, and ribosomal RNA). MISEV also emphasizes transparent reporting of isolation methods, storage conditions, and pre-analytical variables, and encourages deposition of methods in the EV-TRACK database. Although the MISEV guidelines do not prescribe rigid acceptance criteria, they provide a framework for ensuring reproducibility and comparability across studies. As the field moves toward clinical translation, adherence to MISEV principles will be critical for regulatory submissions and quality assurance in aesthetic and regenerative-wellness products.

In summary, the MSC secretome, composed of soluble growth factors, cytokines, and functionally diverse extracellular vesicles, orchestrates tissue repair through paracrine mechanisms highly relevant to aesthetic medicine. Understanding its biology, cargo diversity, and mechanisms of action lays the foundation for rationally designed, cell-free interventions in skin rejuvenation, hair restoration, and regenerative wellness.

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CHAPTER 1

# Why the Wharton's Jelly (Neonatal) Cell Source Matters

MSC-derived secretomes and EVs are not all equivalent. The donor tissue source, donor age, and manufacturing process profoundly influence the composition, potency, and reproducibility of the final product. Although MSCs can be isolated from practically any vascularized tissue (including bone marrow, adipose tissue, and umbilical cord), evidence from the literature indicates that Wharton's jelly–derived umbilical-cord MSCs (WJ-MSCs) offer several biological and operational advantages for scalable, cell-free aesthetic and regenerative applications.

## Biological Rationale: Neonatal Origin and Developmental Potential

During human fetal development, MSCs first appear in the aorta-gonad-mesonephros (AGM) region and subsequently migrate to the fetal liver, bone marrow, and ultimately populate the gelatinous connective tissue of the umbilical cord known as Wharton's jelly. This neonatal origin confers intrinsic differences in proliferative capacity, telomere length, and functional properties compared with adult-tissue MSCs.

Preclinical studies consistently report that umbilical-cord-derived MSCs demonstrate higher proliferative rates, robust clonogenicity, and longer telomeres than their adult bone-marrow or adipose counterparts. Comparative analyses show that neonatal WJ-MSCs can be expanded for up to passage 10 without loss of multipotent progenitor characteristics, whereas adult bone-marrow MSCs exhibit earlier replicative senescence. Telomerase activity, nearly absent in most adult MSCs, remains more robust in umbilical-cord populations, delaying the onset of senescence-associated β-galactosidase activity and growth arrest.

For secretome-based products, donor senescence is not a trivial concern. Senescent cells produce an altered secretory phenotype characterized by reduced expression of pro-angiogenic growth factors (such as VEGF and basic FGF), diminished extracellular-matrix remodeling proteins, and increased inflammatory cytokines. In aesthetic applications targeting hair follicle vascularization and dermal matrix remodeling, the relative absence of senescent cells in neonatal WJ-MSC cultures translates directly to a more potent, pro-regenerative secretome composition.

## Donor Age and Functional Variability

Donor age significantly impacts MSC number, viability, proliferation rate, and differentiation potential. Investigations comparing adult-derived and child-derived bone-marrow MSCs have revealed reduced colony-forming-unit fibroblast (CFU-F) generation and increased levels of reactive oxygen species, p21, and p53 proteins in samples from elderly donors. Similar age-dependent declines affect adipose-tissue MSCs, with murine and human models showing enhanced apoptotic traits, senescence, and impaired angiogenic and wound-healing properties with advancing donor age.

By contrast, WJ-MSCs are harvested from discarded umbilical-cord tissue at full-term delivery, representing a developmentally young, uniform donor cohort. Gestational age at collection remains a critical selection criterion; evidence suggests that planned selection of starting material from healthy, full-term births (negative for infectious agents including HIV, HBV, HCV, CMV, and parvovirus B19) enables consistent manufacturing input. Importantly, the non-invasive procurement of WJ-MSCs avoids donor-site morbidity and ethical concerns, and sidesteps the functional compromises that may arise when autologous products are derived from patients with comorbidities, medication use, or advanced age.

## Secretome Composition and Potency

The secretory profile of WJ-MSCs is enriched for pro-angiogenic, anti-inflammatory, and matrix-remodeling factors relevant to hair and skin regeneration. Conditioned medium from umbilical-cord MSCs contains extracellular-matrix components (collagen, fibronectin, lumican, periostin), growth factors (basic FGF, TGF-β1, pigment epithelium-derived factor), and diverse cytokines that enhance cellular migration, proliferation, and angiogenesis in vitro and in preclinical wound-healing models. Comparative data suggest that umbilical-cord MSCs possess higher immunoregulatory scores and superior immunosuppressive function than bone-marrow MSCs in mixed lymphocyte reactions and mitogen-induced assays, although direct head-to-head comparisons of secretome composition across tissue sources remain an active area of investigation.

For aesthetic applications, these properties map directly to desired mechanisms: follicular dermal papilla revascularization, perifollicular matrix remodeling, and dermal fibroblast activation. The relative youth and developmental plasticity of WJ-MSCs may underlie the observed potency differences, although secretome composition is also influenced by culture conditions, passage number, and priming stimuli.

## Allogeneic Off-the-Shelf Scalability and Consistency

From a manufacturing standpoint, WJ-MSCs enable an allogeneic, off-the-shelf production model that is difficult to achieve with autologous adult-tissue sources. Umbilical cords represent a freely available, discarded tissue source with planned procurement at delivery, allowing batch-to-batch donor selection based on health, gestational age, and infectious-disease screening. This contrasts sharply with the unpredictable availability and variable quality of autologous bone-marrow aspirates or adipose-tissue lipoaspirates from individual patients.

Industry practice has increasingly moved toward harmonized, xenogeneic-free expansion protocols, employing closed automated bioreactors and cryobanked formulations that eliminate bedside manipulation. Transcriptomic analyses of WJ-MSC manufacturing batches cultured under Good Manufacturing Practice (GMP) conditions demonstrate consistent stability of expression signatures across production stages, supporting the feasibility of reproducible, large-scale secretome and EV manufacturing.

Nevertheless, inherent MSC heterogeneity remains a challenge. Pooling strategies that combine cells from multiple pre-selected, high-performing donors have been explored to reduce donor-dependent variability and improve batch-to-batch immunomodulatory consistency. Such strategies may prove essential for achieving the reproducible EV yields and angiogenic potencies required for clinical-grade aesthetic products, although regulatory frameworks for pooled allogeneic secretomes are still evolving.

In summary, the neonatal origin, low senescence burden, potent secretome profile, and allogeneic scalability of WJ-MSCs position this source as particularly well-suited for secretome and EV production targeting hair restoration and skin rejuvenation. The choice of starting cell source is not merely operational convenience, it is a fundamental determinant of product quality, consistency, and biological activity.

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CHAPTER 2

## Hair Restoration: MSC Secretome and Androgenetic Alopecia

Androgenetic alopecia (AGA), or pattern hair loss, is a common progressive condition affecting both men and women. Conventional therapies include topical minoxidil, oral finasteride, and platelet-rich plasma (PRP) injections. More recently, the secretome of mesenchymal stromal cells (MSCs) and their extracellular vesicles (EVs, commonly called exosomes) have emerged as investigational approaches in hair restoration. Although these materials remain research-use-only (RUO) and no disease-treatment claims are established, preclinical studies and a limited number of early-stage human case series provide insight into potential mechanisms and preliminary safety. This chapter summarizes the mechanistic basis for MSC-derived secretome and exosomes in follicular regeneration, reviews evidence from preclinical models and early clinical reports, and outlines delivery strategies being explored in the aesthetic-medicine setting.

## Mechanistic Rationale for MSC Secretome in Hair Growth

Hair follicle cycling depends on a complex interplay of growth factors, signaling pathways, and cell–cell communication. Key molecular pathways implicated in hair follicle stem cell activation and dermal papilla (DP) cell proliferation include Wnt/β-catenin signaling, vascular endothelial growth factor (VEGF)-mediated angiogenesis, and microRNA-mediated regulation of cell proliferation and differentiation.

**Wnt/β-catenin signaling activation.** Preclinical studies have shown that MSC-derived EVs can carry Wnt ligands (Wnt4, Wnt11) and activate canonical Wnt/β-catenin signaling in target cells. One report demonstrated that human umbilical-cord MSC-derived exosomes transport Wnt4 and Wnt11, promoting cell proliferation and activating β-catenin in recipient cells. In a murine model, cutaneous injection of human dermal-papilla exosomes increased the anagen-to-catagen ratio, stimulated proliferation of outer-root-sheath cells, and elevated β-catenin expression. A similar study using three-dimensional-cultured dermal papilla cells found that EVs from these cultures increased Ki67-positive cells in cultured hair follicles and induced follicle formation in mice implanted with human dermal papilla spheres, effects attributed to activation of Wnt and bone morphogenic protein (BMP) signaling pathways.

**MicroRNA cargo and cell proliferation.** Exosomes contain bioactive microRNAs that regulate proliferation and differentiation of hair follicle stem cells. For instance, research on goat dermal-papilla exosomes identified 34 differentially expressed miRNAs involved in follicle stem cell function. Although direct evidence linking specific miRNAs in human MSC-EVs to AGA treatment is limited, one preclinical study investigated transdermal delivery of miR-218 into the mouse scalp dermis, reporting promotion of dermal papilla cell proliferation and enhanced hair regrowth, suggesting that miRNA-based mechanisms may contribute to follicular regeneration.

**Paracrine growth factors and angiogenesis.** MSC-EVs are known to deliver vascular endothelial growth factor (VEGF), insulin-like growth factor-1 (IGF-1), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β), cytokines that support follicular vascularization and dermal papilla cell activity. In an in vitro study, mouse bone-marrow MSC-EVs promoted proliferation of human dermal papilla cells and induced secretion of VEGF and IGF-1, both of which are essential for sustaining the anagen (growth) phase of the hair cycle. Although these findings derive from preclinical models and cannot be extrapolated directly to human clinical efficacy, they provide a mechanistic framework for understanding how MSC secretome might influence follicular health.

## Evidence From Preclinical Models

The majority of mechanistic data on MSC exosomes in hair regrowth comes from rodent models and ex vivo human follicle cultures. Animal studies demonstrate that intradermal or topical application of MSC-derived EVs can accelerate hair regrowth in depilation-induced mice and improve follicle density and caliber. For example, one study using a depilation-induced mouse model reported that exosomal miR-100 from neural stem cells promoted cell proliferation and hair follicle growth via

activation of the Wnt/β-catenin pathway. Another investigation found that bone-marrow MSC-EVs enhanced dermal papilla cell proliferation and secretion of angiogenic growth factors in vitro.

It is critical to emphasize that preclinical models differ substantially from human physiology, and hair-growth patterns in mice do not fully recapitulate the pathophysiology of androgenetic alopecia in humans. These studies establish proof-of-concept for secretome-based strategies but do not constitute evidence of efficacy or safety in human patients.

## Early Clinical Evidence in Androgenetic Alopecia

A small number of human case series and pilot trials have begun to explore MSC-derived EV therapy in AGA. The evidence base is limited, with most reports falling into evidence-level III or IV (retrospective case series, uncontrolled prospective studies) or evidence-level I-II pilot randomized controlled trials (RCTs) with very small sample sizes. These studies provide preliminary safety data and exploratory outcome measures but do not establish definitive clinical benefit.

**Follicle-derived MSC micrografts.** One open-label study enrolled 78 patients (ages 20 to 60 years) with AGA who received micrografts containing human follicle mesenchymal stem cells (HF-MSCs) and associated EVs. At 12 months, hair density increased significantly by approximately 28 hairs per square centimeter in female pattern hair loss and 30 hairs per square centimeter in male pattern hair loss ($p < 0.05$). Patient satisfaction was reportedly high (80 percent indicating good satisfaction regarding scalp coverage), and minor adverse events included itching, redness, numbness, and headaches, none severe. This study used a combined micrograft and EV approach, making it difficult to isolate the contribution of EVs alone.

**Bone-marrow-derived MSC EVs.** A retrospective open-label series (evidence level IV) evaluated 31 patients with male and female pattern hair loss who received a single intradermal injection of bone-marrow MSC-derived EVs, sometimes combined with microneedling and low-level laser therapy. Responders (definition not uniformly specified) experienced an 11.1 to 24.2 percent increase in hair density over six months. High levels of satisfaction were reported by males (88.9 percent satisfied to extremely satisfied) and females (54.5 percent very satisfied). No severe adverse events were observed; transient swelling or pain was attributed to the microneedling component.

**Umbilical-cord-derived MSC exosomes.** A single-patient prospective interventional study (evidence level II-III) reported that one male with AGA received scalp injections of exosome-rich conditioned medium derived from umbilical cord MSCs. Significant improvements in hair density and thickness were observed at six months, with no serious adverse reactions. The single-case design limits generalizability.

**Commercial humanized and autologous exosome preparations.** A case series described initial experience with both commercial allogeneic (humanized) exosome products and autologous blood-derived exosome preparations administered intradermally for AGA. The authors noted visible improvements in hair density, scalp coverage, and patient satisfaction over the observation period and concluded that exosome therapy was well tolerated. However, this report lacked standardized outcome measures, control groups, and long-term follow-up.

**Plant-extract-containing exosome formulations.** One pilot RCT (evidence level I) evaluated an exosome formulation containing extracts of *Ecklonia cava* (a brown seaweed) and *Thuja orientalis* in 20 males with AGA. Details on outcome measures and duration were limited, but the study represents an early attempt at a controlled trial design. Plant-derived exosome-like nanovesicles remain highly experimental.

Overall, clinical studies to date are small, heterogeneous, and often combine MSC-EV injection with other modalities (microneedling, low-level laser therapy), complicating interpretation. One systematic review noted that exosome therapy "demonstrates promising hair regrowth results that appear broadly comparable to PRP and potentially superior to minoxidil in the short term," but acknowledged that "due to the limited number of small human trials on exosomes, this comparison remains preliminary." Another review concluded that only a few small-scale clinical studies or case series exist, standardized protocols are lacking, and large-scale randomized controlled trials are needed to optimize production, dosing, and combination strategies.

## Delivery Strategies and Administration Protocols

Multiple routes of administration are being explored for MSC secretome and EV delivery to the scalp.

**Intradermal injection.** Direct injection of exosome preparations into the dermis has been the most commonly reported method in case series. Injection allows targeted deposition around hair follicles but may be associated with transient pain, swelling, or bruising.

**Microneedling-assisted topical application.** Microneedling creates microchannels in the stratum corneum, enhancing penetration of topically applied exosomes. Several case series and a scoping review noted that microneedle-based delivery systems improved targeted and uniform deposition, as well as longer retention of exosomes within the dermal layer and around hair follicles, compared to intradermal injections. One report described use of a single-pass microneedle stamp weekly for self-application of a commercial MSC-conditioned medium. Microneedling may reduce discomfort relative to injection but introduces variability in technique and depth.

**Microneedle patches.** Emerging preclinical work has explored microneedle patches incorporating hair-derived microparticles, growth factors (VEGF, basic fibroblast growth factor), and zinc oxide nanoparticles for reactive oxygen species scavenging. These devices are investigational and not yet validated in human AGA trials.

**Treatment protocols.** Early case series commonly report treatment intervals of once monthly for three to four sessions, though regimens vary widely. One practitioner guideline suggested one session per month for four months, with individual variability. The long-term durability of exosome-induced hair regrowth remains unknown. Maintenance protocols have not been established, and whether repeated treatments are necessary to sustain benefit is an area of ongoing investigation.

## Safety Profile and Adverse Events

Across published case series, MSC-derived EV therapies for AGA have been described as generally well tolerated. Reported adverse events are minor and transient, including mild pain or tenderness at injection sites, transient swelling, itching, redness, numbness, and occasional headaches. No severe adverse events (infections, scarring, systemic reactions) have been documented in the small cohorts studied to date. However, the absence of long-term follow-up data and the limited number of treated patients mean that rare or delayed adverse events cannot be excluded.

## Evidence Quality, Regulatory Status, and Research-Use Context

It is essential to emphasize the current limitations of the evidence base. Most human studies are retrospective case series (evidence level IV) or small prospective uncontrolled studies (evidence level II-III). Only one or two reports describe pilot RCTs with control groups. Sample sizes range from single patients to fewer than 80 participants. Outcome measures are heterogeneous (hair density by trichogram, photographic assessment, patient satisfaction scales), and follow-up durations are typically six to 12 months. Standardized protocols for exosome isolation, characterization, dosing, and administration do not yet exist.

MSC-derived secretome and exosome preparations for hair restoration are not approved by the U.S. Food and Drug Administration (FDA) or other regulatory agencies for the treatment of androgenetic alopecia or any hair-loss disorder. These materials are research-use-only (RUO). Aesthetic practitioners exploring these approaches operate within the boundaries of clinical innovation and patient-informed consent. No disease-treatment claims are permissible, and patients must be counseled that these therapies are investigational.

## Conclusion

Preclinical models provide a mechanistic rationale for MSC-derived secretome and exosomes in hair restoration, with evidence implicating Wnt/β-catenin signaling activation, microRNA-mediated regulation of dermal papilla cell proliferation, and paracrine delivery of angiogenic growth factors. Early human case series and pilot trials suggest that intradermal or microneedling-assisted delivery of MSC-EVs may be associated with modest increases in hair density and patient-reported satisfaction over periods of three to 12 months, with a generally favorable short-term safety profile. However, the evidence base remains limited, study designs are heterogeneous, and long-term efficacy and durability are unknown. Large-scale, rigorously controlled randomized trials with standardized product characterization and outcome measures are urgently needed before MSC-EV therapies can be considered a validated intervention for androgenetic alopecia. Until such data become available, these approaches remain firmly in the research and clinical-innovation domain.

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# Skin Rejuvenation and Anti-Aging

Skin aging comprises intrinsic (chronological) and extrinsic (environmental) pathways that converge on structural degradation, reduced barrier function, and altered pigmentation. Chronic ultraviolet (UV) exposure accelerates photoaging through reactive oxygen species (ROS) generation, extracellular matrix (ECM) breakdown, and chronic low-grade inflammation. Mesenchymal stromal cell (MSC)-derived secretome and extracellular vesicles (EVs) have emerged as bioactive platforms for mitigating these processes and restoring skin homeostasis, although all current formulations remain research-use-only (RUO) and are not FDA-approved for cosmetic or therapeutic disease claims.

## Mechanistic Basis: Growth Factors, Cytokines, and Matrix Remodeling

The regenerative potential of MSC-secretome in skin derives from a diverse cargo of soluble factors and EV-encapsulated molecules. Vascular endothelial growth factor (VEGF) promotes angiogenesis, enhancing nutrient and oxygen delivery to aging dermis. Hepatocyte growth factor (HGF) and basic fibroblast growth factor (bFGF) drive fibroblast migration and proliferation, processes central to wound repair and collagen synthesis. Preclinical models demonstrate that MSC-EVs upregulate type I and type III collagen expression in dermal fibroblasts while concurrently suppressing matrix metalloproteinase-1 (MMP-1) activity, thereby shifting the balance from matrix degradation toward deposition and remodeling (context [17], [24]). This dual action addresses both collagen loss and excessive enzymatic breakdown characteristic of photoaged skin.

Additional mechanistic insights come from anti-inflammatory and antioxidant pathways. MSC-EVs attenuate ROS production in UV-irradiated fibroblasts and reduce the inflammatory infiltrate of M1 macrophages, which otherwise amplify MMP expression and collagen fragmentation (context [17]). By promoting a shift from proinflammatory M1 to tissue-reparative M2 macrophage phenotypes, the secretome may dampen chronic inflammation that perpetuates the photoaging cycle (context [26]). In vitro pretreatment with MSC-EVs or fibroblast-derived EVs protected human dermal fibroblasts from UVB-induced cell death, cell cycle arrest, and senescence markers, likely mediated by upregulation of glutathione peroxidase-1 (GPX-1), an antioxidant enzyme, and increased collagen-1 alongside decreased MMP-1 (context [17], [24]).

Furthermore, exosomes facilitate intercellular communication within the dermis, enhancing collagen and elastin synthesis and increasing dermal adipose content, collectively supporting skin's regenerative capacity and structural integrity (context [1]). Elastin production is particularly relevant for maintaining firmness and reducing the appearance of fine lines, although quantitative elastin endpoints in human studies remain limited.

## Preclinical Evidence: Photoaging and Wrinkle Reduction

Animal models of photoaging provide foundational evidence for MSC-EV efficacy. In UV-irradiated nude mice, adipose-derived stem cell (ADSC)-EVs reduced visible skin wrinkles, promoted epidermal cell proliferation, and decreased macrophage infiltration and ROS production (context [17]). Human umbilical cord MSC-EVs and fibroblast-derived EVs similarly protected dermal

fibroblasts from UVB damage in vitro and in vivo, restoring collagen expression and reducing aging-associated protein p53 (context [19], [24]). A secretome-based gel applied once or twice daily to UVB-exposed mice improved ECM structure and reduced senescence markers compared to sunblock controls (context [12], [19]). These findings collectively suggest that MSC-EVs can mitigate photodamage through combined anti-inflammatory, antioxidant, and pro-reparative mechanisms.

Importantly, plant-derived exosome-like nanovesicles (PENs) have also demonstrated anti-photoaging effects, including collagen stimulation and melanin synthesis suppression, although their molecular cargo and potency differ from mammalian MSC-EVs (context [7], [20]). The translational relevance of PENs for aesthetic applications is emerging but remains distinct from MSC-based platforms.

## Clinical Evidence: Split-Face Trials and Case Series

Human clinical data on MSC-EV interventions for facial skin aging are limited to small case series and short-duration split-face studies. A 12-week prospective randomized split-face trial evaluated adipose tissue stem cell-derived exosome solution combined with microneedling for facial aging. Participants received microneedling followed by topical exosome application on one side and a control treatment on the contralateral side. The exosome-treated side demonstrated measurable improvements in skin texture, pore appearance, and patient-reported satisfaction (context [16], [28]). However, the study did not report objective photographic wrinkle scores, melanin indices, or elasticity measurements using standardized devices.

A separate case series of three patients treated with microneedling plus a lyophilized exosome formulation (containing exosomes 0.5%, hyaluronic acid 0.2%, and an activating solution with polydeoxyribonucleotide, hyaluronic acid, and glutathione) focused on pore reduction in the nose and cheek areas. Patients received a single pass with 0.5-mm needles followed by immediate topical exosome application. Qualitative assessment suggested reduced pore visibility and improved skin surface regularity, although no validated pore-diameter metrics or long-term follow-up were provided (context [8], [23]). These preliminary observations support the feasibility and tolerability of combined microneedling and exosome therapy but do not constitute robust efficacy evidence.

## Hyperpigmentation and Melanin Regulation

Preclinical studies indicate that certain EV preparations can modulate melanogenesis. Plant-derived exosome-like nanovesicles from Yam Bean suppressed melanin synthesis in vitro while promoting cellular migration and collagen production, suggesting potential for depigmentation applications (context [7]). Scutellaria baicalensis extract-induced exosomes were reported to improve skin hydration and barrier function in a clinical study involving fine dust exposure, though melanin index changes were not specifically quantified (context [7]). For MSC-EVs, direct human data on melanin reduction remain sparse. The mechanisms by which EVs might influence melanocyte activity likely involve paracrine signaling that modulates tyrosinase expression or melanosome transfer, but controlled clinical trials with objective melanin-index endpoints are lacking.

## Barrier Function and Wound Repair

Beyond aesthetic endpoints, MSC-secretome accelerates cutaneous wound healing. Preclinical models demonstrate that MSC-EVs enhance re-epithelialization, collagen deposition (reported at approximately 60-80% collagen expression or coverage in treated wounds), and angiogenesis (context [9], [13]). In diabetic wound models, EVs combined with hydrogel carriers promoted granulation tissue formation and accelerated closure rates (context [13]). For aesthetic applications, improved barrier function translates to enhanced skin hydration and resilience, relevant for patients with compromised barrier integrity due to photoaging, environmental stress, or inflammatory dermatoses.

Milk-derived exosomes, applied topically twice daily for 28 days in a small cohort (n=31), maintained skin hydration and reduced wrinkle appearance after UV exposure, with no adverse reactions reported (context [25]). This highlights the potential for non-MSC-derived EVs in cosmetic formulations, although potency and cargo composition differ from MSC sources.

## Delivery Methods: Topical Post-Microneedling and Intradermal Injection

Effective delivery of EVs to dermal targets requires overcoming the stratum corneum barrier. Microneedling (using 0.5-1.5 mm needles) creates transient microchannels that enhance permeability, enabling deeper penetration of nanosized vesicles (context [22], [23]). Topical application immediately following microneedling is the most common clinical approach, leveraging the procedure's dual benefit of mechanical stimulation and enhanced absorption. Serum formulations enriched with MSC-EVs are often applied after fractional CO2 laser or radiofrequency therapy for similar barrier disruption (context [22]).

Intradermal injection of exosome solutions, either alone or combined with scaffolds such as calcium hydroxylapatite (CaHA), has been explored in small case series. One report suggested that exosome priming before CaHA injection enhanced biostimulation effects on skin quality, tone, and texture more rapidly than CaHA alone, although the study lacked a placebo-controlled design (context [25]). Dosage optimization studies indicate a wide range of applied particle concentrations ($10^8$ to $10^{11}$ particles per application), with tissue saturation suggested at approximately $10^{10}$ particles/$cm^2$, underscoring the need for standardized protocols (context [22]).

## Evidence Quality and Regulatory Context

The clinical evidence base for MSC-EV interventions in aesthetic skin applications remains early-stage. Most human data derive from uncontrolled case series, single-arm pilot studies, or small split-face trials with subjective outcome measures. Objective endpoints such as validated wrinkle severity scales, quantitative melanin indices, dermoscopic pore measurements, and biomechanical elasticity assessments (cutometry) are underrepresented. Mechanistic understanding is supported by in vitro and animal models, but dose-response relationships, durability of effect, optimal treatment intervals, and patient selection criteria require systematic investigation.

All MSC-EV and secretome formulations discussed herein are classified as RUO materials. They are not approved by the FDA or other regulatory authorities for any disease treatment, including cosmetic indications. Practitioners employing these materials in clinical settings operate under the

aegis of off-label or investigational use, with informed consent obligations to clarify the experimental nature of such interventions. Standardization of manufacturing (cell sourcing, culture conditions, EV isolation methods), analytical characterization (particle size, surface markers, cargo profiling), and release criteria (sterility, endotoxin, mycoplasma, potency assays) remain areas of active development, guided by cGMP frameworks (21 CFR 210/211, 21 CFR 1271) and international consensus guidelines for extracellular vesicle research.

In summary, MSC-derived secretome and EVs demonstrate mechanistic plausibility and encouraging preclinical signals for skin rejuvenation, photoaging mitigation, and barrier repair. Early human case series support feasibility and tolerability, particularly when combined with microneedling. However, robust randomized controlled trials with objective, standardized endpoints are essential to establish efficacy, refine dosing, and define the patient populations most likely to benefit from these emerging RUO platforms.

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CHAPTER 4

# Regenerative Wellness and Adjacent Applications

While hair restoration and skin rejuvenation remain the best-studied aesthetic indications for MSC-derived secretome and EVs, a rapidly growing body of evidence demonstrates potential in adjacent regenerative-wellness applications that extend the scope of an aesthetic practice. These include anti-inflammatory and immunomodulatory uses, intranasal or nebulized delivery for respiratory and systemic wellness, and intra-articular joint applications. All such uses fall under Research Use Only (RUO) framing and require careful distinction between preclinical models and emerging clinical data.

## Anti-inflammatory and Immunomodulatory Mechanisms

The anti-inflammatory and immunomodulatory capacities of MSCs and their secretome form the mechanistic foundation for regenerative wellness. Preclinical studies consistently demonstrate that MSC-derived secretome and EVs modulate immune cell function, particularly polarizing macrophages toward an anti-inflammatory M2 phenotype while suppressing pro-inflammatory M1 activation. These effects are mediated by soluble factors including tumor necrosis factor (TNF)-stimulated gene 6 (TSG-6), stanniocalcin-1 (STC1), and interleukin (IL)-24, alongside microRNAs carried in extracellular vesicles. By influencing multiple immune cell types—monocytes, macrophages, T cells, natural killer cells, and B cells—the secretome helps restore immune homeostasis in inflammatory conditions.

Literature evidence indicates that MSCs require a degree of inflammatory priming or extracellular-matrix stimulation to activate their full immunomodulatory capacity. The secretome's immunosuppressive properties are therefore not constitutive but rather responsive to the local microenvironment, which can vary dynamically in active inflammatory states. This responsiveness underpins the rationale for regenerative-wellness interventions targeting low-grade systemic

inflammation, stress recovery, or post-procedural healing—contexts in which subtle inflammatory signals may benefit from secretome modulation.

### Intranasal and Nebulized Delivery for Systemic and Respiratory Wellness

Intranasal and nebulized routes of administration represent novel delivery formats that may extend secretome therapy beyond topical or injectable aesthetic applications. These routes target the respiratory mucosa and distal airways, offering the potential for localized lung delivery or systemic absorption through the nasal epithelium.

An early-phase clinical pilot in severe COVID-19 pneumonia explored nebulized human adipose-tissue MSC-derived exosomes delivered via mesh nebulizer for five consecutive days. This study demonstrated feasibility and tolerability of the nebulized route, with EVs sized around 100 nm considered suitable for distal lung deposition. Preclinical rodent models of pneumonia have shown relative improvement in survival with nebulized MSC-EV therapy, and mechanistic studies suggest that EVs exert immunomodulatory effects on pulmonary macrophages and epithelial repair pathways. The nebulized format bypasses intravenous administration and may achieve higher local bioavailability at the lung surface.

For aesthetic-medicine practitioners, intranasal or nebulized secretome delivery could be positioned as a wellness adjunct—supporting respiratory mucosal health, post-viral recovery, or systemic anti-inflammatory maintenance—rather than as treatment for active disease. The literature cautions that most clinical data remain in early-stage or pilot testing, and robust efficacy endpoints are not yet established. Practitioners must frame such applications strictly within RUO contexts and avoid disease-treatment claims.

### Intra-articular and Joint-Wellness Applications

Intra-articular delivery of MSC-derived EVs has been explored in preclinical models of osteoarthritis (OA) and, to a lesser extent, rheumatoid arthritis (RA). In rodent OA models, local joint injection of MSC-EVs derived from bone marrow, umbilical cord, synovial, or gingival MSCs has demonstrated improvements in cartilage histology, reduced synovial inflammation (measured by lower TNF-α and white blood cell counts in synovial fluid), and normalized gait parameters. These studies report inhibition of chondrocyte apoptosis, pyroptosis, and ferroptosis, alongside promotion of chondrocyte proliferation and extracellular matrix reorganization.

For RA—a systemic autoimmune condition affecting multiple joints—preclinical approaches have favored intravenous systemic administration or genetically engineered MSC-EVs (e.g., CTLA4Ig-overexpressing EVs) to enhance immunosuppressive function. Collagen-induced arthritis models in mice show that repeated intravenous EV dosing can reduce arthritis scores and joint damage markers such as C-telopeptide II, a biomarker of cartilage degradation. The dosing protocols in these studies typically involve twice-weekly or once-weekly intravenous injections over several weeks, with each dose derived from the secretome of approximately two million MSCs.

Importantly, the majority of joint-related evidence remains preclinical. Small-animal models do not fully recapitulate human OA or RA pathophysiology, and histological scoring or behavioral assays

carry inherent risk of detection bias when investigators are not blinded. Few studies provide sample-size justifications or independent replication, limiting reproducibility. Early clinical data for intra-articular MSC-EV therapy in human OA are sparse and largely observational.

For aesthetic practitioners, intra-articular secretome or EV delivery could align with regenerative joint-wellness services—supporting mobility, comfort, and quality of life in patients with degenerative joint changes—but must remain clearly RUO and non-disease-curative. Dosing typically employs higher EV concentrations than topical aesthetic formats, and formulations may incorporate bovine serum albumin or other stabilizers. Regulatory and professional-practice guidelines for intra-articular injection of non-approved biologics vary by jurisdiction and require close attention.

### Summary

Regenerative-wellness applications of MSC-derived secretome and EVs leverage the same anti-inflammatory, immunomodulatory, and tissue-repair mechanisms demonstrated in aesthetic indications. Intranasal, nebulized, and intra-articular delivery routes extend the potential scope of practice, but evidence is predominantly preclinical or early-stage clinical. Practitioners must communicate the RUO nature of these interventions, distinguish carefully between animal models and human data, and ensure compliance with local regulations governing the use of unapproved biological products in wellness contexts.

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CHAPTER 5

# Clinical and Preclinical Evidence Landscape

### Overview of the Evidence Base

The clinical translation of mesenchymal stromal cell (MSC)-derived extracellular vesicles (EVs) for aesthetic, cosmetic, and regenerative-wellness indications occupies a zone of rapid growth but modest maturity. The evidence base is structured in three layers: a substantial body of preclinical mechanistic work in cell culture and rodent wound models, a smaller cohort of early-phase human trials, and an expanding registry of ongoing investigations that have yet to report. In the aesthetic arena specifically, the literature is weighted heavily toward dermatologic endpoints (hair restoration, skin aging, hyperpigmentation, scar revision) rather than systemic regenerative applications, reflecting the local-administration feasibility and perceived safety of topical or intradermal routes.

Recent systematic analyses of global trial registries show that between 2014 and 2024 the number of registered MSC-EV studies increased markedly, with a notable surge beginning in 2022. One search of ClinicalTrials.gov conducted in January 2025 identified 15 registered trials investigating MSC-derived exosomes for skin-related and soft-tissue indications, including alopecia, psoriasis, melasma, wound healing, and skin aging. Among these, five focused specifically on alopecia. Trials are distributed across Iran, Turkey, Pakistan, the United States, China, Singapore, Indonesia, and

Spain, with the highest numbers in the United States and China. This geographical diversity underscores global interest but also highlights regulatory heterogeneity and the lack of unified standards for product characterization and manufacturing.

## Evidence Tiers by Indication

For **hair restoration**, clinical evidence is classified as **emerging to moderate**. A 2025 systematic review of exosome therapy in hair regeneration noted that published studies include case series, uncontrolled observational reports, and a small number of prospective trials. Reported interventions involve intradermal injection of MSC-derived EVs, often combined with adjunctive procedures such as microneedling. Across studies, exosome therapy was generally safe and well tolerated, with adverse events predominantly mild and transient (local scalp irritation, redness, swelling, itching). These effects resolved spontaneously and did not necessitate treatment discontinuation. No serious systemic complications, allergic reactions, or long-term adverse effects were reported. The absence of significant immunogenicity or infection across formulations derived from allogeneic sources (placenta, umbilical cord, bone marrow) supports a favorable safety profile when products are prepared and administered under appropriate clinical protocols. Efficacy signals are promising, but outcome measures remain heterogeneous, small sample sizes are common, and placebo or active-comparator controls are rare.

For **skin aging, hyperpigmentation, and scar revision**, the evidence tier is **emerging**. A systematic review of MSC-derived exosome-based therapies for scars, aging, and hyperpigmentation in humans found predominantly early-phase trials, case series, and observational studies. The review noted a recurring pattern of benefit when exosomes were used as adjuncts to microneedling, lasers, or standard dressings, although products, dosing, and outcome measures remain highly heterogeneous. Large-scale, well-designed clinical trials are essential to advance exosome therapy from boutique adjunct to evidence-based standard of care.

For **wound healing**, the evidence base is more developed but still limited. A 2024 systematic review and meta-analysis of human placental MSC-derived exosomes in wound healing and scar therapy pooled data from animal studies (323 animals total) and demonstrated superior outcomes compared with controls across multiple parameters: wound healing rate, neovascular density, re-epithelialization rate, and collagen deposition. Mechanistic studies indicate that MSC-EVs accelerate wound healing through enhanced angiogenesis, reduced inflammation, improved collagen production, and immunomodulatory effects. Most studies utilized rodent models, with limited translation to human trials. Current human evidence remains based on early-phase trials, case series, and observational studies. The review concluded that MSC-exosomes represent a promising therapeutic modality with demonstrated safety and efficacy, but standardization of manufacturing processes and regulatory approval remain critical for widespread clinical implementation.

## Safety Profile

Across indications, the reported safety profile of allogeneic MSC-EVs is consistently favorable. There is compelling evidence of a good safety profile for allogeneic MSCs in both animal studies and clinical trials, and derived EVs are expected to share this safety margin. Preclinical toxicology

screens in immunocompetent rodents receiving repeated intravenous EV doses (for example, $1 \times 10^{11}$ particles per injection, six doses over 10 days) showed no adverse effects on body weight, clinical appearance, serum liver enzymes, or organ histology. EVs derived from adipose-derived stromal cells (ADSCs) and bone marrow MSCs (BMSCs) have been found to be non-immunogenic in in vitro immunogenicity assays.

Early clinical reports in COVID-19-related acute respiratory distress syndrome (ARDS), chronic kidney disease, and graft-versus-host disease showed no serious adverse events attributable to MSC-EV administration. A 2025 meta-analysis of controlled COVID-19/ARDS trials investigating MSC-EVs (three trials, five intervention groups) reported no dose-relevant toxicity and generally mild, transient events. A 2022 early-phase stroke trial in Iran reported that EVs derived from allogeneic placental tissue did not cause serious adverse events within 3 months after intraparenchymal injection. Although serious adverse event reporting in the published literature is often incomplete, the cumulative evidence supports a low risk of immunogenicity, infection, and systemic toxicity when EVs are manufactured and administered under controlled conditions.

## Key Evidence Gaps

Despite these encouraging signals, critical gaps remain. Sample sizes in aesthetic trials are typically small (often fewer than 50 participants), follow-up periods are short (weeks to a few months rather than years), and many studies lack active comparators or placebo controls. Product heterogeneity is profound: EV isolation methods (ultracentrifugation, size-exclusion chromatography, precipitation, tangential-flow filtration) differ, starting cell sources and culture conditions vary, and characterization panels are inconsistent. Dosing units are not standardized (particle number, protein mass, cell equivalents), making cross-study comparison difficult.

Potency assays remain underdeveloped. While general release criteria (identity, viability, sterility, endotoxin, mycoplasma, particle characterization) align with industry-standard good manufacturing practice (cGMP) frameworks (21 CFR 210/211, 21 CFR 1271, ICH Q7/Q9/Q10), validated potency metrics that predict clinical efficacy are lacking. Pharmacokinetic and biodistribution data after intradermal, subcutaneous, or topical administration are sparse, and the mechanisms by which locally delivered EVs exert systemic or distant tissue effects remain incompletely understood.

## Summary

The clinical and preclinical evidence landscape for MSC-derived EVs in aesthetic and regenerative-wellness applications is characterized by substantial mechanistic rationale, a growing number of early-phase human trials, and a consistently favorable safety profile. Evidence tiers for hair restoration and wound healing are emerging to moderate; for skin aging, hyperpigmentation, and scar revision, evidence remains emerging. Whether exosomes transition from boutique adjunct to mainstream standard of care will depend on product standardization, agreed characterization and potency panels, larger controlled trials, and long-term safety and efficacy data.

CHAPTER 6

# Safety, Regulatory Status, and the RUO Boundary

Mesenchymal stromal cell (MSC)-derived secretome and extracellular vesicle (EV) preparations represent a rapidly evolving frontier in regenerative medicine, yet their clinical translation in the United States is governed by a complex and sometimes uncertain regulatory landscape. For aesthetic-medicine practitioners considering these technologies for hair restoration, skin rejuvenation, or regenerative-wellness applications, a clear understanding of regulatory status, enforcement history, and the boundaries of permissible use is essential.

## US FDA Classification: Biologics and Drugs, Not Minimal Manipulation

Under current US regulations, MSC-derived secretomes, exosomes, and other extracellular vesicle products are classified as biological products and drugs subject to licensure under the Public Health Service (PHS) Act Section 351 and the Federal Food, Drug, and Cosmetic (FD&C) Act. This classification places them under the jurisdiction of the US Food and Drug Administration's Center for Biologics Evaluation and Research (CBER). Because secretome and EV products do not meet the criteria for human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated solely under Section 361 of the PHS Act, they require full review and approval through a Biologics License Application (BLA) before they can be lawfully marketed for any human therapeutic or aesthetic application (Wang, Tsai, and Lee 2024; context documents 4, 9, 12).

The distinction is critical: products regulated only under Section 361 are limited to "homologous use," meaning they must perform the same basic function in the recipient as in the donor. Because secretome and EV preparations are intended to exert pharmacological effects through growth factors, cytokines, microRNAs, and other bioactive molecules, they do not qualify for this simpler regulatory pathway. They are instead considered drugs or biologics with therapeutic effects, triggering the requirement for preclinical and clinical evidence of safety and efficacy, chemistry-manufacturing-and-controls (CMC) documentation, and formal approval before marketing (Verma and Arora 2025; context documents 1, 15, 22).

## FDA Enforcement and Safety Alerts

In 2019, following reports of severe adverse events in patients who received unlicensed exosome products, including cases of sepsis in Nebraska, the FDA issued a public safety notification on exosome products. This was followed in 2020 by a consumer alert specifically warning the public about regenerative medicine products, including stem cells and exosomes, being marketed without FDA approval (context documents 1, 6, 7). The alerts emphasized that these products have not been proven safe or effective for the conditions being promoted and that their use outside of properly authorized clinical trials carries significant risks, including infection, immune reactions, and tumor formation.

As of October 2023, the FDA had issued at least six warning letters to companies illegally marketing exosome-based products for therapeutic or aesthetic indications (context documents 4, 9, 15). These warning letters cite violations of drug and biologic licensing requirements under 21 U.S.C. § 321(g)(1) and 42 U.S.C. § 262(i), as well as violations of HCT/P regulations under 21 CFR 1271 when companies misrepresented their products' regulatory status (context documents 5, 15). The FDA's enforcement posture underscores a clear principle: exosome and secretome products being offered for human use in clinical or aesthetic settings, whether through injection, topical application, or other routes, are considered unapproved drugs and biologics and are subject to regulatory action.

## The Research-Use-Only (RUO) Designation

Given the absence of FDA-approved exosome or secretome products for aesthetic or regenerative-wellness applications, most MSC-derived preparations currently available in the United States are labeled as Research-Use-Only (RUO). RUO designation means the material is manufactured for laboratory investigation and is not approved, cleared, or licensed by the FDA for use in humans. RUO products may not be marketed with claims of safety or efficacy for any disease, condition, or cosmetic outcome. They are not subject to the same level of manufacturing oversight as approved biologics, although responsible manufacturers follow good manufacturing practice (GMP) principles and conduct rigorous quality-control testing for identity, purity, potency, and safety (context documents 3, 8, 21).

Practitioners must recognize that RUO materials are fundamentally distinct from FDA-approved products. Use of RUO secretome or EV preparations in patient care does not fall under an approved indication and may only occur in properly designed and approved clinical research studies, such as investigational new drug (IND) applications or institutional review board (IRB)-supervised research protocols. Outside these contexts, the administration of RUO materials to patients is not lawful under current US regulations.

## Responsibility of the Treating Practice

A common misconception in aesthetic and regenerative medicine is that a product's availability for purchase implies its suitability for clinical use. The regulatory responsibility, however, rests with the treating practice and the individual practitioner. The FDA regulates the product as a drug or biologic, but the act of administering an unapproved product to a patient falls under the practice of medicine, which is governed by state medical boards and professional standards.

Clinics that administer secretome or exosome products to patients outside of approved clinical trials operate in a regulatory gray zone that carries legal, ethical, and professional risks. Some businesses have attempted to market these products as HCT/Ps to exploit perceived regulatory loopholes, claiming they are performing "homologous use" when in fact the intended biological effects are pharmacological rather than structural (context documents 15, 17). The FDA continues to close these loopholes through enforcement actions and clarifications of policy (context documents 6, 9, 15).

Practitioners considering the use of MSC-derived secretome or EVs in aesthetic applications should consult with legal and regulatory advisors, ensure that any patient treatment occurs within a properly authorized research framework, and refrain from making disease-treatment claims or cosmetic-outcome guarantees that are not supported by FDA-approved labeling.

### No Disease Claims, No Therapeutic Representations

Because RUO secretome and EV materials are not approved for any therapeutic or cosmetic indication, no claims regarding their efficacy in treating disease, reversing aging, restoring hair growth, or improving skin quality may be made in marketing or patient communications. Promotional language that implies therapeutic benefit, anti-aging effects, or regenerative healing can trigger FDA enforcement action as evidence of illegal drug marketing (context documents 5, 15). Even well-intentioned educational statements may be interpreted as promotional claims if they suggest a specific outcome or benefit.

The current regulatory landscape for MSC-derived secretome and EVs in the United States reflects a cautious, science-grounded approach that prioritizes patient safety and evidence-based practice. As clinical research advances and manufacturers pursue formal licensure pathways, the field may eventually see FDA-approved products for aesthetic and regenerative applications. Until then, practitioners must navigate the RUO boundary with diligence, transparency, and respect for the regulatory framework designed to protect patients and ensure the integrity of emerging biologic therapies.

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CHAPTER 7

# Manufacturing and Quality: General cGMP Framework

The manufacture of mesenchymal stromal cell (MSC)-derived secretome and extracellular vesicles (EVs) for aesthetic, cosmetic, and regenerative-wellness applications requires adherence to rigorous quality standards, even when materials are produced for research use only (RUO) or as cosmetic ingredients. This chapter describes the **general industry framework** for secretome production and quality-control release testing, grounded in published current good manufacturing practice (cGMP) guidelines applicable to biologics and cell-based products.

### Regulatory and Quality Framework

MSC secretome and EV production draws upon two principal regulatory frameworks in the United States: **21 CFR Parts 210 and 211** (Drug Good Manufacturing Practices), which govern pharmaceutical manufacturing processes, and **21 CFR Part 1271** (Human Cells, Tissues, and Cellular and Tissue-Based Products), which addresses donor eligibility, facility registration, and processing controls for human cell and tissue products. Internationally, manufacturers may apply the European Union's **Good Manufacturing Practice guidelines for Advanced Therapy Medicinal**

**Products (ATMPs)**, and quality-risk principles from **ICH Q7** (Active Pharmaceutical Ingredients), **ICH Q9** (Quality Risk Management), and **ICH Q10** (Pharmaceutical Quality System).

These regulations require establishment of a **quality management system** encompassing documented procedures, traceability, environmental controls (e.g., ISO 14644-classified cleanrooms), personnel training, process validation, and comprehensive release testing. For secretome products, the production environment is typically controlled to at least **ISO Class 7 (Class 10,000) or better**, often with critical aseptic operations performed under ISO Class 5 (Class 100) laminar flow hoods within a classified cleanroom suite.

## General Manufacturing Process Flow

### MSC Expansion and Banking

Production begins with a well-characterized MSC **master cell bank**, derived from qualified human tissue donors screened according to regulatory donor-eligibility criteria. Cells are expanded under controlled culture conditions, using defined, **animal-origin-free or xeno-free media** to minimize adventitious-agent risk and lot-to-lot variability. The literature indicates that xeno-free formulations, including those supplemented with human platelet lysate (HPL), can reduce MSC doubling time, increase exosome yield, and remove the majority of contaminating serum proteins compared to research-grade fetal bovine serum (FBS)-based media.

Throughout expansion, **in-process controls** monitor cell identity (surface marker expression by flow cytometry: CD73+, CD90+, CD105+, with negative markers CD34−, CD45−, HLA-DR−), viability (typically ≥90% by trypan blue exclusion or automated cell counting), population doubling time, and morphology. Sterility, mycoplasma, and endotoxin testing are performed at defined intervals to ensure culture integrity.

### Conditioning and Harvest

Once cells reach an appropriate passage and confluence, secretome production is initiated by a **conditioning phase**. Cells are cultured in **EV-depleted medium**—medium from which serum- or supplement-derived EVs have been removed by ultracentrifugation or size-exclusion chromatography—to ensure that harvested particles originate from the MSCs themselves. Conditioning durations range from 24 to 72 hours in reported protocols, balancing EV yield against potential effects of prolonged serum deprivation on cell physiology.

Conditioned medium (CM) is then harvested and subjected to **clarification** by low-speed centrifugation (typically 2,000–5,000×g for 10–20 minutes) to remove intact cells, cell fragments, and apoptotic bodies larger than ~1 µm.

### Concentration and Purification

Clarified CM undergoes **concentration and diafiltration**, commonly by **tangential flow filtration (TFF)** with a 5–300 kDa molecular weight cut-off (MWCO) membrane. TFF offers scalability,

reproducibility, and compliance with cGMP principles, enabling removal of low-molecular-weight metabolites and buffer exchange into sterile, defined formulation buffers (e.g., phosphate-buffered saline, ultrapure water, or formulation-optimized solutions). Published protocols maintain shear rates between 2,000 and 6,000 $s^{-1}$ and transmembrane pressures below 5 psi to preserve vesicle integrity.

TFF has been shown to yield on the order of $10^{11}$–$10^{12}$ particles per liter of conditioned medium in reported studies, with retained biological activity.

#### Sterile Filtration and Formulation

Following concentration, the secretome preparation may undergo **0.22-µm sterile filtration** (for cell-free, soluble-factor preparations) or aseptic handling under ISO Class 5 conditions (for EV-enriched products, which cannot pass 0.22-µm filters due to particle size). Formulation strategies include addition of **cryoprotectants** (e.g., trehalose, mannitol) and stabilizers to preserve particle structure during freezing or lyophilization. Freeze-dried (lyophilized) secretome products offer extended shelf life, ease of transport, and reconstitution flexibility for clinical or cosmetic applications.

#### Fill-Finish and Primary Packaging

Aseptically processed secretome is dispensed into sterile, single-use vials or syringes under controlled environmental conditions. Each filled unit is labeled with lot number, expiration date, and storage instructions.

### Quality-Control Release Testing

Before release, each production lot undergoes a **comprehensive panel of safety, identity, purity, and potency assays**. Standard industry categories include:

- **Identity**: Confirmation of MSC origin and EV markers (e.g., CD63, CD81, CD9, TSG101, Alix) by Western blot, ELISA, or flow cytometry using EV-capture beads.
- **Particle Characterization**: Size distribution and concentration by **nanoparticle tracking analysis (NTA)** or dynamic light scattering (DLS), with typical exosome size peaks at 30–150 nm and total particle counts quantified per mL or per cell equivalent.
- **Protein Quantification**: Total protein content (e.g., by BCA or Bradford assay) to normalize dosing and assess lot consistency.
- **Sterility**: USP <71> or equivalent bacterial and fungal culture.
- **Endotoxin**: Limulus Amebocyte Lysate (LAL) or recombinant Factor C assay, with typical acceptance thresholds at ≤5 EU/mL for injectable preparations.
- **Mycoplasma**: Culture-based or PCR methods.
- **Residual Host-Cell DNA**: Quantification by fluorometric or qPCR assays.
- **Potency**: Functional bioassays demonstrating relevant biological activity (e.g., macrophage polarization, cytokine modulation, cell migration, or angiogenesis assays in vitro).

- **Stability**: Accelerated and real-time stability studies under ICH-compliant conditions to define shelf life.

This general framework, aligned with published cGMP and ICH guidelines, ensures that MSC-derived secretome and EV preparations meet consistent quality standards for research, cosmetic, and emerging regenerative-wellness applications. All materials remain research-use-only unless further regulatory approvals are obtained.

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