

Review

Regenerative Strategies for Androgenetic Alopecia: Evidence, Mechanisms, and Translational Pathways

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Abstract

Hair loss disorders, particularly androgenetic alopecia (AGA), are common conditions that carry significant psychosocial impact. Current standard therapies, including minoxidil, finasteride, and hair transplantation, primarily slow progression or re-distribute existing follicles and do not regenerate lost follicular structures. In recent years, regenerative medicine has been associated with a gradual shift toward approaches that aim to restore follicular function and architecture. Stem cell-derived conditioned media and exosomes have shown the ability to activate Wnt/ β -catenin signaling, enhance angiogenesis, modulate inflammation, and promote dermal papilla cell survival, resulting in improved hair density and shaft thickness with favorable safety profiles. Autologous cell-based therapies, including adipose-derived stem cells and dermal sheath cup cells, have demonstrated the potential to rescue miniaturized follicles, although durability and standardization remain challenges. Adjunctive interventions such as microneedling and platelet-rich plasma (PRP) further augment follicular regeneration by inducing controlled micro-injury and releasing growth and neurotrophic factors. In parallel, machine learning-based diagnostic tools and deep hair phenotyping offer improved severity scoring, treatment monitoring, and personalized therapeutic planning, while robotic Follicular Unit Excision (FUE) platforms enhance surgical precision and graft preservation. Advances in tissue engineering and 3D follicle organoid culture suggest progress toward producing transplantable follicle units, though large-scale clinical translation is still in early development. Collectively, these emerging biological and technological strategies indicate movement beyond symptomatic management toward more targeted, multimodal approaches. Future progress will depend on standardized protocols, regulatory clarity, and long-term clinical trials to define which regenerative approaches can reliably achieve sustainable follicle renewal in routine cosmetic dermatology practice.

Keywords: androgenetic alopecia; hair follicle regeneration; stem cell therapy; exosomes; platelet-rich plasma (PRP); microneedling; machine learning; robotic follicular unit extraction; 3D bioprinting; follicle organoids; hair follicle cloning



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1. Introduction

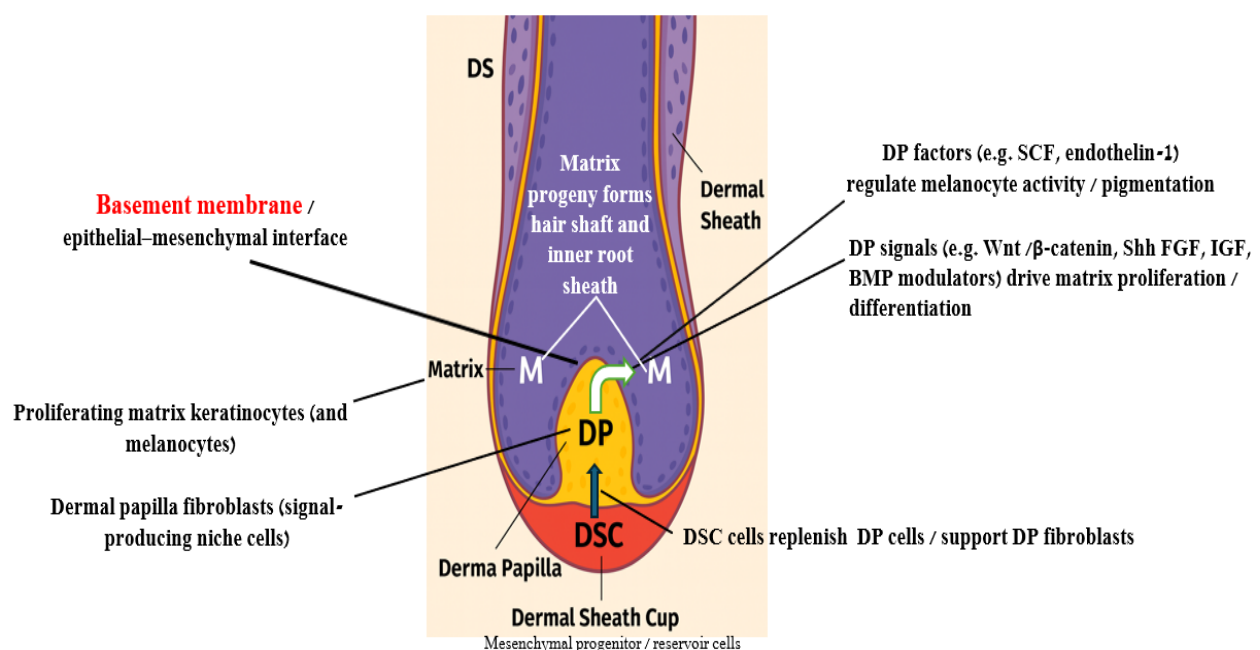
For centuries, hair has carried profound cultural, social, and personal meaning. When it is lost, whether gradually through androgenetic alopecia (AGA) or suddenly in alopecia areata (AA), the impact reaches far beyond the scalp. Millions worldwide live with the daily reminder of thinning hair, and multiple studies have demonstrated significant impairments

in quality of life, self-esteem, and psychosocial functioning in both men and women with pattern hair loss [1,2].

While FDA-approved treatments exist, they often provide only modest relief. Minoxidil, finasteride, and even surgical transplantation cannot halt the ongoing progression in many patients, nor do they offer the possibility of new follicle creation [3–5]. For patients, the disappointment is not only cosmetic; it is psychosocial, economic, and deeply human [6,7].

Recent studies indicate a shift from symptom management to mechanisms that promote follicular regeneration [8,9]. Advances in stem-cell biology, exosome science, and tissue engineering are reshaping what was once thought impossible: the revival, or even rebirth, of the human hair follicle. A systematic review of mesenchymal stem cell-derived exosomes documented consistent increases in hair density (9.5–35 hairs/cm²) and shaft thickness (up to ~13 µm) across early trials, with no serious adverse events reported [10,11] (Figure 1).

Mechanistic organization of the lower hair follicle niche



Mesenchymal niche controlling hair growth and pigmentation via a DSC → DP → matrix (keratinocyte and melanocyte) axis

Figure 1. Mechanistic organization of the lower hair-follicle niche. Schematic representation of the human anagen hair-follicle bulb showing the interactions between the dermal sheath cup (DSC), dermal papilla (DP) and matrix (M). The dermal sheath (DS) surrounds the follicle and terminates distally as the dermal sheath cup (DSC), which contains mesenchymal progenitor/reservoir cells. DSC cells can replenish and support dermal papilla (DP) fibroblasts, thereby helping to maintain DP size and function. Across the basement membrane/epithelial-mesenchymal interface, DP fibroblasts secrete key morphogens and growth factors (e.g., Wnt/ β -catenin, Shh, FGF, IGF and BMP modulators) that drive proliferation and differentiation of matrix keratinocytes. Progeny of these matrix cells forms the hair shaft and inner root sheath. DP-derived factors such as stem cell factor (SCF) and endothelin-1 regulate matrix melanocyte activity and pigmentation. Together, this DSC → DP → matrix axis defines a mesenchymal niche that controls hair growth and pigmentation.

Mechanistic studies further support these findings: Fu et al. demonstrated that human adipose-derived stem-cell exosomes activate the Wnt/ β -catenin pathway by inhibiting GSK-3 β , thereby reversing dihydrotestosterone-induced suppression and stimulating der-

mal papilla cell proliferation [12,13] (Study context: early prospective studies/cohorts with small samples suggest density gains; product characterization and regulation vary—interpret effect sizes cautiously).

Device-assisted strategies are being evaluated as adjuncts; evidence remains limited and heterogenous, and definitive comparative trials are needed. In a prospective clinical trial, exosome therapy combined with microneedling produced mean density gains of approximately 35 hairs/cm² at 12 months, with high patient satisfaction and only mild, transient side effects [14–16].

Reviews of microneedle-based interventions further underscore their synergistic role: by enhancing vascularization, improving local drug and biologic delivery, and promoting follicular survival, microneedling can act as a powerful adjunct to regenerative therapies [17]. (Study context: randomized/evaluator-blinded studies (~12–24 weeks) showed greater hair-count gains when microneedling was added to topical minoxidil vs. minoxidil alone ($p < 0.05$); protocols vary).

Meanwhile, mechanobiology and follicle stem-cell activation have captured renewed interest. A 2025 review highlighted how controlled mechanical stimulation—stretching, microneedling, or wounding—can awaken quiescent hair follicle stem cells via Wnt and BMP signaling, while macrophage-derived growth factors such as Fand IGF-1 support de novo follicle induction [18]. Experimental work by Chu and colleagues further showed that precisely controlled mechanical stretch activates hair follicle stem cells and promotes telogen-to-anagen transition via M2-like macrophage recruitment and Wnt/ β -catenin activation [9] (See Figure 2; Tables 1 and 2).

Table 1. Unified Mechanistic Map.

Therapies	Mechanistic Levers	→ Outcomes
Minoxidil; Finasteride/Dutasteride; Wnt activators; JAKi (AA context)	Angiogenesis ↑; Wnt/ β -catenin ↑; BMP restraint ↓; Immune-niche normalization; DP support	Telogen → Anagen; Sustain Anagen; Prevent Catagen
PRP; Exosomes/MSC secretome; ADSC preparations; DP/DSC cell therapies	Wnt cross-talk ↑; Angiogenesis ↑; Immunomodulation; DP signaling ↑	Telogen → Anagen; Sustain Anagen
Microneedling; LLLT; Mechanobiology; Hair transplantation	Mechanotransduction; Wnt cross-talk; Angiogenesis ↑; DP integrity preserved	Telogen → Anagen; Sustain Anagen; Prevent Catagen
Organoids/iPSC/3D bioprinting	DP signaling ↑; developmental programs (Wnt)	Neogenesis (preclinical); full cycling (models)

Unified mechanistic map linking therapies to core levers and hair-cycle outcomes. Therapies (left column) are mapped to dominant mechanistic levers (middle column)—Wnt/ β -catenin activation, BMP restraint, angiogenesis, mechanotransduction, immune-niche normalization (primarily in alopecia areata), and restoration of dermal papilla (DP) signaling—which in turn drive hair-cycle outcomes (right column): telogen→anagen initiation, anagen maintenance, and prevention of premature catagen. Arrows (→) indicate direction of influence; ↑ denotes up-regulation/activation and ↓ denotes down-regulation/inhibition. JAK inhibitors are included for context given their role in immune-niche normalization in AA; evidence for AGA is limited. “Neogenesis” refers mainly to preclinical organoid/iPSC/bioprinting models rather than established clinical outcomes. Abbreviations: AGA, androgenetic alopecia; AA, alopecia areata; DP, dermal papilla; LLLT, low-level light therapy; MSC, mesenchymal stromal cell; PRP, platelet-rich plasma.

In addition, novel molecular candidates are entering the pipeline. Liu et al. introduced EX104, a small molecule shown to remodel the follicular microenvironment, promotes angiogenesis, and reactivate miniaturized follicles, outperforming minoxidil in murine AGA models [19]. Related platforms targeting HF stem cells and Wnt/ β -catenin signaling

further illustrate how small molecules and bioengineered exosomes may complement traditional pharmacologic agents [20,21].

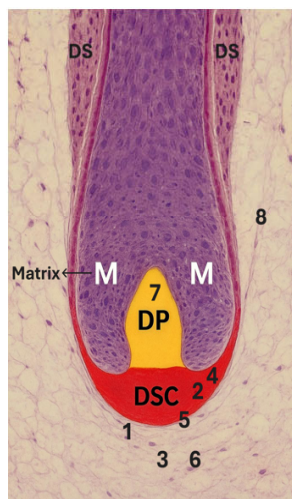
Hair follicle growth

Mechanisms (match numbers markers).

1. Wnt/ β catenin activity (DP ligands)
DP-derived Wnt/ β -catenin signals promote matrix proliferation and anagen maintenance.
2. BMP restraint at/around the DP
Local BMP signaling shapes the DP niche and limits excessive activation.
3. Mechanotransduction/wound cues at the DSC interface
Mechanical and injury-related signals at the dermal sheath cup (DSC) influence DP behavior.

Support/trafficking.

4. Angiogenesis/perfusion (peripapillary)
Peripapillary blood vessels provide oxygen/nutrient support to the DP and lower bulb.
5. Neurotrophic cues (e.g., GDNF) directed to the DP
Nerve-derived factors such as GDNF target the DP and modulate hair growth.
6. DS $\leftrightarrow$ DP fibroblast trafficking (DSC)
Bidirectional trafficking of fibroblasts between the dermal sheath (DS) and DP helps maintain DP size and composition.
7. IGF-1 at the DP-matrix interface
(survival/metabolic support).
IGF-1 supports survival and metabolic activity of matrix keratinocytes and melanocytes.
8. TGF- β (especially β 2) at upper bulb/ORS
(catagen-promoting cue).
TGF- β signals at the upper bulb/outer root sheath provide catagen-promoting cues.



Principles.

DP size correlates with anagen duration.
DP inductivity determines hair-shaft caliber and type.
HF stem cells are required for cycling, but mesenchymal DP signals constrain caliber and growth pattern.

Potential confounding factors

Procedure-related effects

(e.g., injection / needling alone stimulates growth)

Crossover in split-scalp designs

(diffusion of signals/drug from treated to “control” side)

Inconsistent outcome measures

(different studies use different endpoints)

Selective reporting of positive studies

Outcomes

Telogen $\rightarrow$ Anagen transition

Sustain anagen phase

Delay / prevent catagen onset

Promote de novo formation of new hair follicles

(demonstrated mainly in experimental models)

Figure 2. Hair follicle growth: mesenchymal mechanisms, support pathways, confounders and outcomes. Histological image of a human anagen hair follicle bulb. Numbers 1–8 indicate representative mesenchymal mechanisms that influence hair growth. (1) Wnt/ β -catenin activity from DP ligands promotes matrix proliferation and anagen maintenance. (2) Local BMP signaling restrains activity at/around the DP and shapes the niche. (3) Mechanotransduction and wound-related cues at the DSC interface modulate DP behavior. (4) Peripapillary angiogenesis/perfusion provides oxygen and nutrient support to the DP and lower bulb. (5) Neurotrophic cues (e.g., GDNF) are directed to the DP and modulate growth. (6) Bidirectional trafficking of fibroblasts between DS and DP via the DSC helps maintain DP size and composition. (7) IGF-1 at the DP–matrix interface supports survival and metabolic activity of matrix keratinocytes and melanocytes. (8) TGF- β (especially β 2) signals at the upper bulb/outer root sheath provide catagen-promoting cues. Principles on the right summarize how DP size and inductivity govern anagen duration, hair-shaft caliber and type, while potential confounding factors highlight procedural effects, crossover in split-scalp designs, inconsistent outcome measures and selective reporting. Collectively, these pathways influence key outcomes: telogen $\rightarrow$ anagen transition, maintenance of anagen, delay/prevention of catagen onset and, in experimental models, de novo formation of new hair follicles.

Finally, 3D bioprinting and organoid engineering are at a preclinical stage; clinical feasibility and durability remain unproven. Recent reports of 3D-printed or bioprinted skin constructs containing hair follicles demonstrate de novo follicle-like structures and cycling in animal models, yet translation to humans will require solutions for vascularization, innervation, and scalable manufacturing [22]. A 2025 review of functional follicle regeneration underscores that the central challenge remains replicating embryonic epithelial–mesenchymal interactions and sustaining cyclical follicle activity [9].

Taken together, these developments signal a shift in the therapeutic paradigm: from purely symptomatic management toward mechanism-based attempts at follicular rescue and, eventually, regeneration. For clinicians and researchers, the task now is to convert

this expanding body of preclinical and early-phase clinical data into safe, standardized, and accessible treatments [8]. For patients, evidence to date supports modest, incremental benefit, while regenerative endpoints remain under active investigation.

Table 2. Pharmacologic Therapies for Androgenic Alopecia.

Therapy	Typical Clinical Effect	Evidence Quality	Durability	Limitations/Safety
Topical Minoxidil	Small–moderate density/thickening gains	High-quality RCTs + long-term data	Requires continuous use, regression after stopping	Dermatitis, shedding; adherence issues
Low-dose Oral Minoxidil	Moderate global improvement; useful in diffuse AGA	Prospective cohorts; limited long-term data	Continuous systemic therapy required	Hypertrichosis, edema; BP monitoring
Finasteride/Dutasteride	Stabilizes loss; moderate density gain	Extensive RCTs; high-quality long-term evidence	Durable while on therapy	Sexual/mood adverse events; teratogenicity (women)

Pharmacologic Therapies for Androgenetic Alopecia. Topical and oral Minoxidil, as well as 5-alpha-reductase inhibitors, are compared in terms of typical effect size, strength of clinical evidence, long-term maintenance requirements, and known adverse-event profiles.

2. Machine Learning in Hair Disorders

2.1. Background and Rationale

Hair is an important evolutionary trait conserved across mammals for its roles in thermoregulation, protection from UV exposure, and environmental sensing [23–27].

Hair loss disorders such as AGA affect a large proportion of men and women worldwide [28]. Beyond its biological function, hair also plays a central role in appearance, identity, and mental well-being [29].

Ongoing research has greatly improved our knowledge of how molecular and cellular processes regulate follicle development and cycling [30–32]. Yet, detailed study of the hair fiber itself has been neglected. Fiber-level deviations, like thinning, brittleness, and graying, have been linked to hormonal imbalance, stress, aging, and neurodegenerative disease [33–37].

These changes are often only noticed once advanced, making early intervention difficult [38,39]. For example, AGA is usually diagnosed when visible hair loss is already established [40]. Treatments can slow loss but cannot reverse permanent follicle damage [40].

Monitoring hair fiber phenotypes early could improve outcomes, but fiber-level assessment is technically challenging. Traditional methods are visual, labor-intensive, and lack reproducibility [41–45]. This is where artificial intelligence (AI) and machine learning (ML) provide new possibilities.

2.2. Computer Vision and Deep Phenomics

Advances in computer vision have already improved detection of skin cancers, scars, and other dermatologic conditions [46–49]. Automated analysis of trichoscopy images has shown promise in assessing scalp health and hair density [50,51]. However, trichoscopy alone cannot capture the structural information within full-length hair fibers. Extracting intact hairs for analysis has been difficult due to overlapping strands, irregular curvature, and varied orientations [52,53].

Deep learning, a branch of machine learning designed to recognize complex and high-dimensional patterns, has transformed image analysis across many fields [54,55]. By enabling the measurement of features that were previously only described qualitatively, it

allows researchers to capture subtle biological traits with much greater precision [56,57]. Applications already include identifying seed varieties, counting nematodes, and tracking nuanced biological changes [58–60]. Collectively, this approach is known as deep phenotyping, the systematic, high-resolution measurement of biological features using advanced computational tools.

Applied to hair research, this gives rise to deep hair phenotyping: AI-driven segmentation and quantification of individual hair fibers. Using synthetic training data, a sliding-window method, and convolutional neural networks (CNNs), our group has developed a model capable of analyzing hair at single-strand resolution. Early results demonstrate that this approach can detect microstructural changes invisible to the naked eye, changes that are closely linked to endocrinological, developmental, and aging processes.

2.3. Diagnostic, Prognostic, and Therapeutic Applications

Machine learning is now being applied to every stage of hair medicine, from diagnosis and severity assessment to treatment planning and monitoring.

2.4. Diagnosis and Severity Scoring

ML models such as modified Xception networks can analyze trichoscopy, dermoscopy, and OCT images with diagnostic accuracies > 92%, outperforming traditional methods and rivaling expert interpretation [61–63]. Algorithms like HairComb, validated in over 400 patients, objectively score alopecia severity with error margins of just 1–9% compared to manual scoring, and correlate strongly with established clinical scales [64,65].

2.5. Prognostic Tools

ML models can predict treatment outcomes and disease progression. One model predicted which AA patients would fail therapy with ~80% accuracy, helping to guide intensity of treatment [66]. Others integrate clinical and genetic data to forecast progression to severe forms of alopecia [66].

2.6. Therapeutic Discovery

AI-guided screening has identified new drug candidates. For example, a manganese-based “nanozyme” with superoxide dismutase–mimetic activity promoted stronger regrowth than minoxidil in mice, even at reduced dosing frequency, by reducing oxidative stress in follicles [67].

2.7. Limitations and Challenges

Despite these advances, challenges remain. Less than 20% of dermatology AI studies report ethnicity or skin type. Models often perform poorly on underrepresented skin tones unless retrained on diverse datasets [68,69]. Preprocessing methods like color normalization can improve accuracy, but diverse image libraries remain essential. AI tools require large volumes of sensitive images, yet transparency around storage and usage is limited [70]. Most dermatology AI systems lack FDA or EMA approval and have limited clinical validation, raising concerns about safety and efficacy [71,72]. Clinicians worry about opaque “black box” algorithms, unclear accountability, and liability. Limited dermatology involvement in AI design adds to skepticism [73–77].

2.8. Conclusions

AI and ML may transform hair medicine. From precise diagnostics and objective severity scoring to predictive models and novel therapies, the opportunities are substantial. Yet adoption depends on overcoming barriers: diversifying training data, safeguarding privacy, ensuring regulatory oversight, and earning clinician trust.

AI will not replace dermatologists but can serve as a powerful co-pilot, bringing objectivity, efficiency, and personalization to the care of hair disorders. If developed responsibly, these technologies could shift the field from subjective observation to precision-driven, regenerative care.

3. Robotic Hair Restoration—ARTAS

AI and ML have already been integrated into mechanical platforms for hair transplant surgery. The ARTAS[®] robotic follicular unit excision system (FDA cleared in 2011) uses image guidance and ML to identify optimal donor follicles and create recipient sites (Figure 3). In practice, ARTAS can harvest 500–1000 grafts per hour [78] and create approximately 1593 recipient sites per hour, achieving high patient satisfaction scores. Complication rates are low, with postoperative crusting being the most common [79]. Prospective multicenter trials have shown that ARTAS achieves transection (follicle damage) rates around 6.6%, comparable to an experienced surgeon and much better than a beginner operator [80]. In other words, robotic FUE can standardize the most technically demanding steps of surgery, reducing the steep learning curve for new practitioners. In addition to efficiency, robotics minimizes scarring and operator fatigue, which may improve patient safety and outcomes [81,82].

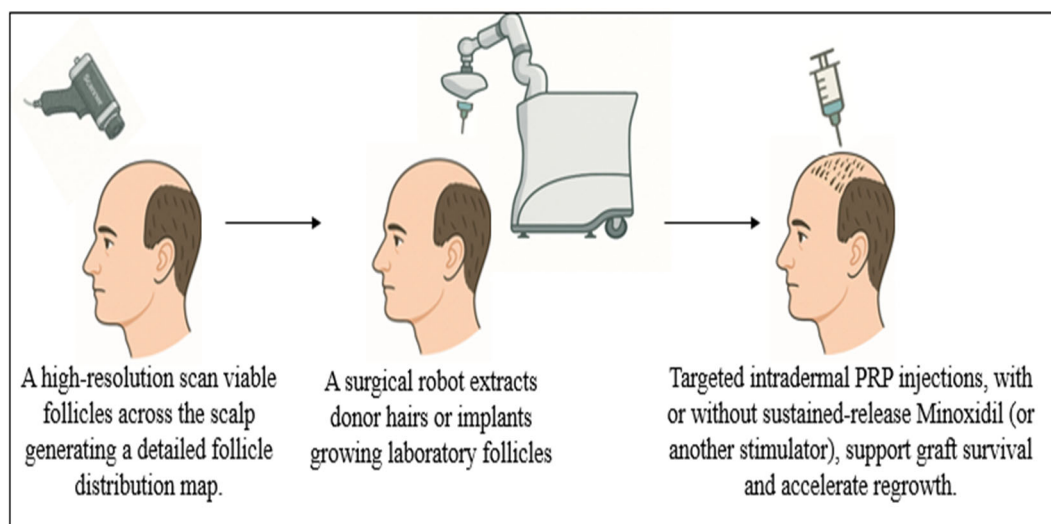


Figure 3. Practical steps toward clinical adoption. Translating AI-guided, cell-based hair regeneration into routine dermatologic practice follows a three-step pathway: (1). A high-resolution scan charts every viable follicle across the scalp, generating a precision density map. (2). A surgical robot either extracts healthy donor hairs or inserts laboratory-grown follicles exactly where coverage is sparse, matching the natural growth angle. (3). Platelet-rich plasma (PRP) or other stimulators support the regrowth of new grafts, reduce inflammation, and accelerate hair regeneration.

The FDA has specifically approved the ARTAS system for use in male patients with brown or black hair. The system incorporates exclusive imaging technology, a computer interface terminal, multiple video cameras, a video display, robotic arm, a suction system for raising harvested grafts, and a specially designed chair for patient positioning. After applying a tensioner, the system calculates the angle between the follicle's surface exit and its underlying structure. The robotic arm's dual-bore needle, consisting of a sharp inner tip for initial penetration and a blunt outer needle for deeper dissection, reduces the risk of follicle transection and eases graft removal. The sharp needle includes graduated markings to guide depth. Harvesting is guided by mathematical algorithms that allow randomization and adjustability, reducing human error. Importantly, ARTAS is the only

system where the physician operates through a computer interface rather than manually handling the punch tool, reducing ergonomic strain on the operator.

3.1. Advantages Engineered

The advantages of ARTAS include a significantly shorter learning curve compared to manual FUE, the ability to perform repetitive actions without fatigue, and the selection of optimal follicles for harvesting [83]. For early-career practitioners, the robot lowers the barrier to entry into hair restoration by reducing reliance on large teams of assistants, unlike strip harvesting. Typically, one assistant is employed to help control the robot through the interface, while the physician guides harvesting parameters. This streamlined workflow also enhances the robot's value as a marketing tool for clinics [78].

Robotic follicular unit graft selection algorithms have also been shown to increase the number of hairs per harvest attempt and per graft, improving donor area efficiency [84]. The field continues to evolve, with future directions focusing on more advanced AI integration, improved instrumentation, and potential full automation of both harvesting and implantation [64,85,86].

3.2. Limitations

Despite these advantages, ARTAS has important limitations. The system is expensive, requiring substantial capital investment, maintenance, and consumables, resulting in higher procedural costs than manual FUE [78,87]. Literature to date does not support a clear cost-benefit advantage for routine clinical practice.

Performance challenges also exist. Transection rates are higher in lateral areas such as the supra-auricular region, where hair angles are acute. Variable hair directions, softer tissue at the nape, and regions with scarring or fibrosis from prior strip harvesting can all reduce yield and increase difficulty. The system is also less effective in harvesting curly or tightly coiled hair, particularly in patients of African descent, where angulation and follicle curvature complicate extraction [87–89].

In such cases, outcomes may be inferior compared to skilled manual techniques.

3.3. Training and Outcomes

Training challenges are present but not prohibitive. Robotic systems are designed to minimize the learning curve, enabling surgeons of varying experience levels to achieve consistent results. Cosmetic outcomes and patient satisfaction scores are similar across operators, suggesting accessibility of the technology [79]. Nonetheless, optimal use still requires familiarity with device-specific nuances, troubleshooting, and seamless workflow integration.

Patient-reported outcomes are generally favorable, with mean satisfaction of 4.13/5, rapid recovery, and minimal donor scarring [78,79]. Complications such as crusting, itching, and folliculitis are infrequent and comparable to manual FUE. The absence of a linear scar and reduced postoperative discomfort remain highly valued by patients [88].

3.4. Future Directions

Integration with regenerative therapies remains experimental. Robotic systems are being adapted for the implantation of engineered hair follicles derived from stem cells or organoids, potentially enabling true follicle regeneration rather than redistribution [90,91]. Automation and precision may facilitate large-scale, standardized transplantation of bio-engineered follicles. However, clinical feasibility has not been established, and translation is constrained by technical and regulatory hurdles.

As these technologies mature, broader adoption will depend on lowering costs and familiarizing surgeons with robotic workflows. Collaborative models, where dermatologists

and hair restoration surgeons work together in combined clinics, could further enhance training and patient access.

4. Cellular and Regenerative Therapies

4.1. *Moving Beyond Symptom Control*

Currently approved drugs such as minoxidil and finasteride remain the cornerstone of androgenetic alopecia treatment, but they provide only partial benefit, primarily slowing or stabilizing hair loss rather than regenerating new follicles (See Tables 1 and 2). Their effects often plateau, and many patients experience limited cosmetic improvement or treatment fatigue. These limitations underscore the urgent need for next-generation approaches that move beyond symptom control to true regeneration of follicle structures.

With millions affected by alopecia, research is rapidly moving beyond symptom control toward true regeneration of hair follicles. Two major directions stand out: hair follicle neogenesis, once thought impossible in adults but now supported by animal and early translational studies, and precise pathway modulation, especially the Wnt/ β -catenin axis that switches follicles from rest to growth [8,92]. In wound-induced hair follicle neogenesis (WIHN), new follicles can form after sufficiently large wounds. Studies in mice, other mammals, and limited human observations show that signals during healing can restart the follicle program. Key immune cells, such as specialized T cells ($\gamma\delta$ T cells) and macrophages, play a central role in this process by sending molecular “go” or “stop” signals that influence whether hair stem cells remain dormant or re-enter the growth phase [93–96]. This discovery has shifted attention to the concept of an “immune niche,” where the immune system does not just fight infection but also acts as a regulator of regeneration, helping stem cells decide when to rest and when to grow.

4.2. *Wnt/ β -Catenin Pathway Modulation*

In parallel, Wnt/ β -catenin has become a prime therapeutic target: when it is activated, follicles grow; when it is blocked, they regress [8,97]. Peptide and small-molecule strategies that relieve CXXC5-mediated braking on the pathway, such as PTD-DBM and next-generation activator KY19382, have boosted regrowth and even enhanced WIHN in preclinical models, offering a clearer mechanistic path than classic drugs [98–100]. Adjunctive therapies such as low-level laser therapy also influence this pathway, stimulating follicular regrowth [8]. Collectively, these signals act on the dermal papilla–dermal sheath–matrix axis (Figure 1). These Wnt-pathway activators currently have robust preclinical support, but human efficacy and long-term safety remain unknown, and no Phase III trials have yet been completed.

4.3. *Cellular Sources: Autologous vs. Allogeneic*

Cellular and regenerative therapies for AGA encompass a heterogeneous group of interventions. It is important to distinguish between autologous and allogeneic cell sources, as well as between follicular cells (dermal papilla cells, follicle stem cells) and adipose-derived stem cells (ADSCs). Most clinical studies have focused on autologous sources, particularly ADSCs and follicular stem cells, due to lower risks of immune rejection and ethical issues compared to allogeneic or perinatal sources [101–103]. These autologous approaches have shown promising short-term improvements in hair density, shaft thickness, and overall scalp coverage, with relatively favorable safety profiles. However, variability in protocols, small study sizes, and lack of long-term follow-up continue to limit firm conclusions. Overall, these cell-based strategies should still be regarded as preliminary and experimental, based on early-phase cohorts and small randomized trials; Phase III data are not yet available. In contrast, allogeneic and perinatal sources, such as umbilical cord–

derived mesenchymal cells, offer the potential for standardized “off-the-shelf” therapies but raise additional challenges, including regulatory hurdles, scalability, and theoretical risks of immune rejection [101–104].

4.4. Regulatory and Compliance Considerations

At present, no stem cell, exosome/secretome, or cloning/iPSC-derived therapy has approval from the U.S. Food and Drug Administration for the treatment of hair loss. Accordingly, all cell-based interventions (e.g., dermal papilla/dermal sheath cup cells, adipose-derived stem cell/stromal vascular fraction products, iPSC-derived cells, organoids, and 3D bioprinting approaches) and all cell-free secretome/exosome preparations should be regarded as investigational. Clinical use—outside of minimal-manipulation autologous blood products such as platelet-rich plasma—should occur only under appropriate regulatory pathways (e.g., IND/IDE or country-specific equivalents), with GMP-compliant production, product characterization and release testing, donor screening where applicable, and IRB/ethics approval. Regulatory agencies have cautioned against the marketing of unapproved “exosome” products; clinicians and patients should be alert to such claims. In this review, references to these modalities are descriptive and do not constitute endorsement of unapproved clinical use.

4.5. Adipose-Derived Stem Cells and Secretome

ADSCs and their conditioned media (ADSC-CM) are gaining traction because they release growth factors and anti-inflammatory signals that “wake up” follicles. Randomized and controlled studies in AGA show improvements in hair density, shaft thickness, and global impression, alone and when combined with minoxidil, with good tolerability [104–107]. Standardization of ADSC-derived products as topical or injectable secretome therapies is particularly attractive. (Study context: early prospective studies/cohorts with small samples suggest density gains; product characterization and regulation vary—interpret effect sizes cautiously.)

Systematic reviews and meta-analyses confirm that stem cell-derived conditioned media can significantly increase hair density and thickness in AGA, with pooled mean differences of ~9–15 hairs/cm² and diameter increases of 2.8–34.6 µm, especially with longer treatment durations [108,109]. A 2024 randomized trial showed that autologous hair follicle mesenchymal stem cell suspensions increased terminal hair proportion and shaft diameter in advanced AGA, especially in follicles <60 µm, with no major adverse events [110]. The available clinical studies of ADSC-derived preparations and follicular stem-cell suspensions are early-phase (typically n < 100 with ≤12-month follow-up) and heterogeneous in protocol; larger, Phase III trials are needed to define durability and long-term safety.

4.6. PRP in Alopecia: Promise, Limits, and Evidence Gaps

Platelet-rich plasma (PRP) has rapidly become one of the most widely used regenerative adjuncts in the treatment of androgenetic alopecia (AGA). Enthusiasm stems from its biologic plausibility and ease of office delivery; however, a balanced appraisal is required to avoid overstating efficacy. Below we synthesize current evidence, explicitly addressing variability in preparation and outcomes, short-term versus durable effects, and randomized controlled data, including trials showing no significant benefit over placebo. (Study context: randomized, double-blind, split-scalp RCT (n = 35) found no significant superiority of PRP over placebo; meta-analyses show heterogeneity and possible publication bias (Table 3).

Table 3. PRP in androgenetic alopecia: mechanism, sources of variability, and clinical impact.

Preparation variability	Composition (patient-specific)	Dominant drivers
• Single vs. double spin • Activation (Ca²⁺/thrombin) • Yield, purity, leukocytes	• VEGF, PDGF, IGF-1 • GDNF variability • Cytokine signatures	• Angiogenic (VEGF/PDGF) • Neurotrophic (GDNF) • DP-activating cues
Mechanism A: Angiogenesis and metabolism ↑ Perfusion; DP survival	Mechanism B: Neurotrophic support (GDNF) Rescue of miniaturized follicles	Mechanism C: Dermal papilla activation Paracrine to matrix/HFSC
Confounder 1: Procedural/placebo effects Needle micro-injury; split-scalp diffusion		Confounder 2: Study heterogeneity and bias Protocols, dosing, endpoints; publication bias
Clinical signal (3–6 months) ↑ Hair density (consistent). Hair thickness: variable		Durability/maintenance Peak by ~3–12 months; Booster sessions commonly needed

The table traces platelet-rich plasma (PRP) from preparation (left) through composition to dominant biological drivers (angiogenesis, neurotrophic support, dermal papilla activation), then links these to mechanistic axes that promote telogen-to-anagen transition and sustain anagen (middle). The confounders panel highlights factors that can inflate apparent effect (procedural micro-injury and study heterogeneity). The outcomes panel summarizes the typical clinical signal (near-term density gains are more consistent than shaft thickening) and the frequent need for maintenance to preserve benefit. Methodological notes: “Single vs. double spin” refers to the centrifugation protocol, which alters platelet/leukocyte yields and may change biological activity. “Split-scalp diffusion” indicates potential crossover of biological or injury signals between treated and controls halves of the scalp in split-scalp randomized trials, which can attenuate between-group differences. “Endpoints” denote the primary outcome measures used across studies (e.g., terminal hair density, shaft diameter, global photographic scales, patient-reported outcomes) and vary by trial and timepoint. “Publication bias” reflects preferential publication of positive findings; meta-analyses of PRP report heterogeneity and possible bias, so effect sizes should be interpreted with caution. Abbreviations: DP, dermal papilla; HFSC, hair follicle stem cell; VEGF, vascular endothelial growth factor; PDGF, platelet-derived growth factor; IGF-1, insulin-like growth factor-1; GDNF, glial cell line-derived neurotrophic factor, arrows ↑ denotes up-regulation/activation.

4.6.1. Mechanistic Rationale

PRP is not a single product but a family of autologous preparations with differing concentrations of platelets, leukocytes, and plasma proteins. Candidate mechanisms relevant to follicle rescue include angiogenic support (e.g., VEGF/PDGF), paracrine stimulation of dermal papilla–matrix crosstalk, and neurotrophic influences. While early work emphasized angiogenesis and mitogenic signaling in dermal papilla cells [104,105], a randomized, blinded pilot identified glial cell line–derived neurotrophic factor (GDNF) as the factor most strongly correlated with density improvement [106], suggesting that patient-specific cytokine ‘signatures’ may determine responsiveness. This composition-dependence provides a biologic basis for heterogeneous clinical outcomes. (Study context: randomized, double-blind, split-scalp RCT (n = 35) found no significant superiority of PRP over placebo; meta-analyses show heterogeneity and possible publication bias.)

4.6.2. Clinical Signals: Meta-Analyses and Cohort Studies

Multiple meta-analyses report that PRP tends to increase hair density at 3–6 months relative to controls, whereas effects on shaft thickness are less consistent; heterogeneity and risk of bias across studies remain high [97–99]. Several prospective series describe cosmetic improvement and patient satisfaction, with some reports suggesting stronger density gains in specific subgroups (e.g., male AGA), though sex-related differences remain uncertain [99]. Translational data from a humanized mouse model of AGA further support biological activity closer to human scalp physiology [103]. (Study context: randomized, double-blind, split-scalp RCT (n = 35) found no significant superiority of PRP over placebo; meta-analyses show heterogeneity and possible publication bias.)

4.6.3. Randomized, Placebo-Controlled Trials and Procedural Bias

A pivotal split-scalp, double-blind, placebo-controlled RCT reported that both PRP-treated and placebo-injected sites exhibited density gains, with no statistically significant superiority of PRP over placebo [100]. This finding raises two concerns for trial design and interpretation: (i) injection-related micro-injury may induce a regenerative response independent of PRP content; and (ii) diffusion or cross-talk between split-scalp fields may diminish between-arm contrasts. Together with heterogeneous protocols, such procedural effects likely inflate apparent responses and complicate assessment of true PRP-specific benefit. (Study context: randomized, double-blind, split-scalp RCT (n = 35) found no significant superiority of PRP over placebo; meta-analyses show heterogeneity and possible publication bias).

4.6.4. Durability and Maintenance Requirements

Across studies, the clinical signal of PRP most often peaks within ~3–12 months. Sustaining benefit commonly requires maintenance sessions (e.g., every 3–6 months). Long-term durability beyond 12 months without ongoing treatment is rarely documented, and regression after discontinuation is common. These features argue for positioning PRP as a supportive adjunct rather than as a definitive disease-modifying monotherapy in AGA. (Study context: randomized, double-blind, split-scalp RCT (n = 35) found no significant superiority of PRP over placebo; meta-analyses show heterogeneity and possible publication bias).

4.6.5. Variability in Preparation and Reporting

Inter-study variability is substantial. Key parameters—including single versus double spin, activation method (e.g., Ca^{2+} /thrombin), final platelet/leukocyte content, injection schema, dosing intervals, and endpoints—differ widely, limiting reproducibility and the comparability of effect sizes. Meta-analytic signals must therefore be interpreted cautiously, with several analyses noting heterogeneity and potential publication bias [97–99,107]. Standardized operating procedures and transparent reporting of cellular/protein yields are necessary to refine the clinical signal and identify true responders.

4.6.6. Safety, Limitations, and Patient Selection

PRP is generally well tolerated; the most frequent issues are injection pain, transient erythema/edema, and procedural inconvenience. However, costs, variable access, and the need for repeated sessions are non-trivial. Importantly, current evidence suggests that PRP primarily augments the function of miniaturized existing follicles rather than inducing true follicle neogenesis; therefore, expectations should be calibrated toward incremental cosmetic gains rather than curative regeneration. Response appears strongest when baseline miniaturization is present but scarring is absent.

4.6.7. Role in Multimodal Care

Given its mechanism and durability profile, PRP is best deployed as an adjunct—paired with disease-stabilizing pharmacotherapy (e.g., Minoxidil, 5- α -reductase inhibitors) and/or procedural strategies (microneedling, transplantation). Combination regimens may leverage complementary pathways (angiogenesis, DP signaling, mechanical cues) while spreading the burden of maintenance across modalities.

4.6.8. Standardization Priorities and Future Directions

To meet the bar set by the reviewer and the field, we outline priorities: (i) harmonized preparation/activation protocols with reporting of platelet and leukocyte yields; (ii) stratification by baseline disease pattern and miniaturization burden; (iii) adoption of

objective endpoints (phototrichogram, hair caliber distribution) with pre-registered outcomes; (iv) sham-controlled designs that mitigate injection-related bias; and (v) exploration of biomarker-guided personalization, including GDNF-enriched signatures, to pre-select likely responders. Only with such standards can we resolve conflicting RCT signals and define durable, generalizable benefit.

4.6.9. Conclusions

PRP remains a biologically plausible and clinically accessible adjunct for AGA, with short-term density gains observed in many patients. However, placebo and injection-related effects, protocol heterogeneity, composition-dependent variability, and limited durability—including randomized trials showing no significant superiority over placebo—must be explicitly recognized [97–100,106,107]. Accordingly, PRP should be framed as an adjunct within multimodal care rather than a stand-alone regenerative therapy. Future studies should prioritize standardized preparation and reporting, sham-controlled designs that minimize procedural bias, and biomarker-guided patient selection to improve reproducibility and long-term outcomes.

4.7. Microneedling: A Regenerative Adjunct with Promising but Temporary Effects

Microneedling has gained attention as a regenerative adjunct in alopecia therapy by inducing controlled micro-injury to the scalp, which activates wound-healing pathways and transiently increases the local release of growth factors such as VEGF, PDGF, and Wnt-related signals. Preclinical work shows that repeated microneedle stimulation up-regulates Wnt3a, β -catenin, and VEGF expression, leading to enhanced follicular activity and visible hair regrowth in mice [111]. Clinical data, although limited, are encouraging: randomized and prospective studies demonstrate that microneedling alone, or combined with minoxidil, produces greater improvements in hair density and shaft thickness than minoxidil monotherapy [111], including in both male and female pattern hair loss [112]. (Study context: randomized/evaluator-blinded studies (~12–24 weeks) showed greater hair-count gains when microneedling was added to topical minoxidil vs. minoxidil alone ($p < 0.05$); protocols vary).

Device-assisted strategies are also emerging: combining microneedling radiofrequency with topical exosome therapy or exosome complexes alone has yielded density gains of ~30–35 hairs/cm² at 12 months with high patient satisfaction and minimal side effects [16,113]. Still, the effects appear largely temporary, reflecting the short-lived boost in growth factors triggered by wound healing. A 2021 systematic review covering 22 clinical studies and >1000 patients concluded that microneedling is most effective as an adjunct (with minoxidil, PRP, or exosomes), while durability beyond one year remains uncertain [114]. A more recent 2025 meta-analysis confirmed that microneedling plus minoxidil significantly outperformed minoxidil alone, though trial sizes were small and protocols varied [115]. Altogether, microneedling remains a promising but still supplementary strategy in regenerative hair medicine, requiring larger and longer trials to clarify its true role. In particular, microneedling should be viewed as an adjunctive, early-phase intervention: most trials are small of limited duration (~3–12 months), and use variable or absent sham controls, so reported effect sizes must be interpreted cautiously.

4.8. Broader Stem Cell Strategies

Other studies of autologous follicle micro-grafts, stromal vascular fraction, and cultured dermal-sheath-cup or mesenchymal stromal cells show short-term gains in density and thickness, usually 10–30% above baseline for 3–9 months, but often plateau within a year [102,116]. Combination therapy with ADSC-conditioned media and minoxidil has also demonstrated significant improvements, though differences between concentrated

and non-concentrated preparations were not statistically significant [105]. (Study context: pilot RCTs and cohorts report density/diameter improvements vs. controls; preparation methods and cell yields differ widely; longer-term durability remains uncertain.)

4.9. Evidence Gaps and Regulatory Status

Preclinical and early clinical studies are also exploring cell-free secretome therapies and Wnt/ β -catenin modulators, but these remain investigational [8,117]. Importantly, no stem-cell product or processing method is approved by the FDA or other major authorities for AGA. In April 2024, the FDA issued a consumer alert clarifying that all marketed stem-cell and exosome treatments for hair loss remain unapproved investigational biologics requiring full regulatory oversight.

Systematic reviews emphasize major gaps: study numbers remain small, protocols vary widely, and outcome measures lack standardization [116,118,119]. Risks such as tumorigenicity and immune rejection are theoretical, especially with allogeneic or manipulated cells, but have not been reported in limited autologous trials [103,104].

4.10. Future Outlook

Looking ahead, biologics and antibody therapies that precisely target key regulators of follicle cycling, along with dermal papilla and stem-cell-based strategies, offer the potential to rebuild follicles “from within,” moving beyond finasteride and minoxidil [92]. The promise lies in combining immune-guided regeneration, Wnt-pathway precision and stem-cell/secretome therapies into a predictable, patient-friendly model. Yet until larger, long-term trials confirm efficacy and safety, stem-cell therapy for pattern hair loss remains experimental and should not be presented as standard care.

5. Biotechnologies: 3D Bioprinting

Beyond administering cells, researchers are actively trying to engineer hair follicles in the laboratory. Three-dimensional bioprinting and organoid culture offer routes to create hair-bearing skin grafts from scratch. In one recent study, scientists printed dermal papilla cell and endothelial cell spheroids directly into a collagen-based dermal matrix [120]. Over time, the tissue self-organized into structures that mimicked native hair follicles, complete with associated epidermal and melanocyte components. In effect, this work produced miniature hair follicles in vitro that could (at least in theory) be implanted as grafts. In a related tissue-engineering advance, researchers used 3D-printed molds to pattern collagen gels: by seeding human dermal papilla cells into hair follicle-shaped microwells, they generated follicle-like structures. When keratinocytes were added on top, the assembled units closely resembled hair follicle stem cell niches with physiological cell organization [120].

Scalable and automated preparation of hair follicle germ-like grafts has been achieved by printing adjacent collagen droplets containing mesenchymal and epithelial cells; these microgel-based constructs contract and enrich cell density, facilitating mesenchymal–epithelial interactions that efficiently regenerate hair follicles and shafts upon transplantation, and guide-inserted microgels have improved hair shaft sprouting through the skin by controlling graft orientation [121]. Recent studies have demonstrated that multilayer composite scaffolds using gelatin/alginate hydrogels can simulate the native hair follicle microenvironment, supporting the formation of self-aggregating dermal papilla spheroids and promoting the expression of hair-inductive genes such as ALP, β -catenin, and α -SMA; these bioprinted constructs, when transplanted into full-thickness wounds in animal models, have shown the ability to regenerate entire hair follicles in vivo with appropriate orientation and physiological organization [120,122].

Three-dimensional bioprinting has also enabled the incorporation of hair follicle-like structures into engineered skin tissues: spheroids of dermal papilla and endothelial cells printed within pre-gelled dermal layers containing fibroblasts matured into follicle-like structures, supported by keratinocyte and melanocyte migration, closely mimicking native skin appendages [123].

Multicellular micropatterning with vascular-cell networks and biomimetic substrates has enhanced both follicular potential and angiogenic capacity, resulting in efficient hair regrowth in animal models [124], and additional advances include the use of skin stem cells and multicomponent hydrogels to fabricate artificial skin via 3D bioprinting, enabling regeneration of epidermis, dermis, hair follicles, blood vessels, and sebaceous glands in wound models [124]. Microenvironmental reprogramming and co-culture systems have further improved the hair-inductive properties of dermal papilla cell aggregates, supporting large-scale production for tissue engineering applications [125,126]. Organoid models and 3D spheroid cultures have demonstrated enhanced extracellular matrix production, improved cell viability, and upregulation of trichogenic signaling pathways, which are critical for folliculogenesis and drug screening [127–131], and these models have shown responsiveness to known hair-growth promoters and inhibitors and can be used for high-throughput screening and mechanistic studies. Despite these advances, technical limitations remain, including scalability issues; producing thousands of functional units for clinical application is not yet feasible at industrial scale [121,126].

High-throughput systems have been proposed, but maintaining cell viability, inductivity, and reproducibility during upscaling remains problematic. Cost is another significant factor. The use of specialized biomaterials (e.g., gelatin/alginate hydrogels, collagen matrices), growth factors, and advanced bioprinting hardware increases production expenses, which may limit accessibility for widespread clinical use [121,122,126]. Additionally, the need for GMP-compliant cell sources and rigorous quality control further elevates costs. Translational challenges include the difficulty of recapitulating the complex epithelial–mesenchymal interactions and microenvironmental cues necessary for long-term follicle function and cycling. While *vitro* follicle-like structures can be generated and even induce hair shaft formation in animal models, these constructs often fail to sustain normal hair cycling and integration *in vivo* [9,132,133]. The mismatch between *in vitro* morphology and *in vivo* functionality is attributed to incomplete microenvironmental reconstitution, insufficient vascularization, and the lack of proper signaling for hair cycle regulation [120].

The field continues to progress toward functional reconstruction of hair follicles, with ongoing research focused on optimizing cell sources, biomaterials, and microenvironmental cues [91,132,134]. At present, organoids, iPSC-derived follicles, and 3D-bioprinted constructs remain preclinical; human durability, safety, and scalability are unknown, and no Phase III clinical trials have been conducted.

6. Cloning for Alopecia

The hair follicle is a complete mini-organ, making it a powerful model for research in stem cell biology, organ regeneration, and ultimately cloning strategies to restore hair. In this context, “cloning” does not mean genetic duplication, but rather the expansion of follicle-inductive cells outside the body and their use to form new, healthy follicles in areas affected by alopecia (Figure 4). The overarching goal is to create a renewable, reliable source of transplantable follicles, moving beyond the donor limitations of traditional hair transplantation [133].

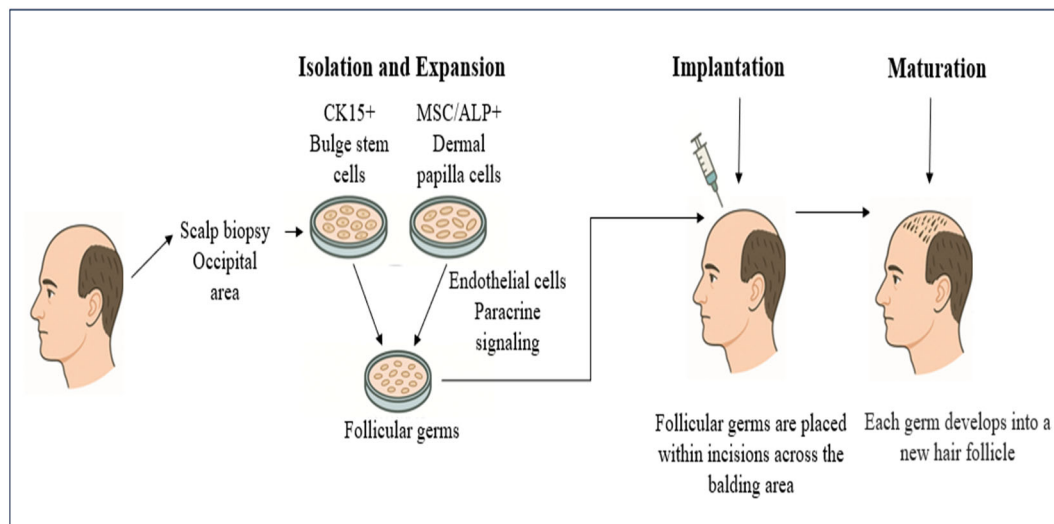


Figure 4. Hair cloning workflow for androgenic alopecia. Hair cloning protocols described in the recent literature generally [135] follow a multi-step process beginning with a small punch biopsy from the permanent occipital scalp to harvest healthy hair follicles. From these follicles, two primary stem cell populations, dermal papilla cells (mesenchymal stem cells, MSCs) and outer root sheath cells (epithelial stem cells), are isolated and expanded separately under conditions that preserve their hair-inductive properties. These stem cells, along with endothelial cells, are then recombined in three-dimensional micro-scaffolds or hanging-drop spheroids to form miniature follicular “germs” that replicate early hair-bud architecture. After in vitro quality control, such as alkaline phosphatase positivity (ALP+) in dermal papilla cells, K15 expression in epithelial cells, and confirmation of cell viability and structural integrity, the germs loaded into fine-gauge needles and implanted via microincisions into balding scalp regions. Upon engraftment, each germ matures into a fully functional hair follicle capable of normal cycling and fiber production, potentially providing an essentially unlimited donor supply. This approach remains at the preclinical or early-phase stage, with limited published data, and is not yet approved for clinical use.

6.1. Experimental Approaches

Early laboratory studies demonstrated that dermal papilla (DP) cells, the key inductive mesenchyme of the follicle, lose their hair-forming power in two-dimensional culture. However, this power can be restored when DP cells are cultured as three-dimensional spheroids, which successfully induced *de novo* hair follicles in preclinical models [132]. Parallel work with human pluripotent stem cells (hPSCs) has generated *skin organoids* containing hair follicles, which, when grafted onto immunodeficient mice, formed hair-bearing skin [136]. Another strategy, termed the *organ germ method*, recombines epithelial and mesenchymal cells to bioengineer follicular “germs” that can develop into innervated, cycling follicles after transplantation [133].

More advanced approaches include assembling dermal papilla, keratinocyte, and endothelial cells into three-cell aggregates, which significantly improved hair yield and activated anagen-associated genes such as LEF1 and VEGF in animal models [135]. In addition, direct reprogramming methods have been developed to convert human fibroblasts into DP-like cells using single small molecules, providing a potentially scalable source of hair-inductive cells [137].

6.2. Clinical Translation

Several early human programs attempted to move hair cloning toward the clinic. Intercytex (ICX-TRC) tested autologous DP cell injections, showing proof-of-concept hair growth but with variable and limited outcomes, preventing approval [138,139]. Aderans Research Institute advanced similar DP-based strategies through multiple clinical trials but

eventually discontinued its program, although its innovations continue to inform newer companies [139–144]. Taken together, these efforts indicate that hair-follicle “cloning” remains at the preclinical and early-clinical stage, with no approved products and no completed Phase III trials.

A key figure in the development of follicle cell-based therapies is Kevin McElwee, an academic scientist and co-founder of RepliCel Life Sciences. His pioneering work on isolating and expanding dermal sheath cup (DSC) cells laid the foundation for the first-in-human studies of autologous cell injections for AGA [145]. The RCH-01 program, originally developed by McElwee and colleagues at the University of British Columbia and advanced through RepliCel, was later licensed to Shiseido in Japan, enabling a series of early clinical trials. A pivotal milestone came with a randomized, placebo-controlled, double-blind phase II study published in JAAD [146], which evaluated DSC injections in 65 patients with androgenetic alopecia. Small scalp biopsies were harvested, expanded in culture, and injected into four randomized treatment sites per participant. At the 3.0×10^5 cell dose, treated sites demonstrated significant increases in hair density and cumulative hair diameter at 6 and 9 months compared with placebo, while no major adverse events were reported. Importantly, the observed benefits appeared to result from the revitalization of miniaturized follicles rather than true de novo follicle formation, and effects diminished by 12 months, suggesting the need for repeat dosing or combination strategies.

A subsequent multi-center, open-label trial involving 36 participants reported that two rounds of DSC injections led to global photographic improvement in approximately 30% of patients after 12 months [147]. Mechanistic studies suggest that treatment outcomes may depend on the molecular phenotype of the injected cells: DSC subpopulations enriched for integrin $\alpha 6$ (ITGA6) expression demonstrated higher migratory activity and better hair growth outcomes, while those expressing smooth muscle-related genes such as SRF, CALD1, and ACTA2 correlated with reduced efficacy [148]. These findings underscore both the promise and the challenges of DSC-based therapies, showing that cultured follicular support cells can indeed rescue miniaturized follicles in humans, but that durability, consistency, and optimization of cell populations remain major hurdles before widespread clinical adoption [149]. (Study context: randomized, placebo-controlled, double-blind phase II trial ($n = 65$) of dermal sheath cup cells showed significant gains at 6–9 months vs. placebo; effects diminished by ~12 months.)

At present, Stemson Therapeutics is advancing induced pluripotent stem cell (iPSC)-derived engineered follicular units (EFUs), which have successfully generated human hair follicles in humanized mouse models and are slated for early human trials in 2025–2026 [90]. In parallel, the RIKEN/Organ Tech group in Japan has pioneered organoid-based follicle regeneration platforms, producing robust cycling follicles in mice. Meanwhile, HairClone (UK) has initiated follicle banking, cryopreserving patient follicles for future expansion and reinjection, though this remains preclinical [150].

6.3. Challenges

Despite clear progress, significant barriers remain. (1) DP and dermal sheath cells rapidly lose their hair-inductive signature in standard culture, making 3D culture systems and optimized signaling environments essential [132]. (2) Follicles are complex, requiring epithelial–mesenchymal crosstalk, vascularization, innervation, and correct orientation to yield natural hair growth. Organoid and organ-germ systems attempt to mimic this, but human translation is incomplete [133]. (3) Living, multi-cell constructs must be reproducible, cost-effective, and compliant with Good Manufacturing Practice (GMP) standards, which is a major hurdle. (4) In the United States, the FDA classifies any cultured cell or exosome-based therapy for hair restoration as an unapproved investigational biologic. No

such product has received approval to date. Similarly, in Europe, the EMA regulates these products as Advanced Therapy Medicinal Products (ATMPs), requiring rigorous safety and efficacy data before approval [151].

6.4. Current Status and Outlook

At the biological level, we now know that human cells can be guided into forming follicle-like structures using approaches such as DP spheroids, hPSC-derived skin organoids, and organ germ engineering [133,135]. Translationally, first-generation trials by Intercytex and Aderans demonstrated feasibility but lacked durable, consistent results. Newer approaches using iPSCs, direct reprogramming, and organoid-based EFUs offer a clearer roadmap for reproducibility and eventual large-scale clinical use [90,137].

Nevertheless, most evidence remains confined to animal studies and small, short-term human cohorts. Long-term safety data, standardized protocols, and large controlled trials are missing. Regulatory agencies, as well as the International Society of Hair Restoration Surgery (ISHRS), stress that hair cloning remains experimental and investigational, not a proven therapy [152].

If successful, a future workflow might involve taking a small scalp biopsy or generating iPSCs from the patient, expanding the necessary follicular cells in a 3D environment, assembling them into engineered follicular units, and implanting them as grafts. Unlike traditional hair transplantation, this would create new follicles rather than redistribute existing ones, potentially solving the donor limitation once and for all.

7. Discussion

The field of hair restoration is undergoing substantial change, driven by advances in regenerative medicine, biomaterials, and bioengineering. Emerging technologies, ranging from refined transplantation techniques and robotic implantation systems to exosome- and stem-cell-based approaches, are expanding what is clinically feasible. Over the next decade, these modalities may prove safer and more accessible, contingent on adequately powered trials and formal regulatory review. Automation, artificial intelligence, and reproducible regenerative formulations may reduce costs and broaden access, moving therapies from specialized centers toward routine dermatologic practice (Table 4).

To integrate the signaling pathways discussed, we provide a mechanistic synthesis (Table 1, Figures 1 and 2 and Supplements Tables S1 and S2) that maps each therapy to its dominant molecular lever—Wnt/ β -catenin activation, BMP modulation, angiogenesis, mechano-transduction, immune-niche normalization, and dermal papilla signaling—and clarifies how these converge to influence telogen–anagen–catagen transitions. Complementing this framework, a comparative clinical overview (Tables 1–7) summarizes typical effect sizes, study quality, durability, and key limitations across principal pharmacologic and regenerative therapies. Together, these tables highlight convergent biological pathways while documenting heterogeneity in the strength and durability of clinical evidence among modalities.

Table 4. Hair Restoration Technologies Overview.

	Description	Clinical Use/Regulatory Status	Advantages	Challenges	Representative Evidence/Sample Details
Minoxidil [3–5,153,154]/ Finasteride [3–5,155]	Pharmacologic agents slowing AGA progression by vasodilation and DHT inhibition; no follicle creation.	Routine clinical use (first line) Long-term benefit only with continuous use	Well-established, low-cost, accessible	Limited regrowth; no regenerative capacity; requires continuous use	Multiple large RCTs and post-marketing cohorts in thousands of adult men and women with AGA; topical and low-dose oral minoxidil assessed in long-term human scalp studies, with biomarkers of follicular aging measured in human AGA scalp biopsies.
Platelet-Rich Plasma (PRP) [119,156,157]	Autologous platelets concentrate releasing growth factors to stimulate follicular activity and angiogenesis [104,105] Glial cell line derived neurotrophic factor (GDNF) as the most correlated factor with density improvement [106].	Adjunctive therapy (multiple small RCTs)	Safe, minimally invasive, enhances density mostly 3–6 months benefit, Humanized mouse model of AGA supports biological activity closer to human scalp [103]	Protocol variability; short-lived effects; inconsistent results, maintenance required Can cause pain, erythema, inconvenience costly, Effect on shaft thickness are less consistent	Evidence derived from multiple small RCTs and cohorts in adult AGA, typically n ≈ 20–60 per trial, using autologous peripheral blood-derived PRP; includes a randomized, double-blind, split-scalp RCT (n = 35) showing no significant superiority over placebo [97–100]; meta-analyses pool dozens of small studies with heterogeneous protocols [107].
Microneedling [17] (±PRP/Exosomes)	Controlled micro-injury activates Wnt/BMP pathways and improves biologic delivery to follicles [111]	Increasing use; prospective trials positive	Synergistic, simple, inexpensive Microneedling alone: RCTs with greater hair-count gains vs. minoxidil alone, 12–24 weeks [111,112,115] Exosome + microneedling: ~30–35 hairs/cm ² at 12 months [16,113]	Temporary effect; protocol heterogeneity, Temporary effect (weeks–months) Exosomes: cell-free but unregulated; unknown long-term safety	Clinical data from randomized/evaluator-blinded trials (~12–24 weeks) and prospective cohorts in adult men and women with AGA [112], with typical sample sizes n ≈ 20–100; one systematic review covers >22 studies and >1000 patients; interventions include microneedling alone and in combination with topical minoxidil, PRP, or exosomes [114].
Adipose-Derived Stem Cells [104–107] (ADSCs) and Conditioned Media	Autologous stromal cells or secretome delivering regenerative cytokines, anti-inflammatory effect and growth factors.	Early clinical trials and meta-analyses no Phase III data.	Paracrine repair, anti-inflammatory, safe, +9–15 hairs/cm ² , diameter +2.8–34.6 μm, early-phase, n < 100	Small studies, short follow-up, lack of standardization. Theoretical tumorigenicity and immune issues; so far not seen in small autologous trials but still experimental, Unknown long-term durability	Human evidence from early-phase prospective cohorts and small RCTs (typically n < 100, ≤12-month follow-up) in adult AGA patients. Samples include autologous lipoaspirate-derived ADSCs, stromal vascular fraction, and ADSC-conditioned media (topical or injectable). Systematic reviews/meta-analyses pool multiple small trials;
Mesenchymal Stem Cell-Derived Exosomes [12,103,110,158]	Cell-free vesicles transmitting regenerative signals; activate Wnt/β-catenin and dermal papilla proliferation [12,13]	Early human data: systematic reviews show density gain and thickness [102,116]	Scalable, standardized, safe	Costly, unregulated, no long-term data	Based on preclinical models (murine AGA and human DP cell cultures) plus early human pilot cohorts. A systematic review of MSC-derived exosomes reports density gains of ~9.5–35 hairs/cm ² and shaft-thickness increases up to ~13 μm in small human AGA trials (each typically n < 50); products derive from adipose tissue, bone marrow, or perinatal sources [10,11]. Long-term human data is lacking.

Table 4. Cont.

	Description	Clinical Use/Regulatory Status	Advantages	Challenges	Representative Evidence/Sample Details
Mechanobiology/ Follicle Activation [9,18,24,159–161]	Mechanical cues → macrophage polarization → Wnt/ β -catenin, BMP modulation → HFSC activation [97]	Early translational research stage	Non-pharmacologic, complements biologics	No standardized human protocols. Not a Therapy per se	Primarily pre-clinical animal models (e.g., murine wounding and mechanical stretch) and ex vivo human scalp explants. Representative work includes controlled mechanical stretch in mice showing telogen-to-anagen transition via M2-like macrophages and Wnt/ β -catenin activation; human data are limited to small mechanistic studies, not powered clinical trials.
Small Molecule EX104 [19,162]	Novel compound remodeling follicular microenvironment and promoting angiogenesis; superior to minoxidil in mice.	Preclinical	Targeted molecular approach	No human data; unknown toxicity	Evaluated in murine AGA models only; sample types include C57BL/6 or similar mouse strains with androgen-induced alopecia. Outcomes include hair-density and shaft-thickness measurements; notrials reported to date.
AI and Machine Learning Applications [50,62,66]	Deep-learning models for trichoscopy, dermoscopy, and OCT image analysis (>92% accuracy).	Prototype/validation phase Performance influenced by dataset size, skin-type representation, and regulatory constraints	Objective diagnostics, predictive potential	Dataset bias, privacy and regulatory issues [163,164]	Algorithms trained and validated on retrospective trichoscopy, dermoscopy, and OCT image datasets, usually hundreds to several thousand images from adult patients with AGA, AA, and other alopecies. HairComb, for example, was validated in >400 patients [165,166], comparing automated severity scores with manual clinical scales; most datasets are single- or few-center and skewed toward lighter skin types.
ARTAS® Robotic FUE System [78,84,87]	Image-guided robotic harvesting with algorithm-based follicle targeting	FDA-cleared (male AGA, brown/black hair)	High precision, reproducibility, reduced fatigue [81,82], low complication rate, shorter learning curve for surgeons, Selection of the best follicles for harvesting [83].	High cost [78,87], less efficient in curly hair [87–89], scars, etc. Permanent relocation of follicles	Data from prospective multicenter human trials and real-world cohorts in adult men with AGA, typically brown or black hair, undergoing robotic FUE. Reports describe harvesting rates of 500–1000 grafts/hour, ~1593 recipient sites/hour [79], and transection rates around 6.6% comparable to experienced surgeons [80]. Sample origin: occipital donor scalp follicles; no animal data.
Three-dimensional Bioprinting and Organoid Engineering [122,123,134]	Lab-grown follicle-like units using epithelial–mesenchymal co-culture and hydrogel scaffolds [124].	Preclinical/tissue engineering	Mimics follicle architecture, potential de novo growth [127–131].	Scalability, vascularization, and cost limitations [121,126]. Mismatch between in vitro morphology and in vivo functionality [120].	Evidence from in vitro human cell constructs and animal wound-healing models. Sample types include human dermal papilla cells [125,126], keratinocytes, melanocytes, fibroblasts, endothelial cells, assembled in collagen/gelatin/alginate hydrogels. Typical experiments use dozens to hundreds of bioprinted constructs and murine full-thickness wounds; no human clinical trials yet.

Table 4. Cont.

	Description	Clinical Use/Regulatory Status	Advantages	Challenges	Representative Evidence/Sample Details
Hair Follicle Cloning (DP/DSC Cell Therapy) [133]	Expansion and reinjection of inductive dermal papilla/sheath cells to regenerate miniaturized follicles [133].	Early clinical (Phase II trials)	Proof-of-concept regenerative restoration	Loss of trichogenicity; transient benefit; regulatory hurdles	Includes historical DP-cell programs (Intercytex, Aderans) [138–144] and newer dermal sheath cup (DSC) cell trials [145]. A key randomized, placebo-controlled, double-blind Phase II trial (n = 65) used autologous DSC cells from small scalp biopsies injected into AGA scalp, showing significant density/diameter gain at 6–9 months, waning by 12 months [146]. A subsequent multi-center open-label study (n = 36) reported global photographic improvement in ~30% of patients [147]. All samples are autologous human follicular cells; no approved products.
Wound-Induced Hair Neogenesis (WIHN) [94–96,167]	De Novo follicle formation through immune-mediated regeneration after large wounds.	Experimental/translational	Demonstrates adult regenerative potential	Uncontrolled, non-reproducible in humans	Data are largely from mouse and other mammalian models with full-thickness skin wounds of sufficient size to trigger WIHN, plus limited human case observations in surgical scars. Sample types include animal dorsal skin and human scalp/skin wounds; no controlled human interventional trials.
Multimodal Integration (Combined Therapies) [168]	Combination of pharmacologic, PRP/exosome, microneedling, and AI-guided approaches.	Conceptual translational framework	Personalized, synergistic, precision-driven	Needs multicenter validation, GMP standards, regulation	Data are largely from mouse and other mammalian models with full-thickness skin wounds of sufficient size to trigger WIHN, plus limited human case observations in surgical scars. Sample types include animal dorsal skin and human scalp/skin wounds; no controlled human interventional trials.

Overview of emerging technologies for hair loss treatment. This table summarizes key advanced approaches in hair loss therapy, including AI and machine learning, robotic follicular unit extraction (FUE), stem cell therapies, 3D bioprinting, and hair follicle cloning. For each technology, applications, current developmental status, potential benefits, and major challenges are outlined to provide a comprehensive overview of the progress and hurdles toward clinical adoption.

Table 5. Minimally Invasive and Device-Based Therapies.

Therapy	Typical Clinical Effect	Evidence Quality	Durability	Limitation/Safety
PRP	Moderate density/thickness gains	Multiple trials; heterogeneity in methods	Maintenance every 3–6 months	Technique-dependent; cost
Microneedling (±topicals)	Strong additive effect with Minoxidil	Controlled studies; moderate evidence	Requires repeated sessions	Irritation, PIH, risk with overuse
LLLT/Photobiomodulation	Small–moderate improvement	Sham-controlled trials; variable quality	Requires frequent ongoing use	Cost, adherence burden

Minimally Invasive and Device-Based Therapies. Modalities such as PRP, microneedling, and photobiomodulation. Each therapy is evaluated according to its average.

Table 6. Cell-based and secretome-based regenerative therapies.

Therapy	Typical Clinical Effect	Evidence Quality	Durability	Limitations/Safety
ADSC-based preparations	Meaningful density + thickness gains	Small RCTs/cohorts; protocol variability	Durability beyond 12–18 months unclear	Regulatory complexity; cost
Exosomes/MSC secretome	Visible cosmetic improvement	Early-phase clinical data	Durability unknown; series-based	Investigational; product variability
DP/DSC cell therapies	Partial reversal of miniaturization	Small human studies; strong preclinical basis	Durability unclear; repeat dosing likely	Technical challenges; high cost

Cell-based and secretome-based regenerative therapies. Comparison of ADSC-derived preparations, exosome/MSC-secretome therapies, and dermal papilla/dermal sheath cup cell-based approaches. ADSC preparations remain experimental, with small RCTs/cohorts and substantial protocol variability; Phase III trials are lacking. Exosome/MSC-secretome therapies are likewise early-phase and investigational, with no Phase III data or regulatory approvals for hair loss to date, and standardized manufacturing and characterization are still needed.

Table 7. Surgical and Advanced Regenerative Therapies.

Therapy	Typical Clinical Effect	Evidence Quality	Durability	Limitations/Safety
Hair Transplantation (FUE/FUT)	Immediate density restoration	Decades of observational data	Permanent donor-zone follicles	Surgical risks; limited donor supply
JAK inhibitors (AA; exploratory AGA)	Strong effect in AA; minor AGA data	High-quality RCTs in AA; rare in AGA	High relapse on stopping	Systemic safety concerns; costly
Wnt-modulators (e.g., KY19382)	Strong preclinical activation/neogenesis	Robust mechanistic/animal data	Human durability unknown	Experimental; long-term safety unknown
Organoids/iPSC/Bioprinting	De novo follicle formation (animal models)	Advanced preclinical evidence	Human durability unknown	Experimental and cost challenges

Surgical and Advanced Regenerative Therapies. Surgical follicle redistribution (FUE/FUT) alongside cutting-edge technologies including JAK inhibitors (in AA), Wnt-modulating compounds, and emerging follicle-engineering platforms such as organoids, bioprinted follicles, and iPSC-derived units. Strengths, limitations, durability, and translational challenges are summarized.

A striking example of this evolution is Minoxidil. Once a purely topical treatment for AGA, it is now recognized to act systemically as well. Low-dose oral Minoxidil has proven effective in promoting hair growth and is increasingly used off-label as a systemic

therapy [153]. In vivo human scalp studies further show that long-term topical use can rejuvenate aged follicles in AGA skin, upregulating biomarkers such as Lamin B1, SIRT1, and collagen XVIIA, while reducing p16^{INK4A} and p-S6—indicating anti-aging effects within the follicle itself [169].

This evolution, from topical to systemic use, illustrates how established treatments are moving toward true follicular rejuvenation, not just symptomatic improvement.

At the same time, hair transplantation, the most established surgical approach, has undergone a major transformation. Innovations such as FUE and robot-assisted implantation have dramatically improved precision, graft survival, and esthetic outcomes. Automated follicle harvesting and AI-guided donor–recipient mapping have reduced procedure time and scarring, while bioengineered scaffolds and exosome- or platelet-rich preservation media enhance graft viability. Together, these developments are shifting transplantation from a mechanical procedure to a bio-optimized regenerative intervention, bridging traditional surgery with tissue engineering. In the near future, combining transplantation with stem-cell activation or growth-factor therapy could yield denser, more natural regrowth while lowering costs and broadening accessibility.

Simultaneously, progress in follicle biology is charting the course toward genuine regeneration. Work on the Wnt/ β -catenin pathway, notably by Ralf Paus and colleagues, has shown that blocking the Wnt inhibitor SFRP1 enhances hair-shaft production and delays follicle regression ex vivo [170]. This insight originated from studies on cyclosporine A (CsA), a well-known immunosuppressant long observed to promote hair growth. CsA's stimulatory effect was traced not to immune suppression but to downregulation of SFRP1, thereby releasing Wnt/ β -catenin signaling from inhibition. This discovery bridges pharmacology and regenerative biology, transforming incidental drug observations into target-driven follicle regeneration.

In parallel, Janus kinase (JAK) inhibitors have emerged as powerful tools for immune-mediated AA [171]. While their use in AGA remains limited, they exemplify how molecularly targeted therapies can reshape the therapeutic landscape. In time, such agents may merge synergistically with regenerative or gene-based platforms to deliver more comprehensive outcomes.

Beyond molecular modulation, recent years have witnessed groundbreaking bioengineering advances. Techniques in 3D bioprinting, hair-follicle organoid culture, and tissue-engineered skin constructs now enable partial or even complete follicle reformation in the laboratory. Multicellular constructs combining dermal papilla cells, fibroblasts, keratinocytes, and melanocytes within collagen or hydrogel matrices have generated vascularized, pigmented, hair-bearing skin in preclinical models. Developments such as iPSC-derived dermal papilla-like cells, dermal sheath cup (DSC) cell injections, and follicle organ germs mark major steps toward clinical follicle neogenesis. Combined with optimized extracellular matrices and controlled Wnt activation, these techniques could eventually restore full follicular cycling and pigmentation in humans.

The potential of exosome-based therapy is also increasingly evident. Extracellular vesicles from dermal papilla or mesenchymal stem cells can transfer microRNAs and growth factors that reactivate dormant follicles, stimulate angiogenesis, and modulate immune responses, offering a cell-free regenerative option with fewer safety concerns and easier scalability. Exosome and MSC-secretome therapies are therefore best considered experimental, early-phase interventions; published clinical studies involve small pilot RCTs and cohorts with short follow-up, and Phase III data or regulatory approvals for hair loss are not yet available.

Looking further ahead, even the meaning of alopecia may evolve. With ongoing advances in gene editing and molecular repair, permanent prevention of follicular miniatur-

ization may become achievable, potentially rendering AGA and similar disorders obsolete. At the same time, changing social attitudes may redefine the importance of hair itself: as technologies that democratize appearance and identity emerge, the decision to restore or embrace baldness may shift from medical necessity to personal expression.

Ultimately, the convergence of pharmacologic innovation (Minoxidil, Wnt modulators), molecular targeting (JAK inhibitors), and regenerative engineering (organoids, exosomes, iPSC-derived follicles) highlights active preclinical and early clinical investigation, with uncertain clinical effectiveness and durability pending larger, controlled trials.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cosmetics13010019/s1>, Table S1: Mechanistic Integration (Part 1); Table S2: Mechanistic Integration (Part 2).

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