Review

Nanotechnology-Based Strategies for Hair Regeneration: Mechanistic Insights and Translational Perspectives for Androgenetic Alopecia

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Review

Nanotechnology-Based Strategies for Hair Regeneration: Mechanistic Insights and Translational Perspectives for Androgenetic Alopecia

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Abstract

Androgenetic alopecia (AGA) is the most prevalent form of hair loss on a global scale. However, the current FDA-approved therapies, including minoxidil (MXD) and finasteride, are often limited by suboptimal follicular targeting, variable patient compliance, and systemic adverse effects. Recent advancements in nanotechnology have yielded promising strategies for the management of AGA. These strategies involve the delivery of drugs to specific follicles, the controlled release of drugs, and the modulation of the follicular microenvironment. Herein, we summarize recent progress in nanotechnology-based approaches for AGA treatment, with emphasis on the following: disease pathophysiology; nanocarrier design principles; nano-enabled microneedle systems; and multifunctional nanomaterials capable of regulating oxidative stress, angiogenesis, inflammation, as well as hair follicle stem cell activity. A discourse is also initiated on the subjects of safety considerations, manufacturing challenges, and regulatory perspectives that are pertinent to clinical translation. Overall, nanotechnology provides a versatile framework for addressing the key limitations of conventional AGA therapies and exhibits considerable potential for future clinical application.

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1. Introduction

Hair follicles are highly dynamic and complex mini-organs embedded within the skin, characterized by a tightly orchestrated cyclical process consisting of growth (anagen), regression (catagen), and rest (telogen) phases [1–5]. This cyclic regeneration is governed by intricate interactions among epithelial cells, dermal papilla cells, surrounding mesenchymal tissues, immune components, and vascular networks. Precise temporal and spatial regulation of signaling pathways-including Wnt/β-catenin, Sonic hedgehog (Shh), transforming growth factor-β (TGF-β), and bone morphogenetic protein (BMP) signaling-is essential for maintaining normal hair follicle homeostasis and sustaining hair shaft production [6–12].

Disruption of this finely tuned hair cycle leads to a spectrum of alopecia disorders, among which androgenetic alopecia (AGA) represents the most prevalent and clinically significant form [13–16]. AGA is a chronic, progressive condition characterized by the gradual miniaturization of hair follicles, shortening of the anagen phase, and prolongation of telogen, ultimately resulting in thinner, shorter, and less pigmented hairs [14,17–22]. Epidemiological studies indicate that AGA affects more than 50% of men and a substantial proportion of women over the course of their lifetime, with incidence increasing with age and genetic predisposition [23–25]. Beyond its physical manifestations, AGA imposes considerable psychosocial burdens, including diminished self-esteem, increased anxiety,

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and reduced quality of life, underscoring the need for effective and well-tolerated therapeutic interventions.

Currently, conventional pharmacological management of AGA predominantly relies on topical minoxidil (MXD) and oral finasteride, both of which have received regulatory approval and are widely used in clinical practice [26-29]. MXD is thought to promote hair growth primarily through vasodilation, potassium channel activation, and indirect stimulation of dermal papilla cell function, whereas finasteride exerts its effects by inhibiting type II 5α-reductase, thereby reducing dihydrotestosterone (DHT) levels in the scalp [30-32]. Despite their established efficacy, clinical outcomes remain highly variable, and long-term treatment is often required to maintain therapeutic benefits [33, 34].

Importantly, these conventional therapies suffer from several intrinsic limitations, including insufficient follicular bioavailability, rapid clearance from the scalp, and poor patient adherence due to frequent application or systemic exposure [29, 35]. Topically applied drugs face formidable barriers such as the stratum corneum and uneven follicular penetration, while systemic administration of antiandrogens may lead to undesirable side effects that limit widespread acceptance [26, 36]. Consequently, there exists a substantial unmet clinical need for innovative therapeutic strategies capable of achieving efficient, localized follicular targeting, sustained drug retention, and minimal off-target effects. Addressing these ch[26–29allenges has catalyzed growing interest in advanced drug delivery platforms-particularly nanotechnology-based approaches-as next-generation solutions for AGA treatment.

Nanotechnology offers unprecedented opportunities to overcome the formidable anatomical and physiological barriers presented by the skin and hair follicle, which have long limited the efficacy of conventional topical and systemic therapies [26,37–41]. The stratum corneum, complex extracellular matrix, and dynamic immune surveillance collectively restrict drug penetration and retention, resulting in suboptimal exposure of therapeutics at critical follicular compartments [42]. By contrast, nanoscale delivery systems can be rationally engineered with tunable size, surface charge, and chemical functionality to enhance penetration, prolong residence time, and achieve controlled release within the pilosebaceous unit [43–46].

Notably, the unique architecture of the hair follicle provides a privileged and biologically relevant gateway for nanomaterials. The follicular infundibulum and sebaceous duct function as a natural reservoir capable of selectively accumulating nanoparticles, thereby enabling localized drug storage and sustained delivery directly to the vicinity of dermal papilla cells and hair follicle stem cell niches [26,37,47]. This follicular targeting effect allows nanotechnology-based systems to bypass the stratum corneum barrier while minimizing systemic exposure, a critical advantage for long-term management of androgenetic alopecia [48–52]. Furthermore, the physicochemical properties of nanomaterials can be tailored to exploit follicle-specific features such as sebum affinity, cyclic hair movement, and size-dependent penetration, collectively enhancing therapeutic precision.

Beyond serving as passive carriers, emerging nanotechnology-enabled platforms increasingly function as active modulators of the follicular microenvironment [37,53–56]. Advanced nanomaterials have been designed to regulate oxidative stress, promote angiogenesis, modulate inflammatory responses, and activate hair follicle stem cells, thereby addressing multiple pathogenic drivers of AGA simultaneously [17,53,56–60]. Such multifunctional capabilities distinguish nanotechnology-based approaches from traditional formulations and align with the growing recognition that effective hair regeneration requires coordinated modulation of both cellular and microenvironmental cues.

Herein, we present current knowledge and emerging trends in nanotechnology-based strategies for hair regeneration, with a particular emphasis on AGA. We critically examine nanocarrier design principles, follicular targeting mechanisms, and nano-enabled therapeutic modalities, while highlighting mechanistic insights and translational challenges. By integrating recent experimental advances with clinical perspectives, this review aims to provide a comprehensive framework for the rational development of next-generation nanotechnology-enabled therapies for AGA.

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2. Pathophysiology of AGA

The pathogenesis of AGA is multifactorial, involving genetic susceptibility, androgen signaling, chronic inflammation, oxidative stress, and microvascular impairment [19,61–64]. Central to AGA progression is DHT, which binds androgen receptors in dermal papilla cells and induces transcriptional programs that suppress Wnt/β-catenin signaling and anagen maintenance [14,15,65].

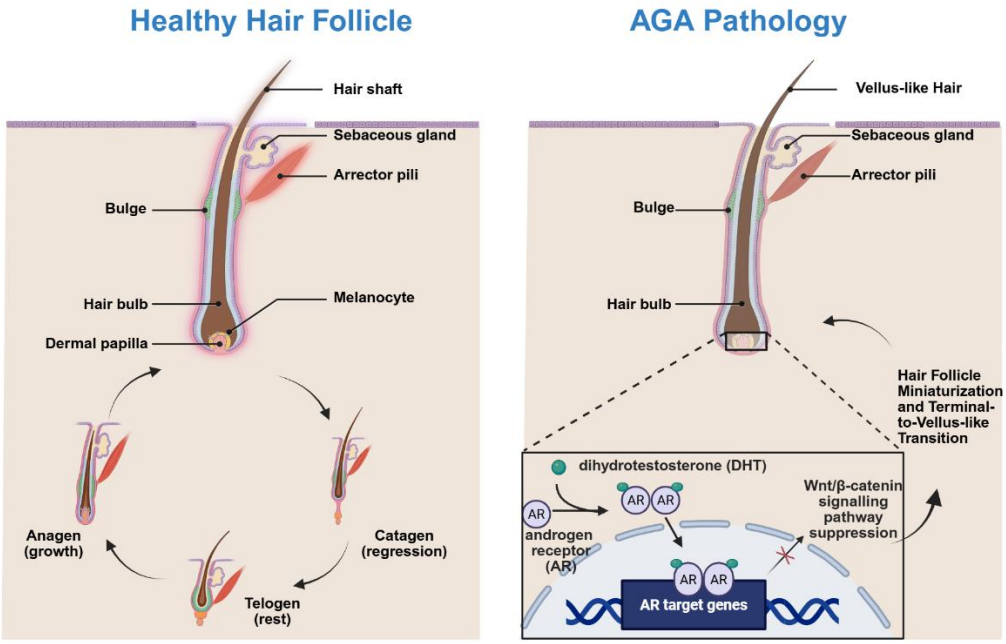

Figure 1. Schematic illustration of hair follicle anatomy and pathological alterations in AGA.

Beyond androgen signaling, increasing evidence highlights the contribution of perifollicular inflammation, elevated reactive oxygen species (ROS), and impaired angiogenesis to follicular miniaturization [19,59,66–68]. Oxidative stress accelerates cellular senescence within dermal papilla cells and disrupts hair follicle stem cell niches. These insights underscore the necessity for multifunctional therapeutic approaches capable of simultaneously modulating multiple pathological pathways [69,70].

3. Nanocarrier-Based Drug Delivery Systems for AGA

Nanocarrier systems have been extensively explored to enhance the follicular delivery and therapeutic efficacy of AGA drugs [26,36,48,49,55,71,72]. Polymeric nanoparticles, lipid-based carriers, nanocrystals, and inorganic nanomaterials represent the major classes investigated to date [37,45,50,53,73–76].

Polymeric nanoparticles fabricated from PLGA, chitosan, or hyaluronic acid improve drug stability and enable sustained release within hair follicles [77]. Lipid nanoparticles and nanoemulsions enhance skin penetration and follicular retention through sebum affinity [39,78]. Drug nanocrystals maximize loading capacity and dissolution rates, allowing dose reduction and improved patient compliance [79,80]. Collectively, these nanocarriers significantly outperform conventional formulations in follicular targeting efficiency [36,78,79,81–84].

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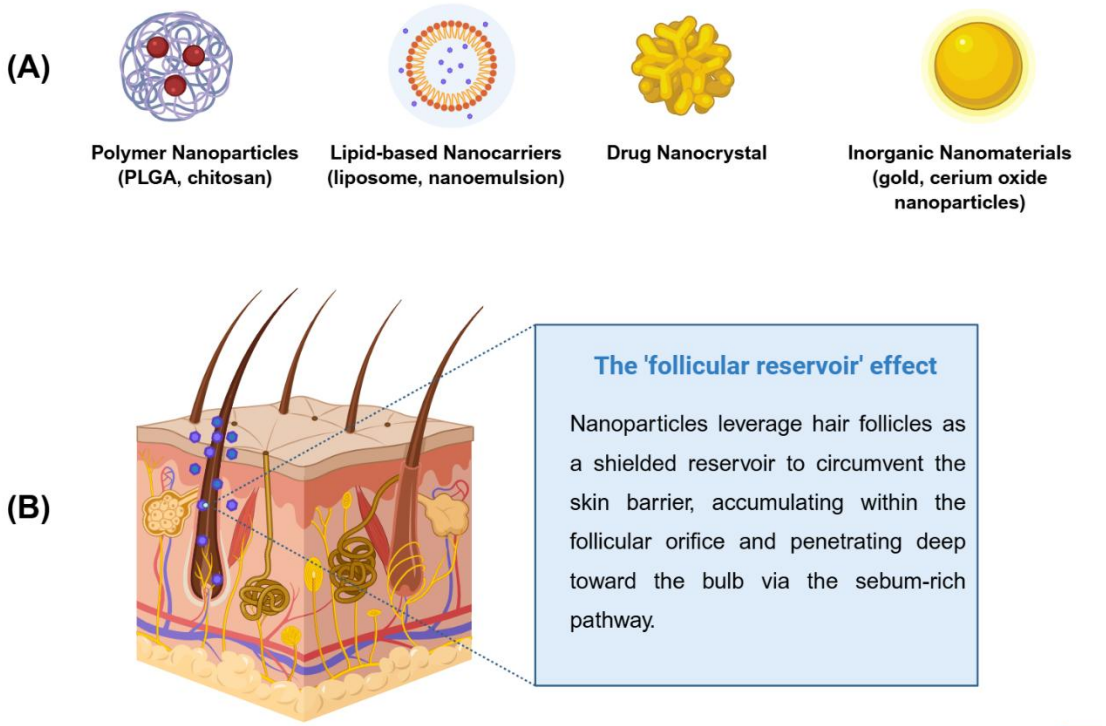

Figure 2. Classification of nanocarrier systems for AGA treatment and follicular targeting mechanisms.

Table 1. Representative nanocarrier systems for AGA treatment.

Nanocarrier Class	Example Materials	Therapeutic Mechanism / Drug Delivered	Key Advantages for AGA
Polymeric Nanoparticles	PLGA, Chitosan, PCL	Encapsulation of Finasteride, Minoxidil, or growth factors.	Provides sustained drug release; protects unstable biomolecules; reduces dosing frequency.
Lipid-based Carriers	Liposomes, Ethosomes, Nanoemulsions	Delivery of hydrophobic drugs; targeted to the sebaceous gland.	High affinity for follicular sebum; enhances skin penetration; biocompatible and low toxicity.
Drug Nanocrystals	Pure drug crystals with stabilizers (PVP, SDS)	High-dose delivery of poorly soluble compounds.	Maximizes drug loading capacity; improves dissolution rates; allows for dose reduction.
Inorganic Nanomaterials	Gold (Au) NPs, Ceria (CeO_2) NPs, Mesoporous Silica	Ceria nanozymes for ROS scavenging; Gold NPs for photothermal or delivery.	Intrinsic antioxidant and pro-angiogenic activities; high surface-to-volume ratio for functionalization.
Exosomes / EVs	Mesenchymal stem cell-derived exosomes	Delivery of regenerative mi-RNAs and proteins to Dermal Papilla cells.	Highly biomimetic; low immunogenicity; promotes Wnt/β-catenin signaling directly.

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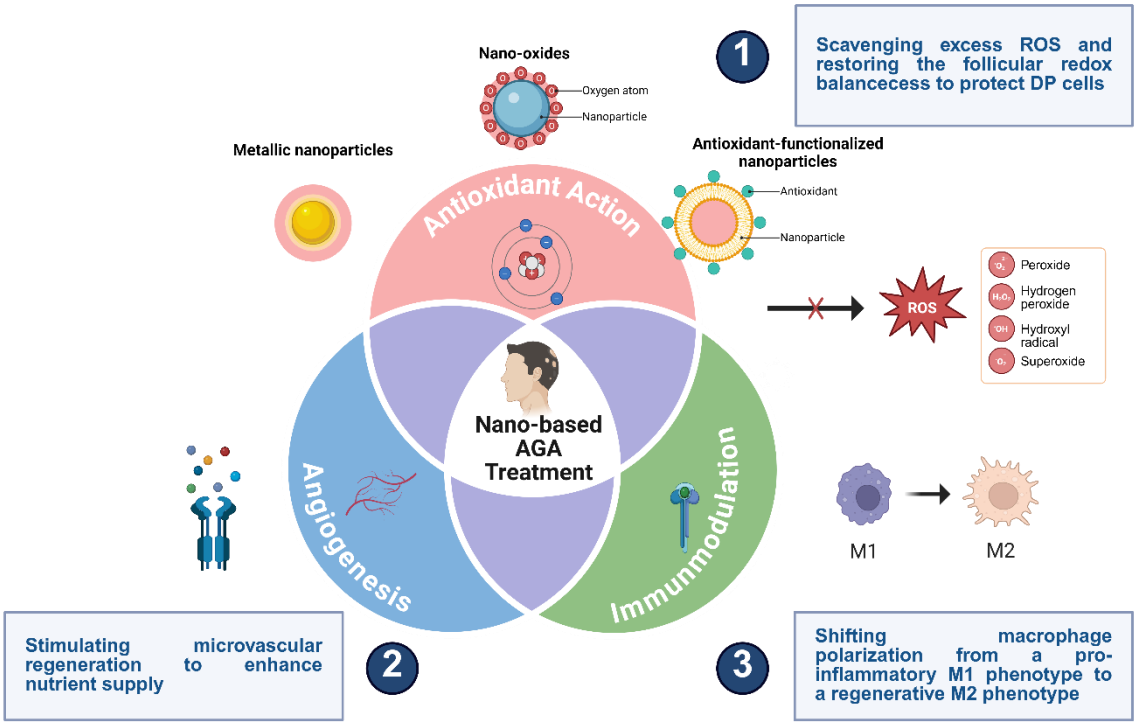

Figure 3. Nano-enabled modulation of oxidative stress, angiogenesis, and inflammation in the follicular microenvironment.

4. Nano-Enabled Microneedle Systems for Transdermal Follicular Delivery

Microneedle (MN) technology provides a minimally invasive approach to bypass the stratum corneum and directly access follicular and dermal compartments [85–89]. The integration of nanotechnology into MN systems has further expanded their functional capabilities.

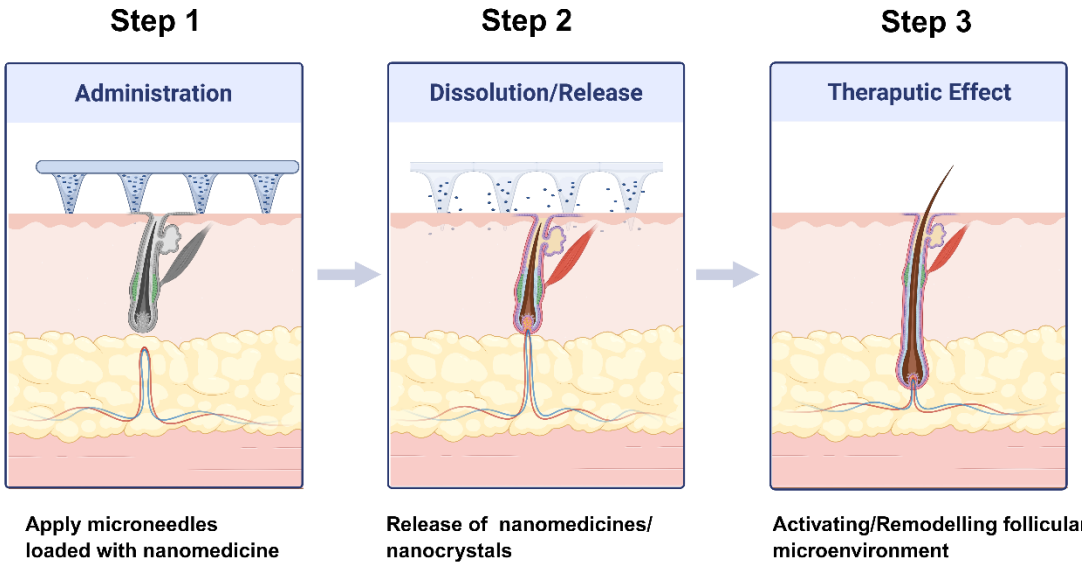

Figure 4. Design and working principles of nano-enabled microneedle systems.

Dissolving MNs loaded with drug nanocrystals or nanoparticles enable precise dosing and sustained release. Advanced designs incorporating nanozymes or growth factor-loaded

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nanoparticles actively regulate oxidative stress, angiogenesis, and inflammation [90–92]. Such multifunctional MN systems have demonstrated superior hair regrowth efficacy in preclinical AGA models compared with conventional topical therapies. For instance, Zhang *et al.* reported a machine learning-guided identification of a highly efficient $MnPS_3$-based SOD mimic and its microneedle patch for the treatment of androgenetic alopecia, which alleviates oxidative stress in hair follicles and promotes superior hair regeneration compared with minoxidil at a reduced application frequency [90]. More recently, Xing *et al.* developed a near-infrared light-triggered nitric oxide (NO)-releasing hyaluronic acid hydrogel (Gel@L-Arg) that enables on-demand NO generation to promote angiogenesis, repair dermal papilla cells, regulate inflammation and androgens, and effectively treat AGA [92].

5. Nano-Enabled Remodeling of the Hair Follicle Microenvironment

Hair regeneration is critically dependent on the follicular microenvironment, including redox balance, vascular support, immune status, as well as stem cell activity [93–96]. Beyond acting as passive carriers, some nanomaterials also possess the capability to actively remodel the local microenvironment [60].

Previous studies have demonstrated that antioxidant nanomaterials, such as polydopamine nanoparticles and ceria nanozymes, effectively scavenge excess ROS and restore redox homeostasis [56]. Pro-angiogenic nanocarriers delivering VEGF or exhibiting intrinsic angiogenic activity enhance perifollicular blood supply. Additionally, nanomaterials modulating macrophage polarization and inflammatory signaling contribute to a regenerative follicular niche conducive to sustained hair growth. Yang *et al* reported that a quercetin-encapsulated and polydopamine-integrated nanosystem (PDA@QLipo) was developed to remodel the perifollicular microenvironment and initiate hair follicle regeneration for AGA treatment. PDA@QLipo exhibits dual functions of ROS scavenging and angiogenesis promotion. In vivo, roller-microneedle-assisted delivery effectively rejuvenated the compromised perifollicular niche, enhancing cell proliferation, accelerating follicle renewal, and restoring hair growth. Notably, PDA@QLipo achieved a higher hair regeneration coverage (92.5%) than MXD (87.8%) with reduced dosing frequency, highlighting its potential for clinical AGA therapy [56]. More recently, a dissolvable microneedle system co-loaded with nickel-copper nanozymes with demonstrated remarkable SOD-like and CAT-like activities and MXD synergistically remodels the hair follicle microenvironment via ROS scavenging and mechanostimulation-enhanced angiogenesis, achieving superior hair regeneration and vascularization compared with MXD alone [60]. In AGA mouse models, this system enhanced hair regeneration coverage to 93.7% (vs 85.1% for MXD alone), increased Ki67+ cell proliferation by 1.9-fold, and significantly thickened regenerated hair diameter. Additionally, this system reduced ROS levels by 2.3-fold and increased CD31+ vascular density by 40%, markedly improving the microenvironment.

6. Safety, Toxicity, and Regulatory Considerations

The clinical translation of nanotechnology-based AGA therapies necessitates rigorous safety and toxicity evaluation [97,98]. Key considerations include nanoparticle size, surface chemistry, biodegradability, and long-term skin exposure [99].

Notwithstanding the encouraging therapeutic potential of nanotechnology-based approaches for hair regeneration, it is imperative to meticulously evaluate the associated risks and uncertainties prior to the extensive clinical implementation of such methods. Although most extant studies report favorable short-term biocompatibility, the long-term safety of repeated or chronic exposure to nanomaterials in the scalp environment remains incompletely understood, particularly with respect to nanoparticle accumulation, immunogenicity, and potential off-target interactions. Furthermore, the presence of variability in nanomaterial composition, manufacturing processes, and formulation parameters has the potential to introduce challenges in terms of reproducibility and quality control, thereby complicating regulatory evaluation. These factors underscore the imperative for

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standardized characterization protocols, rigorous long-term toxicological studies, and well-defined regulatory pathways. It is imperative that these risks are addressed through systematic preclinical validation and interdisciplinary collaboration in order to ensure the safe, reliable and sustainable clinical translation of nanotechnology-enabled therapies for AGA.

7. Clinical Translation and Future Perspectives

Despite encouraging preclinical outcomes, relatively few nano-enabled hair regeneration therapies have advanced to clinical trials. Challenges include scalable manufacturing, cost-effectiveness, and regulatory complexity. Future research is expected to focus on stimuli-responsive nanomaterials, integration with wearable or light-activated devices, and AI-assisted nanomaterial design. Personalized nanomedicine approaches tailored to individual follicular characteristics may further enhance therapeutic outcomes and patient satisfaction.

Table 2. Translational status and challenges of nano-enabled AGA therapies.

Translational Aspect	Current Status & Challenges	Proposed Future Directions
Safety & Toxicology	Potential for long-term accumulation of non-biodegradable NPs in the skin; limited systemic toxicity data.	Extensive chronic toxicity studies and use of biodegradable, "green" nanomaterials.
Manufacturing Scale-up	Batch-to-batch variability; high cost of specialized equipment for complex nanostructures.	Development of microfluidic-based synthesis and standardized manufacturing protocols (GMP).
Regulatory Hurdles	Lack of specific FDA/EMA guidelines for "nano-cosmeceuticals" and complex delivery systems.	Harmonization of international testing standards; close collaboration with regulatory agencies.
Clinical Validation	Most data derived from rodent models; human scalp skin thickness and follicle density differ.	Use of 3D-printed human skin models and humanized mice for more accurate preclinical screening.
Patient Compliance	High frequency of application for topical nanosystems; cost of microneedle-based therapies.	Designing long-acting (e.g., monthly) delivery platforms and low-cost MN manufacturing techniques.

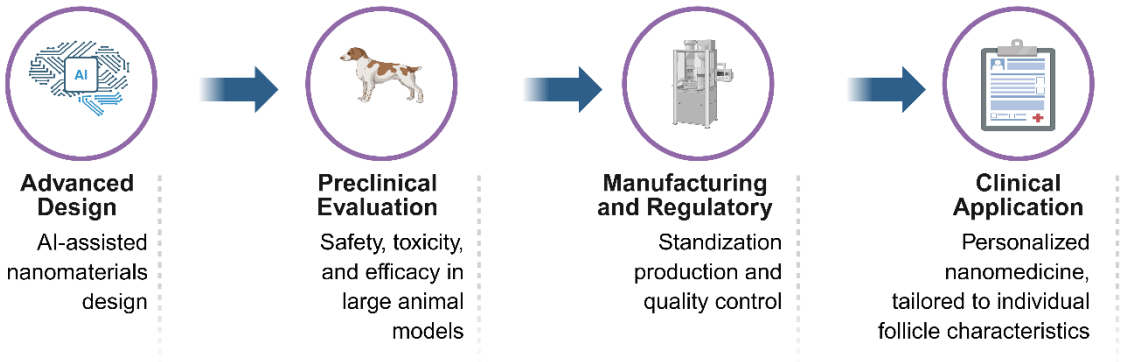

Figure 5. Translational roadmap for nanotechnology-enabled hair regeneration therapies.

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8. Conclusions

Nanotechnology has emerged as a promising strategy for AGA by enabling follicle-targeted delivery, controlled drug release, and modulation of the follicular microenvironment. By overcoming the anatomical and physiological barriers of the skin and pilosebaceous unit, nano-enabled systems enhance the local bioavailability of therapeutics while reducing systemic exposure and off-target effects. Importantly, these platforms not only improve the performance of established agents such as MXD and finasteride but also provide opportunities to address key pathogenic processes in AGA, including oxidative stress, inflammation, impaired angiogenesis, and hair follicle stem cell dysfunction.

Despite substantial experimental progress, the clinical translation of nanotechnology-based AGA therapies remains contingent upon addressing several critical challenges. Long-term safety, scalable and standardized manufacturing, regulatory harmonization, and patient compliance require systematic evaluation. Continued interdisciplinary collaboration and rational nanomaterial design guided by mechanistic insight will be essential to advance these technologies toward clinical adoption, positioning nanomedicine as a viable next-generation approach for AGA management.

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