



REVIEW ARTICLE

PP-405: A NOVEL REGENERATIVE APPROACH FOR ANDROGENETIC ALOPECIA THROUGH MITOCHONDRIAL PYRUVATE CARRIER INHIBITION AND HAIR FOLLICLE STEM CELL REACTIVATION—A COMPREHENSIVE REVIEW

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Received on: 30th June 2025, Accepted on 21st July 2025, Published on: 26th August 2025

ABSTRACT

Androgenetic alopecia (AGA) affects over 80% of men and 50% of women, driven by hair follicle stem cell (HFSC) dysfunction and follicular miniaturization. Regenerative approaches that directly reactivate dormant HFSCs offer promise beyond supportive treatments. To critically appraise PP-405, a first-in-class topical mitochondrial pyruvate carrier (MPC) inhibitor, evaluating its mechanism, preclinical validation, and early clinical efficacy and safety in AGA. A systematic review was conducted analyzing peer-reviewed literature, clinical trial data, and regulatory submissions related to PP-405 and mitochondrial pyruvate carrier inhibition in hair follicle biology. PP-405 operates through mitochondrial pyruvate carrier (MPC) inhibition, redirecting cellular metabolism toward lactate production and subsequently activating dormant hair follicle stem cells. Phase 1 clinical trials demonstrated safety, target engagement, and statistically significant stem cell activation. Phase 2a trials involving 78 participants showed that 31% of men with advanced hair loss achieved greater than 20% hair density increase at 8 weeks, compared to 0% in the placebo group. No systemic absorption was detected, indicating localized scalp activity. PP-

405 inhibits MPC protein complexes, preventing pyruvate entry into mitochondria and forcing cytoplasmic lactate production via lactate dehydrogenase upregulation. This metabolic shift triggers an integrated stress response mediated by the ATF4 transcription factor, ultimately reactivating quiescent hair follicle stem cells and promoting anagen phase entry. PP-405 represents a paradigm shift by targeting HFSC metabolism to regenerate hair follicles rather than merely halting loss. Early clinical data indicate rapid, robust efficacy and an excellent safety profile. Ongoing Phase 2b and planned Phase 3 trials (2026) will clarify durability of response and long-term safety, supporting potential regulatory approval in 2027–2028.

Keywords: *Androgenetic alopecia, Hair follicle, Lactate dehydrogenase, Mitochondrial pyruvate carrier, PP-405, Regenerative medicine, Stem cells*

INTRODUCTION

Androgenetic alopecia (AGA), characterized by progressive miniaturization of scalp hair follicles, affects over 80% of men and 40% of women, leading to significant psychosocial burden [1]. Existing therapies modulate secondary pathways without regenerating dormant follicles. Recent advances in stem cell and metabolic biology have uncovered that hair follicle stem cells (HFSCs) remain viable yet quiescent in balding scalps, their activation contingent on enhanced glycolysis and lactate production. PP-405 is a first-in-class, topical small-molecule mitochondrial pyruvate carrier (MPC) inhibitor developed by Pelage Pharmaceuticals that redirects HFSC metabolism toward glycolysis, elevating lactate dehydrogenase activity and triggering an integrated stress response via ATF4, culminating in anagen reentry. Ex vivo studies demonstrate that single applications of PP-405 increase LDH and Ki67 within 24 hours, confirming target engagement in human

skin. In Phase 1, daily 0.05% topical PP-405 was well tolerated with no systemic absorption and elicited marked HFSC proliferation via Ki67 immunostaining. A Phase 2a study in 78 patients (NCT06393452) showed that 31% of men with advanced AGA achieved over 20% hair density gain at Week 8, with evidence of de novo folliculogenesis. This review comprehensively examines PP-405's mechanism, translational validation, and clinical progress to inform its potential as a novel regenerative therapy. Building on these promising early results, ongoing Phase 2b and planned Phase 3 trials will elucidate the durability of PP-405's regenerative response and its long-term safety profile.

HAIR FOLLICLE BIOLOGY AND STEM CELL REGULATION

Hair follicles are highly regenerative organs that cycle through growth (anagen), regression (catagen), and rest (telogen) phases, driven by stem cells in the bulge region of the outer root sheath. During

telogen, these hair follicle stem cells (HFSCs) remain quiescent, with low metabolic activity and resistance to stress. Activation requires a shift from quiescence to proliferation, orchestrated by signals such as Wnt and BMP inhibition alongside a metabolic switch to enhanced glycolysis and lactate production via lactate dehydrogenase. Paradoxically, HFSCs suppress mitochondrial pyruvate oxidation—controlled by the mitochondrial pyruvate carrier (MPC)—to preserve stemness; inhibiting MPC forces glycolysis, increases lactate, and drives activation. In AGA, HFSCs become refractory—prolonging telogen and causing miniaturization—yet remain viable, highlighting metabolic reactivation (e.g., PP-405) as a promising therapeutic strategy

PP-405: DEVELOPMENT AND MECHANISM OF ACTION

PP-405 emerged from groundbreaking research conducted at the University of California, Los Angeles (UCLA). Their collaborative work, spanning nearly a decade, focused on understanding the metabolic regulation of hair follicle stem cell activation and identifying small molecules capable of manipulating these pathways for therapeutic benefit.

The discovery of PP-405's mechanism originated from fundamental observations about hair follicle stem cell metabolism. UCLA researchers demonstrated that hair follicle stem cells exhibit significantly higher glycolytic activity compared to

other epidermal cells, producing substantially more lactate through enhanced lactate dehydrogenase activity. This metabolic signature was found to be critical for stem cell activation, with genetic deletion of lactate dehydrogenase preventing hair follicle cycling and maintaining cells in a quiescent state [2].

The mitochondrial pyruvate carrier (MPC) complex, consisting of MPC1 and MPC2 subunits, functions as the primary regulator of pyruvate entry into mitochondria [3]. Under normal physiological conditions, pyruvate generated through glycolysis can either enter mitochondria via MPC for oxidative metabolism or be converted to lactate in the cytoplasm via lactate dehydrogenase[4]. The balance between these pathways determines cellular metabolic fate and, in the case of hair follicle stem cells, their activation status [5].

PP-405 functions as a potent, selective inhibitor of the MPC complex, specifically designed for topical application with minimal systemic absorption [6]. When applied to the scalp, PP-405 penetrates hair follicles and blocks MPC function, preventing pyruvate transport into mitochondria. This inhibition forces a metabolic redirection toward cytoplasmic lactate production through upregulated lactate dehydrogenase activity.

The resulting lactate accumulation triggers a cascade of molecular events leading to hair follicle stem cell activation. Lactate functions not merely as a metabolic

byproduct but as an active signaling molecule that promotes stem cell proliferation and differentiation. This process involves activation of the integrated stress response (ISR) pathway, mediated by the transcription factor ATF4, which coordinates the cellular adaptation to metabolic stress while promoting survival and proliferation pathways [7].

Preclinical studies using the mitochondrial pyruvate carrier inhibitor UK-5099 demonstrated that topical application to mouse models resulted in rapid hair growth within days of treatment. More than 10 analogues of UK-5099 were subsequently developed and tested, with several compounds showing superior activity to the original molecule[5]. These studies

confirmed that MPC inhibition represents a viable therapeutic strategy for promoting hair growth and led to the optimization of PP-405 for human clinical development.

The unique aspect of PP-405's mechanism lies in its ability to reactivate dormant hair follicle stem cells rather than merely supporting existing hair growth. Unlike current therapies that work through vasodilation or hormonal modulation, PP-405 directly targets the fundamental biology of stem cell activation, potentially offering regenerative rather than merely preventive benefits for individuals with AGA [8] (Figure 1)

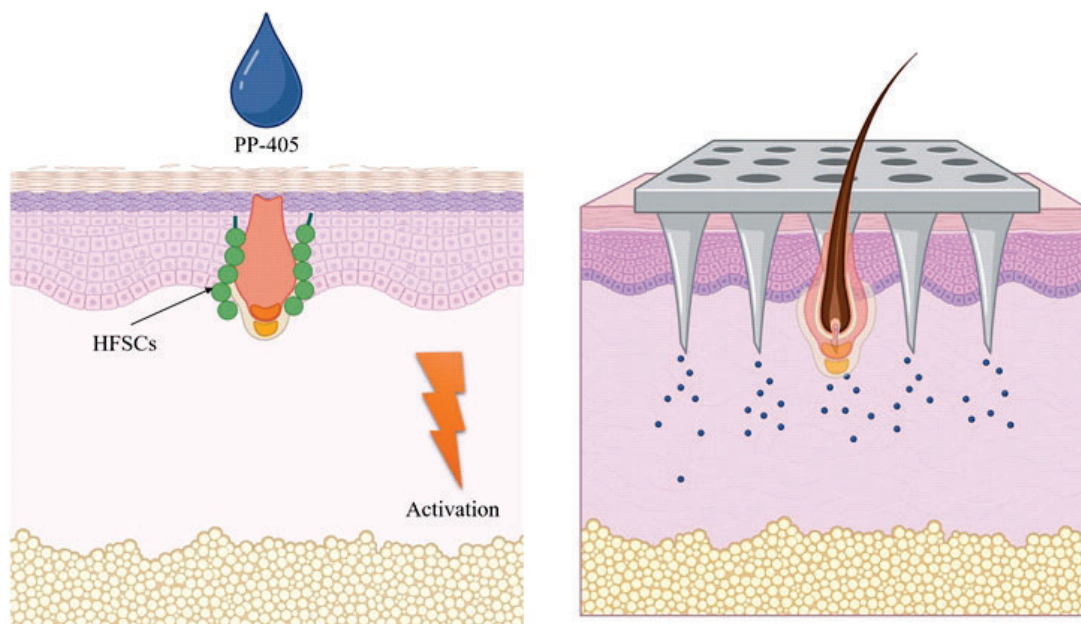


Figure 1: PP-405 Hair Loss Drug

CLINICAL EVIDENCE AND TRIAL RESULTS

The clinical development of PP-405 has followed a systematic progression through Phase 1 and Phase 2a trials, demonstrating both safety and preliminary efficacy in human subjects with AGA. The Phase 1 clinical trial, conducted as a proof-of-concept study, enrolled participants with AGA who received topical PP-405 0.05% gel applied once daily for seven consecutive days [6].

The primary endpoints of the Phase 1 trial focused on safety, tolerability, and target engagement. Importantly, the study demonstrated that PP-405 achieved target concentrations within hair follicles while showing no detectable systemic absorption, confirming the localized activity profile essential for topical hair loss treatments [9]. Scalp biopsies obtained before and after treatment revealed statistically significant increases in Ki67 expression, a well-established marker of cellular proliferation, specifically within the hair follicle bulge region where stem cells reside [10]. This finding provided crucial proof of mechanism, demonstrating that PP-405 successfully engaged its intended target and activated dormant hair follicle stem cells in human subjects.

The Phase 2a clinical trial (NCT06393452) represented a significant advancement in PPelage Announces Positive Results of Phase 2a Trials for Hair Loss Drug PP405P-405's clinical development, designed as a randomized, double-blind,

vehicle-controlled study enrolling 78 men and women with AGA. Participants ranged in age from 18 to 55 years, with males exhibiting Norwood-Hamilton Classification scores of Type III vertex, Type IV, or Type V, and females presenting with Savin classification scores of I-2, I-3, or I-4. This inclusive trial design notably incorporated participants across diverse skin phototypes and hair textures, addressing a significant gap in hair loss research that has historically focused on limited demographic populations [10].

The trial protocol involved daily application of either PP-405 0.05% topical gel or vehicle control for four weeks, followed by an observation period extending to 12 weeks post-treatment initiation. This design allowed researchers to assess both the immediate effects of treatment and the durability of response following treatment cessation.

Primary safety endpoints were successfully met, with PP-405 demonstrating excellent tolerability and no treatment-related serious adverse events. Pharmacokinetic analysis confirmed the absence of systemic drug absorption, indicating that PP-405 activity remains localized to the scalp application site [10]. This safety profile represents a significant advantage over systemic treatments like finasteride, which carry risks of sexual dysfunction and other systemic side effects.

The efficacy results, while preliminary, demonstrated remarkable promise for a novel mechanism of action. At week 8

(four weeks post-treatment completion), 31% of men with higher degrees of hair loss who received PP-405 exhibited greater than 20% increases in hair density, compared to 0% of participants in the placebo group. This rapid response timeline is particularly noteworthy, as conventional hair loss treatments typically require 6-12 months of continuous use before demonstrating visible improvements [11].

Perhaps most significantly, the trial provided evidence of PP-405's regenerative potential. The treatment induced new hair growth from follicles where no hair was previously present, suggesting true follicular reactivation rather than merely supporting existing hair [11]. This finding validates the underlying hypothesis that dormant hair follicle stem cells in AGA can be pharmacologically reactivated to resume hair production.

Following the completion of the randomized portion, participants who received a placebo were eligible to enroll in a three-month open-label safety extension to assess longer-term safety and potential efficacy. Based on these encouraging Phase 2a results, Pelage Pharmaceuticals has announced plans to initiate Phase 3 studies in 2026, designed to further evaluate the safety and efficacy of PP-405 in larger, more diverse patient populations.

COMPARATIVE ANALYSIS WITH CURRENT TREATMENTS

The emergence of PP-405 as a potential treatment for AGA necessitates careful comparison with existing therapeutic options to understand its relative advantages and positioning within the treatment landscape. Current FDA-approved therapies, primarily minoxidil and finasteride, operate through fundamentally different mechanisms and demonstrate distinct efficacy and safety profiles compared to PP-405's novel approach [12].

Minoxidil, available in both 2% and 5% topical formulations, functions primarily as a vasodilator and potassium channel opener, promoting hair growth through enhanced follicular blood flow and prolongation of the anagen phase [13]. Clinical studies demonstrate that minoxidil achieves visible hair regrowth in approximately 30-40% of users after 6-12 months of continuous application [14]. However, the mechanism is largely supportive rather than regenerative, primarily maintaining existing hair rather than reactivating dormant follicles. In contrast, PP-405's 31% response rate at just 8 weeks, with evidence of new follicle activation, suggests superior kinetics and potentially greater regenerative capacity [11].

Network meta-analyses comparing minoxidil concentrations and administration routes have established that oral finasteride 1 mg daily demonstrates

superior efficacy to topical minoxidil for increasing terminal hair count, with the greatest improvements observed at 48 weeks. Finasteride's mechanism involves 5 α -reductase inhibition, reducing dihydrotestosterone levels by approximately 70% and effectively slowing androgenic hair loss progression. While highly effective for hair preservation, finasteride's hormonal mechanism carries risks of sexual dysfunction and mood changes and is contraindicated in women of childbearing potential due to teratogenic effects [1].

PP-405's non-hormonal mechanism offers significant advantages over finasteride, particularly regarding safety and universal applicability. The absence of systemic absorption eliminates concerns about sexual dysfunction, hormonal disruption, or teratogenic effects, making PP-405 suitable for all genders and age groups [15]. Additionally, PP-405's regenerative mechanism may benefit patients who have failed to respond to hormonal therapies, as it targets stem cell biology rather than androgen pathways.

Combination therapy represents an important consideration in modern hair loss management. Recent studies examining topical formulations combining minoxidil and finasteride have demonstrated superior efficacy compared to monotherapy with either agent [16]. The non-overlapping mechanisms of PP-405 and existing treatments suggest potential for synergistic effects when used in

combination. PP-405's stem cell activation could complement minoxidil's anagen prolongation and finasteride's DHT reduction, potentially offering comprehensive treatment addressing multiple pathophysiological aspects of AGA.

Emerging treatments such as platelet-rich plasma (PRP) therapy and low-level laser therapy (LLLT) provide additional comparative context for PP-405's development. PRP therapy, involving autologous growth factor injection, demonstrates modest efficacy comparable to minoxidil but requires invasive procedures and lacks standardized protocols [14]. LLLT shows promise for hair density improvements but requires significant time investment and expensive equipment. PP-405's topical application offers convenience advantages over these modalities while demonstrating superior early efficacy signals [17, 18].

Patient selection considerations favor PP-405 for several populations currently underserved by existing treatments. Women with AGA, particularly those seeking pregnancy or experiencing hormonal contraindications to finasteride, represent a significant population that could benefit from PP-405's safety profile. Additionally, patients experiencing inadequate response to conventional therapies or those seeking regenerative rather than merely preservative treatment may find PP-405's mechanism particularly appealing. The rapid onset of action

demonstrated in Phase 2a trials could also benefit patients seeking faster therapeutic responses compared to the extended timelines required for conventional treatments.

FUTURE PERSPECTIVES AND CLINICAL IMPLICATIONS

The successful completion of Phase 2a trials positions PP-405 for advancement to Phase 3 clinical development, with Pelage Pharmaceuticals announcing plans to initiate pivotal trials in 2026 [15]. These larger studies will be critical for establishing the long-term safety and efficacy profile necessary for regulatory approval while also providing opportunities to explore optimal dosing regimens, treatment duration, and patient selection criteria.

The Phase 3 program will likely involve multiple randomized, controlled trials designed to meet FDA requirements for new drug approval. Given the encouraging Phase 2a results showing rapid efficacy, these studies may evaluate various treatment durations and maintenance regimens to optimize therapeutic outcomes. The trials will also need to demonstrate durability of response and establish whether continued treatment is necessary for maintained benefit or whether intermittent dosing can preserve hair regrowth.

PP-405's unique mechanism of action creates compelling opportunities for combination therapy development. The

non-hormonal, stem cell-targeting approach could synergize with existing treatments targeting different pathophysiological pathways. Combination with minoxidil could potentially enhance both the speed and magnitude of hair regrowth, while concurrent use with finasteride might provide comprehensive treatment addressing both stem cell activation and DHT-mediated miniaturization. Such combination approaches could potentially offer superior efficacy to any single agent while maintaining PP-405's favorable safety profile.

Beyond AGA, PP-405's mechanism suggests potential applications in other alopecia conditions characterized by hair follicle dormancy or dysfunction. Alopecia areata, telogen effluvium, and even certain scarring alopecias might benefit from stem cell reactivation therapy, particularly if viable hair follicle stem cells remain present in affected areas. The broad applicability of metabolic modulation for stem cell activation could establish PP-405 as a platform therapy for multiple hair loss conditions.

The regenerative medicine implications of PP-405 extend beyond hair loss treatment. Success in hair follicle stem cell reactivation could validate similar approaches for other stem cell-dependent tissues, potentially informing the development of therapies for skin aging, wound healing, and other regenerative medicine applications. This broader

potential has likely contributed to the significant investment interest from Google Ventures and other major stakeholders in Pelage Pharmaceuticals.

Manufacturing and accessibility considerations will be crucial for PP-405's clinical success. The topical formulation appears to be relatively straightforward from a manufacturing perspective, potentially allowing for cost-effective production and broad patient access. Unlike complex biologics or surgical procedures, PP-405's small molecule nature should facilitate global distribution and affordability once regulatory approval is achieved.

The regulatory pathway for PP-405 appears favorable given the demonstrated safety profile and novel mechanism of action. The FDA has shown increasing receptiveness to regenerative medicine approaches, and PP-405's localized activity without systemic absorption addresses many traditional safety concerns associated with new molecular entities. Successful FDA approval could facilitate regulatory acceptance in other major markets, including Europe and Asia, potentially enabling global commercialization by 2027-2028.

LIMITATIONS AND CHALLENGES

PP-405's Phase 2a data derive from only 78 subjects over four weeks, limiting insights into optimal dosing, long-term safety, and durability of effect. The primary efficacy signal—a 31% response

rate in a small men's subgroup—relies on a secondary analysis; full results across sexes and all hair-loss severities remain unpublished, and a 20% density gain may fall short of patient expectations. Chronic mitochondrial pyruvate carrier inhibition poses unknown risks for follicular metabolism, despite no systemic absorption in early trials. Regulatory approval will hinge on extended toxicology and large-scale Phase 3 efficacy studies, potentially delaying timelines. Commercially, PP-405 must justify premium pricing against low-cost generics by demonstrating clear, durable regenerative benefits and will require formal health-economic analyses to secure reimbursement and market uptake.

CONCLUSION

PP-405 heralds a new era in AGA therapy by uniquely reawakening dormant hair follicle stem cells via mitochondrial pyruvate carrier inhibition and lactate-mediated activation. In early trials, 31% of men achieved $\geq 20\%$ hair density gains within eight weeks of a four-week regimen, with no systemic absorption and an excellent safety profile. Beyond transforming expectations for hair regrowth, PP-405's non-hormonal, universally applicable mechanism may pave the way for regenerative treatments across diverse alopecias and other stem cell-dependent disorders. Ongoing Phase 3 studies must define optimal dosing, treatment duration, long-term safety, and combination strategies, as well as explore

efficacy in additional hair-loss conditions, to fully realize PP-405's breakthrough potential.

REFERENCES:

1. Kayal, P., Raghul, R., Sahoo, U. K., & Jawahar, N. (2025). Nanocarrier-based approaches for enhanced management of androgenetic alopecia: Advancements and future prospects. *International Journal of Applied Pharmaceutics*, 17(3), 13 – 27. <https://doi.org/10.22159/ijap.2025v17i3.53645>
2. Flores, A., Schell, J., Krall, A. S., et al. (2017). Lactate dehydrogenase activity drives hair follicle stem cell activation. *Nature Cell Biology*, 19(9), 1017–1026. <https://doi.org/10.1038/ncb3575>
3. Tavoulari, S., Sichrovsky, M., & Kunji, E. R. S. (2023). Fifty years of the mitochondrial pyruvate carrier: New insights into its structure, function, and inhibition. *Acta Physiologica*, 238(4), e14016. <https://doi.org/10.1111/apha.14016>
4. Politte, H., Maram, L., & Elgendy, B. (2025). Advances in the development of mitochondrial pyruvate carrier inhibitors for therapeutic applications. *Biomolecules*, 15(2), 223. <https://doi.org/10.3390/biom15020223>
5. Liu, X., et al. (2021). Development of novel mitochondrial pyruvate carrier inhibitors to treat hair loss. *Journal of Medicinal Chemistry*, 64(4), 2046 – 2063. <https://doi.org/10.1021/acs.jmedchem.0c01570>
6. HairLossCure2020. (2025, June). *Pelage Pharmaceuticals Phase 2 trials for PP405 started*. <https://www.hairlosscure2020.com/category/mitochondrial-pyruvate-carrier/>
7. Pye, D., Scholey, R., Ung, S., Dawson, M., Shahmalak, A., & Purba, T. S. (2024). Activation of the integrated stress response in human hair follicles. *PLoS ONE*, 19(6), e0303742. <https://doi.org/10.1371/journal.pone.0303742>
8. Parsamohebi Hair Restoration. *PP405: The breakthrough stem cell technology that could redefine hair restoration and rejuvenation*. Retrieved July 21, 2025, from <https://parsamohebi.com/pp405-the-breakthrough-stem-cell-technology-that-could-redefine-hair-restoration/>
9. Dermatology Times. (2024, August 19). *Q&A: Pelage's novel PP405 advances to Phase 2a for androgenetic alopecia*.

<https://www.dermatologytimes.com/view/q-a-pelage-s-novel-pp405-advances-to-phase-2a-for-androgenetic-alopecia>

10. HairLossCure2020. *Pelage announces positive results of Phase 2a trials for hair loss drug PP405*. Retrieved July 21, 2025, from <https://www.hairlosscure2020.com/pelage-pharmaceuticals-clinical-trials/>
11. The Derm Digest. (n.d.). *Regenerative medicine in action: Topical PP405 shows promise in androgenetic alopecia*. Retrieved July 21, 2025, from <https://thedermdigest.com/regenerative-medicine-in-action-topical-pp405-shows-promise-in-androgenetic-alopecia/>
12. Kaiser, M., Abdin, R., Gaumond, S. I., Issa, N. T., & Jimenez, J. J. (2023). Treatment of androgenetic alopecia: Current guidance and unmet needs. *Clinical, Cosmetic and Investigational Dermatology*, 16, 1387 – 1406. <https://doi.org/10.2147/CCID.S385861>
13. Anastassakis, K. (2022). *Androgenetic alopecia from A to Z: Vol. 2 Drugs, herbs, nutrition and supplements*. Springer International Publishing. <https://doi.org/10.1007/978-3-031-08057-9>
14. Khan, A., Agarwal, D., & Talwar, A. (2023). Comparison of microneedling with platelet-rich plasma vs minoxidil (5%) + finasteride (0.1%) topical therapy in androgenetic alopecia: A randomised clinical study. *Journal of Clinical and Diagnostic Research*. <https://doi.org/10.7860/JCDR/2023/62102.17569>
15. Business Wire. (2025, June 17). *Pelage Pharmaceuticals announces positive Phase 2a clinical trial results for PP405 in regenerative hair loss therapy*. <https://www.businesswire.com/news/home/20250617338859/en/Pelage-Pharmaceuticals-Announces-Positive-Phase-2a-Clinical-Trial-Results-for-PP405-in-Regenerative-Hair-Loss-Therapy>
16. Indian Journal of Trichology. Comparative efficacy of topical finasteride (0.25%) in combination with minoxidil (5%) against 5% minoxidil or 0.25% finasteride alone in male androgenetic alopecia: A pilot, randomized open-label study. https://doi.org/10.4103/ijt.ijt_72_22
17. Gentile, P., Cole, J. P., Cole, M. A., Garcovich, S., Bielli, A., Scioli, M. G., Orlandi, A., Insalaco, C., & Cervelli, V. (2017). Evaluation of not-activated and activated PRP in hair loss treatment: Role of growth factor and cytokine concentrations obtained by different collection systems.

International Journal of Molecular Sciences, 18(2), 408.
<https://doi.org/10.3390/ijms18020408>

18. Anastassakis, K. (2023). Low-level laser therapy (LLLT) and AGA. In *Androgenetic alopecia from A to Z: Vol. 3 Hair restoration surgery, alternative treatments, and hair care* (pp. 597–624). Springer International Publishing.
<https://doi.org/10.1002/lsm.22170>