

Approaches to and Characterization of Hair Growth

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ABSTRACT: *There is still more to learn about hair growth control and the mechanisms that influence the follicle. The translation of what has been learned into effective treatments is not keeping pace. This review offers some biology of the hair cycle and comments on differences between types of hair and hair treatments.*

Men, especially, know that hair thins with age and that there are many products on the market to assist with hair growth—but what exactly is meant by a hair growth solution? Does it deliver more hair, thicker hair, hair that grows longer before it breaks or hair that grows faster? Biologically, hair growth is a well-described cycle involving four phases: growth (anagen), regression (catagen), resting (telogen) and shedding (exogen).¹⁻⁴ This cycle occurs in virtually all hair-bearing species and the dynamics of the hair cycle have been the subject of recent studies.⁵

The hair follicle is a multicellular tissue that retains an element of developmental dynamics recapitulated in the adult hair cycle. This is reflected in the continual interplay between the mesenchymal and

epithelial elements. This review offers a brief summary of some of the biology of hair growth and comments on some of the differences between hairs that are critical to describing what kind of hair is produced by hair growth technologies.

Hair growth is not completely understood, despite a rapid increase in research in recent years. Although factors regulating the transition between the key stages in adult hair cycling are well-documented,⁵ it is perhaps not surprising that the two US Food and Drug Administration (FDA) approved treatments for hair loss were existing drugs for which hair growth is a side effect of their primary use. Originally, minoxidil was developed for hypertension, and finasteride was designed for prostate disease. Disappointingly, few clues about hair follicle changes in hair loss have been gleaned from these serendipitous findings.⁶

History of Growth Technologies

The commercial potential to treat hair loss in a cosmetic yet effective way was realized by the early work with minoxidil. Upjohn translated its hair growth side effect into a topical product with clinical proof and widespread use. This success was followed by increased research interest in hair biology. Questions still being addressed include: How is the hair cycle regulated? What is the genetic basis for androgen-driven hair loss? Is blood supply to the follicle relevant to hair loss? What drives the changes from small, fine, vellus hair to larger, terminal hair and back again? Is there a link to overall diet, stress and other lifestyle factors?

There are now scores of treatments in development or on the market making claims for prevention of hair loss and hair re-growth (see **Table 1.1**). Note that of those listed, only minoxidil and finasteride have proven activity in trials acceptable to the FDA. Many others are contained in marketed products that have some support, if not FDA review.

The diversity of technologies and modes of action are driven by both the assay tools available for discovery and through serendipity. Assays available include hair follicle cell cultures, the culture of whole human hair follicles and mouse models. The two FDA-approved routes have led to significant follow-up research. Interestingly, little

attempt has been made to develop products based on two other drugs with well-described hair growth side effects: cyclosporine A and latanoprost, which are immunophilin and prostaglandin analogs, respectively.

Table 1.1. Selected candidate agents with anti-hair loss potential

| Agent | Product | Claimed Routes |
|---------------------------------|-------------------------------|--|
| Minoxidil | Regaine/Rogaine | |
| Adenosine | Adenogen | |
| Copper peptides | Tricomin | Stimulate proliferation, anti-apoptotic, antioxidant and protective to the hair bulb |
| Procyanidin | | |
| Proteasome inhibitor (NEOSH101) | Niosil (in Phase II clinical) | |
| Ketaconazole | Nizoral | Anti-inflammatory/antifungal |
| Finasteride | Propecia | |
| Saw Palmetto | Revivogen* | Anti-androgen to inhibit 5 α -reductase |
| Azeleic acid | Crinagen* | |
| Aminexil (2,4 DPO) | Dercos Kopexil | Anti-fibrotic |

* mixtures with other actives **Note:** Only minoxidil and finasteride have proven activity in trials acceptable to the FDA. Many others are contained in marketed products that have some support if not FDA review.

Examples of hair loss treatments can be found in more traditional approaches in Chinese and ayurvedic medicines as well as in herbal remedies. These combine several ingredients such as bringraj, black sesame, ginkgo, silica, he shou wu and saw palmetto for a personalized holistic approach to treatment to restore hair growth. Often these treatments are consumed as opposed to applied topically and their use is surrounded by strong belief systems. Translating these into topical formulations brings challenges including delivery through the skin and into hair follicles, as well as the possibility for skin reactions and sensitization.

The pharmaceutical approach to developing a novel treatment for a disorder is to identify a key drug target, develop suitable screening tools, discover or design materials to alter the function of the selected target, and then test these treatments *in vivo*. This can take many years. So why has this approach not been adopted within the cosmetics industry?

Possibly an analysis of costs, development time and the risk associated with the complexity of the hair follicle and hair cycle have led to a belief that finding the right target, in the right cell type, at a specific stage in the cycle of hair growth, may be too great a challenge. From a hair biologist's perspective the more interesting question might be which of the more recent research findings provide directions for future technology searches?

The fact that hormones do affect hair growth is without question. Consider puberty, for example. The actual mechanisms of hormonal activity, however, are still not fully understood.

One exception is the work done to demonstrate the importance of the enzyme 5- α in the metabolism of testosterone within the pilosebaceous unit.⁷ The role of estrogens in hair cycle dynamics remains a conundrum. Evidence from studies with 17 β -estradiol in mice suggests that it acts via the estrogen receptor ER α to delay the telogen to anagen transition.^{8,9} In humans, it is not yet clear whether estrogens are important for anagen maintenance and delay in hair shedding; however, this is purported to be the case in pregnancy.^{10,11} It is also possible that estrogen receptor signaling may well delay hair shedding in mice by delaying anagen onset.

Interestingly, during pregnancy, hair diameter has been shown to increase,¹² suggesting some anabolic actions at the level of the follicle during anagen. The use of estrogen treatment for male pattern baldness has not been pursued.

The follicle is influenced by its surrounding dermis, although concrete evidence for the mechanisms remains only associative. Both male and female pattern hair loss appears to be associated with fibrosis.^{13,14,15} Even in hair loss with a strong inflammatory component, Olsen¹⁶ suggests that visible inflammation is lacking and that visual inspection may not reveal an underlying degree of inflammation. In contrast, Deloche¹⁷ claims that peripilar signs around hair

follicles correlate with inflammation of hair follicles in subjects with androgenic alopecia (AGA).

Current Approaches

Recent clinical studies with ketoconazole and zinc pyrithione indicate that targeting the scalp microflora can relieve symptoms of balding in men. Pierard-Franchimont,^{18,19} Berger,²⁰ and Mahe²¹ hypothesized that micro-inflammation is relevant in about one-third of men with AGA. Dandruff cycling was studied in relation to telogen hair loss²² and although an association was found in periodicity between telogen loss and dandruff, it could not be concluded that these were linked causally.

All this suggests that the correlation between dermal inflammation and hair loss is complex and variable. The human hair follicle has long been considered as immune-privileged.^{23,24} Ito et al.²⁵ re-visited this phenomenon employing the human hair follicle model. They showed that the immune cytokine, interferon gamma, could force the collapse of the immune privilege in vitro, confirming the inflammatory link to hair loss. Such findings are particularly relevant for the more immune-mediated hair loss disorder *Alopecia areata*.

The neuro-endocrine system of skin has been the subject of a recent study.^{26,27,28} Skin is now acknowledged as a peripheral neuro-endocrine organ that needs no central regulation but provides frontline defense and contributes to general homeostasis. Interestingly, the hair follicle itself expresses the full complement of these stress factors, which suggests hair follicles can be influenced by local and central neuro-endocrine factors.²⁶ Chronic stress has been suggested to influence hair loss in women,²⁷ although as yet, no mechanistic studies exist to provide evidence for a direct link. However, this type of research might lead to both local and holistic routes to treatment of hair loss.

Demonstrating Hair Growth

The outcomes tracked in hair growth studies include consumer self-assessments, clinical grades, and photographs of hair and style.²⁹