Approaches to and Characterization of Hair Growth

Gillian E. Westgate, PhD
Westgate Consultancy Ltd., Bedford, UK

Don Harper, K. Ramaprasad, PhD; and Peter D. Kaplan, PhD
TRI/Princeton, Princeton N.J., USA

KEY WORDS: hair growth, hormones, follicle, stress, hair diameter

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 kinds 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). This cycle occurs in virtually all hair-bearing species and the dynamics of the hair cycle have been the subject of recent studies.

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.

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). This cycle occurs in virtually all hair-bearing species and the dynamics of the hair cycle have been the subject of recent studies.

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, 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.

Hair growth is a side effect of the two FDA-approved treatments for hair loss.

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). 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.

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, gingko, 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. 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 ERα to delay the telogen to anagen transition. 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. It is also possible that estrogen receptor signaling may well delay hair shedding in mice by delaying anagen onset.

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 ERα to delay the telogen to anagen transition. 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. It is also possible that estrogen receptor signaling may well delay hair shedding in mice by delaying anagen onset.

**Evidence of chronic stress influencing hair loss could lead to local and holistic treatments of hair loss.**

Interestingly, during pregnancy, hair diameter has been shown to increase, 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. Even in hair loss with a strong inflammatory component, Olsen suggests that visible inflammation is lacking and that visual inspection may not reveal an underlying degree of inflammation. In contrast, Deloche 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, Berger, and Mahe hypothesized that microinflammation is relevant in about one-third of men with AGA. Dandruff cycling was studied in relation to telogen hair loss 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. Ito et al. revisited this phenomenon employing the human hair follicle model. They showed

### Table 1. Selected candidate agents with anti-hair loss potential

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

* 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.
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. 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. Chronic stress has been suggested to influence hair loss in women, 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. Some studies have invested in phototrichometry to measure both growth rates and numbers of hairs. Notably, some studies sample the hair and characterize it by careful measurement off of the head.

Successful hair growth treatment requires sufficient change for the growth to be perceived. This can be driven by more hairs per square centimeter or hairs of greater diameter. More hair can also be a result of faster-growing hairs, hopefully of the same diameter. Hair growth solutions should produce terminal hair that is strong and not brittle, not vellus hair.

To better illustrate the importance of the fibers, following are some measurements performed at TRI/Princeton of the variability of hair. These studies were conducted on untreated, blended, virgin European medium-brown hair. The first measurement (Figure 1) shows how variable the hair diameter is along a single fiber.

Each hair was mounted on a special-purpose stage. This stage rotates the hairs in a laser scanning micrometer. The laser micrometer tracks the major and minor axes of the hair with an accuracy of 50 nm or 0.05 µm. This diameter measurement was repeated every millimeter along the fiber, a distance equivalent to approximately two days’ growth.

The combination of regular sectioning and high-precision dimensional measurement illustrates the semi-regular cycling of the hair growth process. It is also clear that there are occasional events when the hair suddenly becomes thinner or thicker. These may include incidental damage to the fiber during the normal regimen of washing, drying and combing.

For these fibers, the diameters vary along the fiber with an average standard deviation of only 2.5%, but the range of diameters along each fiber is a full 14% of the mean. The cross-sectional area within a single fiber similarly has an average standard deviation of 6.5% and an average range of 31%.

In these scans of long fibers, it is obvious that for a single hair type, the fiber diameter can vary widely. To better describe this hair-to-hair variation, the diameters and cross sectional areas...
of 50 fibers of blended virgin European medium brown hair were measured (see Figures 2 and 3). The cross section of these hairs is oval and in this case, the largest dimension or the major axis was plotted in µm. To characterize this distribution, it is fit to a normal distribution with a mean of 88 and a width of 15 µm.

The mean hair in this sample measured 88 µm. The width of the distribution was a full 18 µm, a 20% variation in diameter between hairs.

With this larger sample, the subject of the variability of hair diameter along individual fibers can be revisited. For each hair, the diameters were measured five times. The distribution standard deviations, divided by the mean, are shown in Figure 4.

The vast majority of fibers have a diameter that is constant to within 5%. The distribution, however, is closer to a log-Normal with a long tail representing many highly variable hairs.

Few studies carefully characterize the quality of the hair fibers. The exceptions, however, demonstrate that this information is interesting and valuable. Even the rate of hair growth can vary significantly from fiber to fiber.12,32

Recently, a number of hair fibers were sampled from a single scalp on the 17th day after a hair dye treatment. The length of the newly grown hair in each fiber was measured. The average growth rate was 0.7 mm/day, or 10 in/year, compared with the generally accepted population average growth rate of 6 in/year. Notably, individual hairs grew with different rates; the standard deviation measured was 0.04 mm/day or about 5% between hairs. Perhaps the need for regular styling is, in part, a result of this between-hair variability in growth rates.

Figure 3. Distribution of the cross-sectional area of the hairs whose diameters are plotted in Figure 2. The average area is 4,400 µm² and the standard deviation is 1,215 µm²; more than 25%.

Conclusions

There is still more to learn about hair growth control and what influences the follicle. The translation of this knowledge into effective treatments is not keeping the same pace. Care must be taken to clearly identify the benefit or end point associated with each treatment. Concrete benefits of biological treatments could be increased number, size, strength or growth rates of hair.

With minoxidil and finasteride offering somewhat effective treatments, it would perhaps require a considerable “step-change” in benefit for a new product to compete at the global level; however, the available

---

**Hair growth solutions should produce terminal hair that is strong, not brittle or vellus hair.**

---

hair loss blogsospheres or chat rooms might point to future directions. The informal trials of many and varied combinations of treatments reported with diaries, discussions and photographs suggest that the complex problem of hair loss requires a complex solution, which may not come from the traditional drug-target approach.

Reproduction of all or part of this article strictly is prohibited.

To get a copy of this article or others like it from a searchable database, visit the Cosmetics & Toiletries magazine’s online Article Archives at www.CosmeticsandToiletries.com/articles.

References
Send e-mail to Peter Kaplan, PhD, at info@triprinceton.org.

1. HB Chase, Growth of the hair, Physiol Rev 34(1) 113–26 (1954)
2. AM Kligman, The human hair cycle, J Invest Dermatol 33 307–16 (1959)
8. S Chanda, C Lee Robinette, JF Couse and RC Smith, 17-Estradiol and ICI-1882780 regulate the hair follicle cycle in mice through and estrogen receptor-pathway, Am J. Physiol Endocrinol Metab 278: E202-E210, 2000
9. U Ohnemeus et al, Hair cycle control by Estrogens: Catagen Induction via estrogen receptor (Era) is checked by ERb signaling, Endocrinology 146 (3) 1214–1225 (2005)
34. PE Hutchinson and JR Thompson, The cross-sectional size and shape of human terminal scalp hair, Brit J of Dermatol 136(2) 159–165 (1997)
35. D Van Neste, Thickness, medullation and growth rate of female scalp hair are subject to significant variation according to pigmentation and scalp location during ageing, Euro J of Dermatol 14(1)28–32 (2004)