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Therapeutic strategies for treating hair loss

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Here, we sketch why significant progress in the as yet very unsatisfactory pharmacological management of hair loss demands more rational strategies for 'hair drug' development, which effectively target defined key events in hair follicle cycling and transformation. Chiefly, drugs need to be identified that serve as inhibitors of catagen, exogen and/or the terminal-to-vellus transformation, or that induce anagen. For this, identification of the relevant molecular controls of human hair follicle cycling is an essential prerequisite.

Introduction

Products that claim to be useful for treating hair loss target a steadily growing, multi-billion dollar market worldwide. In consequence, few other life sciences areas sport as many patents – often with sweeping claims – as the ever-expanding circus of certified, potential or dubious 'anti-hair loss' agents. And yet, pharmaceutical hair loss management still occurs within a clinical theatre of Dickensian proportions: 'great expectations' – contrasted by plenty of disappointed hopes [1]. Much of that disappointment appears to result from unrealistic expectations, ill-targeted (and therefore inefficient) drug therapy and insufficient industrial interest in dissecting the basic mechanisms by which hair loss occurs and by which (long-recognized!) human hair growth-promoters exert their effects.

Despite the plethora of patented and advertised 'anti-hair loss' agents, convincing evidence-based medicine still is the exception rather than the rule in this field, and just two FDA-approved 'hair loss drugs' (the dihydrotestosterone-suppressing 5 α -reductase inhibitor, finasteride and the antihyperten-

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sive potassium channel opener, minoxidil [2]) supremely rule in current clinical practice. Tellingly, both are children of serendipity, not of rational hair drug design. Given the widely underestimated psychological burden that hair loss inflicts upon affected patients [3,4], and the limited, transient and somewhat unpredictable efficacy of finasteride and minoxidil in hair loss management [2,5], more and better pharmacological treatment options are urgently needed. To avoid misunderstandings, minoxidil and finasteride have been landmark drugs in the hair loss arena, but we cannot be content with what we currently have.

It is on this sobering background that we explore precisely targeted strategies for rational hair loss management, critically review recent developments in this arena and define specific, as yet under-investigated research avenues that promise to be productive. Owing to their overarching clinical importance, we focus on androgenetic alopecia, alopecia areata and chemotherapy-induced alopecia. Summarizing the pathogenic principles that underlie hair loss, we also highlight selected lead substances whose hair growth effects need to be dissected much more incisively to identify novel targets for optimized hair loss management.

As hair loss mainly results from abnormalities in hair follicle cycling, potent hair cycle-modulators are needed

When confronted with a hair loss patient, one is well-advised to follow established, authoritative guidelines for considering

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Table 1. Key challenge in hair loss management: defining the central problems

1 – Disturbed HF cycling Telogen effluvium, alopecia areata, androgenetic alopecia, chemotherapy-induced alopecia	Alopecia, effluvium
2 – Unwanted HF transformation Androgenetic alopecia	Pattern balding
3 – Defective HF regeneration Lichen planopilaris, pseudopelade, folliculitis decalvoans, traction alopecia, deep necrotizing folliculitis, radiation-induced alopecia	Scarring alopecia
4 – Excessive exogen	Telogen effluvium
5 – Defective hair shaft structure Monilethrix, pili torti, exogenous hair shaft damage	Hair shaft disorders
Or combinations of thereof	

and excluding the chief causes of effluvium (=the dynamic process of excessively shedding hair shafts, usually on the scalp) and/or alopecia (=the consequence of having lost hair shafts in a defined skin region) [5–8]. When it comes to hair loss therapy, however, the single most important challenge to clearly define the hair loss seen in a given patient results from one or several of five basic causes (Table 1).

To understand this list, it suffices to recollect that hair follicles represent unique fiber-producing biofactories, which constantly undergo dramatic remodeling events, the so-called hair cycle [9–11]. During its cycle, the hair follicle switches between phases of growth and regression. During the growth phase (=anagen), which normally lasts 1–6 years on the human scalp, pigmented keratin fibers of very high tensile strength (=hair shafts) are generated in the so-called anagen hair bulb. This contains one of the most rapidly proliferating epithelial cell populations in the mammalian organism (not surprisingly, these are exquisitely drug-, growth factor- and hormone-sensitive). These keratinocytes subsequently undergo terminal differentiation to become trichocytes of the hair shaft and get injected with melanin granules produced by special melanocytes of the hair follicle pigmentary unit [9–12].

Following the dictates of an as yet unknown autonomous oscillator system ('hair cycle clock'), this fiber factory suddenly involutes by massive induction of apoptosis in most of its epithelial and melanocytic cell populations, whereas the hair shaft is transformed into a more loosely anchored club hair and moves upwards to get eventually shed (probably in an actively controlled process: exogen). The rapidly evolving regression phase of the hair cycle (=catagen) is then followed by a period of relative quiescence (=telogen), before a new, fiber-producing anagen hair follicle is reconstructed from epithelial hair follicle stem cells located in the bulge region of the outer root sheath of the follicle (i.e. at the level of the insertion of the arrector pili muscle) [9–12].

Hair cycle disturbances have dramatic effects on visible hair growth. If anagen gets prematurely terminated and catagen occurs too early, this must result in effluvium and

alopecia; the affected skin region will subsequently sport largely catagen and/or telogen follicles, whose loosely anchored club hairs are eventually shed [i.e. the normal anagen/telogen rate on the scalp (roughly 4:1) changes in favor of telogen]. This is exactly what happens, for example, as a consequence of drug-induced damage to the proliferating cells of the anagen hair bulb, for example, in drug-induced telogen effluvium or when inflammatory cells attack the anagen hair bulb in alopecia areata [9,12].

Alopecia areata perfectly illustrates how crucial hair cycle disturbances are for hair loss. This autoimmune disease probably develops in immunogenetically predisposed individuals when the normal immune privilege of the anagen hair bulb collapses [13,14]. Because almost exclusively anagen hair bulbs are attacked in alopecia areata lesions by an inflammatory cell infiltrate, disease susceptibility is tightly coupled to a defined hair cycle segment (probably because the – as yet unknown – autoantigen(s) are expressed only during anagen). This immune attack then causes a dramatic hair cycle abnormality by abruptly catapulting anagen follicles into a dystrophic catagen, and the insufficiently anchored, improperly formed hair shafts are quickly shed [6].

As a consequence, the most effective therapeutic strategies for hair loss therapy in most patients with hair loss are, in declining order of importance (Fig. 1):

- to inhibit catagen development so as to prolong anagen;
- to induce anagen in telogen follicles;
- to inhibit exogen.

Potent catagen and exogen inhibitors as well as anagen inducers are needed

Of these strategies, the most effective, most widely applicable and probably also the least difficult-to-achieve one is to inhibit premature catagen development [9,12] (Table 2) – specifically by blocking the massive apoptosis of hair follicle keratinocytes that underlies hair follicle involution [15,16]. Often, this can simply be achieved by eliminating a catagen-

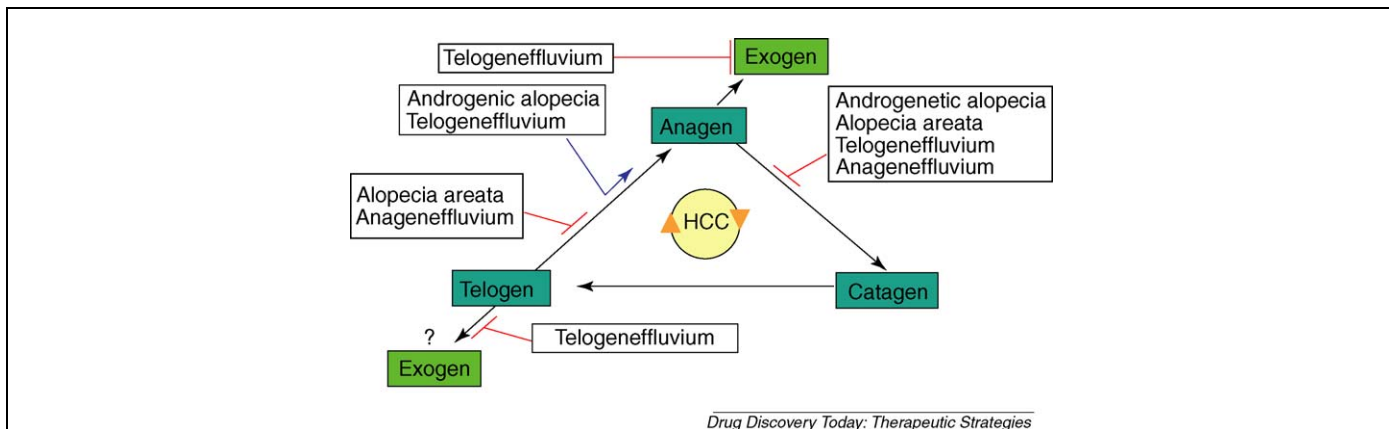


Figure 1. Therapeutic manipulation of hair follicle cycling as key challenge in hair loss management.

inducing drug (e.g. beta-blockers, synthetic retinoids, anticoagulants, antithyroid drugs), by treating a catagen-inducing endocrine disorder (e.g. thyroid dysfunction, hyperandrogenism, hyperprolactinemia) or by substituting a catagen-promoting deficiency (e.g. in serum iron, ferritin, zinc or estradiol) [5,6,8]. Where this does not apply, the pharmaceutical challenge is to develop potent, yet safe catagen inhibitors, anagen inducers and exogen blockers (additional strategies and considerations apply to alopecia areata, chemotherapy-induced alopecia and scarring alopecia, see below). Unfortunately, industry has not even fully appreciated the significance of developing exogen blockers (cf.

[10]) so that little is to be expected on this frontier in the immediate future.

Although both finasteride and minoxidil might indeed exert anagen-inducing and catagen-inhibitory effects in responsive patients [2,17,18], and are reasonably safe drugs, they are undoubtedly not very potent in this respect. Also, they exert these properties rather unpredictably, and are not probable to affect exogen (although this remains to be properly studied). In fact, in terms of their anagen-inducing and catagen-inhibitory power, finasteride and minoxidil are dwarfed by the potent immunosuppressant, cyclosporin A (see [19]) (it remains one of the great mysteries of the hair

Table 2. Targeted therapeutic strategies for more effective hair loss management

Strategy	Targeted hair loss disorder	Predicted main clinical benefit
Catagen inhibition	1–6	Prevention of hair loss progression
Anagen induction	1, 2	Stimulation of hair re-growth
Exogen inhibition	2	Reduction of effluvium
Stimulation of fibroblast trafficking from CTM to DP ^a , inhibition of fibroblast emigration from DP to CTS ^b	1	Prevention of hair-loss progression Stimulation of hair re-growth reconversion of vellus to terminal hair
Telogen arrest	4, 6	Prevention of hair loss progression
Immune privilege restoration	4, (5?)	Prevention of hair loss progression Stimulation of hair re-growth
Dystrophic catagen promotion for accelerated hair follicle recovery	6	Promotion of initial alopecia (!) Stimulation of normal hair re-growth
Epithelial stem cell protection/promotion of stem cell recovery	5	Prevention of hair loss progression Stimulation of hair re-growth
Hair follicle neogenesis from autologous (DP, CTS and/or epithelial stem) cells	5	Restoration of hair shaft formation-capacity

1, androgenetic alopecia; 2, telogen effluvium; 3, anagen effluvium; 4, alopecia areata; 5, scarring alopecia; 6, chemotherapy-induced alopecia (presenting as telogen or anagen effluvium, no scarring).

^a DP, follicular dermal papilla.

^b CTS, connective tissue sheath of the hair follicle.

trade, why industry has not dissected much more rigorously the molecular mechanisms that underlie the unusually potent anagen-inducing, catagen-inhibitory and other hair growth-promoting effects of this immunophilin ligand [19,20] so as to target them directly with drugs that are much less toxic than cyclosporin A!). Even 17- β -estradiol – a very potent hair growth-modulatory hormone that still awaits comprehensive analysis as a key element of human hair growth control [21] – might be a more effective catagen inhibitor for human scalp hair follicles [22,23] than finasteride and minoxidil.

In short, from a strategic point of view, the two currently available FDA-approved standard hair drugs disappoint in that they do not effectively and predictably enough target the three hair cycle-related key points for therapeutic intervention in hair loss management defined above.

Hair follicle miniaturization is another strategic target for anti-hair loss drugs

As indicated in Table 1, besides premature anagen termination, the second major pathogenic principle by which androgens (i.e. dihydrotestosterone) cause alopecia is that they induce a striking process of organ transformation: the miniaturization of very large, well-pigmented terminal hair follicles in androgen-sensitive scalp regions (i.e. vertex, temporofrontal skin) into minute, unpigmented, fluffy vellus hair follicles [6].

The bulk of published studies as well as daily clinical experience suggest that, in androgenetic alopecia in male patients, systemic finasteride (1 mg daily per os) is most effective for both preventing further hair follicle miniaturization and reversing this unwanted transformation, slightly trailed in efficiency by topical minoxidil (2% or 5%, once or twice daily). Minoxidil is the only topically active anti-hair loss drug that is widely acknowledged to be, in principle, capable of promoting a vellus-to-terminal hair reconversion, even in female androgenetic alopecia – albeit in a disappointingly low percentage of minoxidil users (for literature review, see [2,24]). Recent studies, in essence, support this picture (e.g. [25–29]). Despite an earlier report that supports the contrary, first, very preliminary indications now suggest that finasteride might also be of benefit in normoandrogenic postmenopausal women with androgenetic alopecia [30,31].

However, many practitioners of the trade see less satisfactory clinical results than the published studies lead one to expect (e.g. [32]). Together with the usually very long time period needed before the desired cosmetic results become visible to the naked eye, the large percentage of patients that fails to show satisfactory vellus-to-terminal transformation in the cosmetically most crucial scalp skin areas, and the need to continue medication indefinitely, this calls for the development of more effective, longer-lasting vellus-to-terminal hair transformers than minoxidil and finasteride.

It is widely hoped (but far from proven) that newer-generation potassium channel openers [33] and 5- α -reductase inhibitors [34–36] with higher potency will fit this ticket. If so, it will be crucial to rigorously exclude that any increased hair regrowth-promoting effect comes along with unacceptably lower drug safety. Other recent developments that logically follow-up the therapeutic leads provided decades ago by the androgen receptor antagonist, cyproteronacetate and other ‘ancient’ antiandrogens (with their documented efficacy in female pattern hair loss, cf. [37,38]) are the availability of (a) new steroidal antiandrogens (e.g. [35]) and (b) new, topically applicable antiandrogen prodrugs (such as RU 58841-myristate) [39].

It is a pity, although, that neither industry nor most hair researchers have given much attention to the mechanisms that underlie the (supposedly androgen-driven) hair follicle miniaturization as such. Morphometric evidence suggests that it can occur within the course of a single human hair cycle, possibly owing to a loss of inductive dermal papilla fibroblasts [40]. Indeed, in mice, very substantial trafficking occurs between these special morphogenic fibroblasts (whose number and secretory power dictate hair bulb volume and thereby hair shaft diameter, and which might operate as the ‘chief management’ of hair follicle [12]) and the intimately connected dermal sheath fibroblasts of the hair follicle: in early anagen, dermal sheath fibroblasts immigrate into the dermal papilla, whereas dermal papilla fibroblasts emigrate into the dermal sheath in catagen [41].

Even hair follicle transformation, then, is a hair cycle-dependent phenomenon because it probably results from the hair cycle-coupled trafficking of inductive fibroblasts. Androgens might tip the balance in favor of excessive fibroblast emigration from the dermal papilla during the anagen–catagen switch of the hair cycle, whereas hypertrichosis-inducing drugs like minoxidil, diazoxide, cyclosporin A and perhaps finasteride (?) might favor the reverse process during the telogen–anagen switch, thus increasing the volume and morphogenic power of the dermal papilla in the new anagen hair bulb [12,41]. None of this has been systematically explored, although it represents one of most promising research avenues towards more effective hair loss management! We need drugs that selectively stimulate fibroblast immigration from the connective tissue sheath into the hair follicle dermal papilla, thereby promoting vellus-to-terminal transformation of miniaturized hair follicles (and this, ideally, as fast as cyclosporin A manages to do so).

Hair follicle stem cells and hair shaft structural genes are irrelevant targets for most hair loss patients

Table 1 indicates that other important causes for hair loss arise from irreversible damage to the epithelial hair follicle stem cells, from which the follicle regenerates during each new cycle, leading to permanent alopecia. In addition,

inherited or acquired defects in hair shaft structure have to be considered and excluded [2,5,9]. Although there have been few areas in skin biology that have seen such impressive advances throughout the past decade as the fields of hair follicle stem cell biology [42–45] and the unraveling of molecular basis of structural hair defects in mice and human (e.g. [46–49]), this has remained practically without impact on the clinical management of the vast majority of hair loss patients.

This comes as a surprise only to those who uncritically accept ‘stem cells’ or ‘gene therapy’ as the ultimate cure for essentially every disorder that has proven recalcitrant to therapy. However, our patients with androgenetic alopecia, telogen effluvium or alopecia areata (i.e. well over 95% of hair loss patients) – as far as we know to-date – have perfectly healthy hair follicle stem cells, and display no significant structural gene defects. Instead, their basic problems are abnormalities in hair follicle cycling and hair follicle transformation. Thus, targeting structural gene defects in the follicle is a wonderful test arena for gene therapy strategies in general [50], but probably will achieve close to nothing in terms of treating any of the most common hair growth disorders of human.

Likewise, targeting hair follicle stem cells is extremely promising for regenerative medicine, and one day might even allow us to induce the neogenesis of human hair follicles from autologous adult cells *in vitro* [51,52], but offers little (if any) practical help for hair loss management in the routine case. Even the completely bald scalp still sports tens of thousands of rather healthy (although cosmetically unsatisfactory) vellus follicles [6,9], which are just waiting to be retransformed into terminal hair-producing fiber factories. As convincingly demonstrated by the astounding efficacy of hypertrichosis-inducing drugs (e.g. cyclosporine A), this can be easily achieved without any stem cell or gene therapy. We just lack the pharmacological means to do so *where* we want, *when* we desired and *without* using toxic agents ...!

Finally, although we are delighted to learn that we are getting ever-closer to achieving human hair follicle neogenesis from adult hair follicle-associated cell populations [52,53], its advocates tend to play-down the staggering challenge of having to arrange such hair follicles generated *de novo* in perfect geometry and alignment in order for them to be of any cosmetic use (not to mention that few patients will be exactly happy to watch their – very expensively acquired – new hair follicles generating hair shafts that resemble the pubic hair variant, rather than the curls of their youth ...).

In any case, all this does not help to manage the most common causes of alopecia and effluvium. The same goes for gene therapy strategies, which do indeed offer the hope of correcting – very rare – human genodermatoses that display a hairloss phenotype. Although these are beyond the scope of this review, it is interesting to note that epithelial hair follicle stem cells hold particular promise for gene transfer and

reconstitution strategies [45,50,54]. As far as stem cell-targeted therapeutic strategies are concerned, suffice it to state here that stem cell-protective drugs are indeed badly needed in the small minority of hair loss patients where stem cell deletion is the chief pathogenic problem (Table 1), that is, in scarring alopecia (e.g. as a consequence of lichen planopilaris, CDLE or SLE, scleroderma, folliculitis decalvans and radiation-induced alopecia) [9].

However, very little attention has as yet been paid to how autoaggressive, inflammatory attacks on hair follicle stem cells might best be prevented or how the capacity of these stem cells to recover from immunologically or radiation-induced damage might be effectively enhanced. Interesting leads in this respect, which remain to be picked-up and systematically developed, have arisen, for example, from radiotherapy-induced alopecia, where prostaglandins and nitroxins might inhibit the hair loss based on stem cell destruction [55–57]. In addition, this very small minority of hair loss patients would indeed profit from cell-based regenerative medicine leading to hair follicle neogenesis [52] (Table 3) – provided that the primary pathogenic insult that has caused hair follicle stem cell deletion in the first place has been eliminated or suppressed successfully beforehand (which, currently, is often not possible ...!).

‘Telogen arrest’ drugs and restorers of hair follicle immune privilege are needed in alopecia areata

It is almost exclusively anagen hair follicles that are attacked in alopecia areata (probably because the relevant autoantigens are expressed only in anagen and because only the anagen hair bulb is immunologically privileged [14,58]).

Table 3. Additional selected candidate agents with possible hair loss-inhibitory properties

Agent	Refs
Prostaglandin analogs (bimatoprost, latanoprost)	[96–99]
Parathyroid hormone-related peptide antagonists	[100,101]
α -Lactalbumin-derived peptides (Gly-Leu-Phe)	[102]
Tea polyphenolic compounds	[103]
Oral zinc	[104,105]
Epimorphin-derivatives (pep7)	[106]
Asiasari radix extract	[107]
Melatonin	[108]
Soybean extracts (e.g. soymetide-4)	[109]
Tellurium immunomodulator (AS101)	[110]
Thymosin β -4	[111,112]
Protein kinase C inhibitors (procyanidins)	[113–115]

Note: None of these candidate compounds has as yet been conclusively demonstrated to work as both effective and safe agents for human hair loss management (professionally designed, prospective, randomized, double-blind clinical trials of sufficient duration and in a sufficiently large, homogeneous cohort of patients still need to be run in all cases!).

Therefore, besides counter-acting inflammation-induced catagen, a complementary therapeutic strategy is to arrest hair follicles in telogen. Although this would have to be bought with telogen effluvium occurring some months along the line, this would be very effective for stopping the – often dramatic! – disease progression. Regrettably, none of the current treatment regimens for alopecia areata (e.g. glucocorticoids, contact eczema, minoxidil) even so much as considers this sensible management strategy, and this author is not aware of any systematic drug development strategy geared at identifying ‘telogen arrest’ drugs for human skin (even though these would also be immensely useful for treating hirsutism; cf. [12]). In mice, potent glucocorticosteroids [59] and 17- β -estradiol [60,61] are very effective ‘telogen arrest drugs’. However, it remains to be clarified whether they have the same effects in human scalp (this might not be the case).

Although the pathogenesis of alopecia areata remains unclear, mounting evidence suggests that this is an organ-specific, T cell-dependent autoimmune disease, in which collapse of the relative immune privilege of the anagen hair bulb, with the corresponding incapacity to sequester anagen-associated follicle autoantigens from immune recognition, play a key role [14,58]. Current standard therapy consists of immunosuppression by topical and/or systemic glucocorticosteroids or immune deviation therapy by inducing an irritant or allergic contact dermatitis [62] – with generally unpredictable and often unsatisfactory results. The underlying therapeutic strategies target primarily the inflammatory cell infiltrate, rather than hair follicle cycling as such, and do not even attempt to re-establish tolerance to the elusive autoantigen(s) in alopecia areata. As long as this cardinal challenge of alopecia areata therapy cannot be met, it would already constitute a major therapeutic advance, if we could at least re-establish the hair follicle immune privilege in affected patients; this would probably halt disease progression and would allow the hair follicle to quickly recover from inflammation-induced premature catagen development [13,14].

Very promising lead substances that might serve as guardians and restorers of human hair follicle immune privilege have recently been identified in human hair follicle organ culture experiments [13]: the growth factor IGF-1 (which doubles as a potent anagen promoter and catagen-suppressor for human scalp hair follicles [63,64]), tacrolimus (the most powerful immunophilin ligand used in daily clinical practice for suppressing T cell-dependent immune responses, which also induces anagen and suppresses catagen in mice [19,20]) and the neurohormone α -MSH (a pigmentation-stimulatory melanocortin which is even produced locally in normal human anagen hair bulbs [65] and has surfaced as a potent but very well-tolerated general immunosuppressant [66–68]).

Using state-of-the-art hair follicle-targeting vehicles [69], local combination therapy with these three agents or appropriate synthetic agonists, therefore, promises a new level of more effective, pathomechanism-oriented alopecia areata therapy – the novel combination of T cell-focused immunosuppression with hair follicle immune privilege restoration and catagen suppression [13,14]. Alas, owing to lack of industrial interest in systematically following-up these intriguing leads, alopecia areata patients remain stuck with the deeply unsatisfactory treatment options available today.

Chemotherapy-induced alopecia presents a therapeutic conundrum

Just like in alopecia areata, catagen inhibition and telogen arrest are sensible therapeutic strategies in chemotherapy-induced alopecia for maintaining hair follicles in the least chemotherapy-sensitive stage of the hair cycle (i.e. telogen) at the time of chemotherapy. These strategies, however, also have serious drawbacks. A closer look at them nicely illustrates why successful management of chemotherapy-induced alopecia, one of the key unsolved problems in clinical oncology [70], has remained a genuine conundrum.

Catagen inhibition would best be achieved by topically administering potent inhibitors of hair follicle keratinocyte apoptosis [20,16,71–73], using, for example, new liposomal preparations that target the hair follicle [69]. Lamentably, neither properly formulated apoptosis-blocking agents nor reliable ‘telogen arrest’ drugs have as yet been developed for topical use on human scalp – largely owing to the failure of the industry to recognize the crucial importance of doing so if we really wish to substantially enrich our pharmacological armamentarium for treating human hair growth disorders.

Yet, even if such agents were available, they would have to be applied with greatest caution: one would not want to enhance tumor cell survival by administering apoptosis inhibitors or antiproliferative agents that risk to render cell cycle-dependent cytostatic agents ineffective. A similar argument can be invoked against the use of cooling caps for chemotherapy-induced alopecia [74] (apart from cooling caps often being relatively ineffective and poorly tolerated): they reduce scalp perfusion [and thereby drug-access to scalp (micro-)metastases!] and possibly inhibit not only hair matrix but perhaps also tumor cell proliferation, thus rendering the latter unresponsive or less sensitive to chemotherapy. In mice, systemic or topically applied immunophilin ligands are effective suppressors of cyclophosphamide-induced hair matrix keratinocyte apoptosis and subsequent alopecia [20,71]. But is it justified to risk the suppression of tumor immunosurveillance by administering such potent immunosuppressants? In short, what might protect the hair follicle might also aid tumor survival and growth under chemotherapy.

Unfortunately, this is not the only conundrum. Another one arises from the fact that the fastest and most efficient strategy of the hair follicle to repair chemotherapy-induced damage is to immediately shut-off anagen by catagen induction ('dystrophic catagen pathway') and by running through a much-abbreviated telogen phase, to reconstruct a new hair shaft factory (=anagen hair bulb) with maximal speed, as the fastest way to promoting the regrowth of normally pigmented hair shafts. Therefore, antiapoptotic regimens, which favor the 'dystrophic anagen pathway' might reduce the level or retard the onset of alopecia but actually protract the regrowth of normally pigmented hair [71,75].

This strategic dilemma can best be studied in mice. Here, the 'dystrophic catagen pathway' towards the most rapid hair follicle recovery from chemotherapy-induced damage is very effectively promoted, for example, by topical glucocorticoids, calcitriols and 17- β -estradiol; however, these agents also tend aggravate the initial alopecia [71,75–77]. Although this promises to accelerate normal hair growth, owing to the initial, massive promotion of catagen, this therapeutic strategy (which remains to be tested on the human scalp) probably will greatly enhance the degree of chemotherapy-induced alopecia, for starters. It does not take prophetic vision to predict that the number of chemotherapy patients willing to accept a greater cosmetic evil in the beginning, for the sake of eventual cosmetic rewards many weeks or even months later, will be small . . .

To identify the therapeutic strategy, and the drugs, which master these formidable challenges in the pharmacological management of chemotherapy-induced alopecia should be high on the priority list of all serious combatant in the war against hair loss.

Conclusions and perspectives

Despite the disappointing practical advances in pharmacological hair loss management during the past decade, there is hope!

Besides the standard arguments customarily invoked for this purpose [advances in the human genome project and unraveling of ever more genetic defects of rare inherited hair loss disorders which provide novel molecular clues to well-focused drug and gene therapy, dramatic progress in hair follicle stem cell research and in the *de novo* generation of human hair follicles from adult cell populations (see above)] such optimism largely rests upon four pillars:

1. Contrary to generations of physicians before us, the doctor confronted with a hair loss patient, nowadays, can profit from clear-cut, evidence-based guidelines for patient management (e.g. [5,7,8,62]). If applied systematically and with circumspection (without adhering to them slavishly), these are priceless assets.
2. Today, our – once rather vague – concepts of hair loss pathogenesis can be distilled into a few basic processes (Table 1), whose cellular and molecular basis becomes increasingly understood and, therefore, more amenable to selective pharmacological targeting.
3. Related to this, the basic strategies one can employ to tackle the most common causes of hair loss have become more sharply defined than ever before, and novel strategies (Table 2) have been developed.
4. The string of compounds claimed to hold potential as hair growth-promoting agents has been growing so steadily over the past few decades that it is hard to believe that all of them will fail. Although their number is far too large to do this list of candidate hair growth modulators justice and to discuss each individual compound crucially here, Table 3 points the interested reader to a small selection of 'hopeful new kids on the block' and 'old wine in new bottles', which supplements the agents already discussed above.

The candidate 'hair loss drugs' listed above and in Table 3 (as well as chemically or functionally related compounds) now must be subjected to rigorous testing with respect to their efficacy as protagonists for any one of the therapeutic strategies defined in Table 2. Ideally, this is done in human hair follicle organ culture [78–82], so as to probe the effects of the test agent on human scalp hair follicle growth and regression *in vitro*, and by utilizing the best-established mouse model for hair research (C57BL/6J [19,83]), so as to test primarily the hair cycle-modulatory effects *in vivo*, and before testing the candidate agent clinically.

Perhaps, this brief exploration of therapeutic strategies for hair loss is concluded most fittingly with an unashamedly eclectic outlook on three frontiers in the war against hair loss not yet mentioned above that this author currently feels to be particularly exciting.

One of the most intriguing developments in human hair biology is that human scalp hair follicles (especially their epithelium) have turned out to be not only a target, but also a source for ever-more (neuro-) hormones, including CRH, ACTH, α -MSH, cortisol [65,84], melatonin [85] and, most recently, neurotrophins [79], prolactin [81], TRH and TSH [86] and even erythropoietin [87]. Although the full range of functions of all these locally generated hormones for hair biology is still unclear, many of these endogenous bioregulators have turned out to operate as powerful inhibitors of human hair growth-regulators, at least *in vitro* [65,79,80]. Therefore, it is reasonable to expect that future hair loss management might profit from exploiting the astounding endo-, para- and autocrine powers of human hair follicle epithelium by selectively modulating the synthesis of locally generated endogenous growth modulators, for example, by downregulating the follicular production of TGF β , p75NTR

ligands, cortisol and prolactin, whereas upregulating that of IGF-1 [64,65,78,79,80,81].

Another important development is the growing body of evidence that psychoemotional stress, at least in mice, exerts profound hair growth-inhibitory effects [88–90] – thus vindicating those of our (often ridiculed) predecessors who felt that stress can cause hair loss. Because NGF, substance P and its receptor (NK1) as well as mast cells have now been identified as key mediators for stress-induced inflammatory events leading to hair growth inhibition and premature catagen induction in mice [88–90], defined signaling pathways and cells can be targeted pharmacologically to counteract the negative effects of stress. Moreover, quite unexpectedly, the prototypic topical hair drug, minoxidil, is an effective ‘antistress agent’ with respect to hair growth – at least if you are a mouse [91].

Finally, because obtaining pharmacological control over the unruly hair cycle is clinically so all-important in hair loss management (Fig. 1), the ancient hunt for the ‘hair cycle clock’ [12] is heating up with microarray-based characterization of the molecular signature of individual hair cycle switches in mice (e.g. [92,93]) and the advent of mutant mice with primary abnormalities in hair follicle cycling, such as *Msx* knockout mice [94] or mice with a defect in the *fuzzy* gene locus [95]. These recent developments hold out the hope that, at long last, we are getting closer to striking pharmacologically at the heart of hair loss: the elusive molecular oscillator system that drives hair follicle cycling [12].

‘Great expectations’ might not be totally misguided, after all ...!

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