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George COTSARELIS, *et al*
Hair Follicle Regeneration

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A Hair-Raising Solution?

by Dan Cossins

In the long-fought battle against baldness, researchers are finally identifying molecular pathways that can be manipulated to generate new hair follicles.

For some men, few things are more worrisome than the daily sight of an ever-receding hairline in the bathroom mirror, or the peach-fuzz feel of a thinning crown. This creeping nemesis—known as male-pattern baldness or androgenetic alopecia—emerges in genetically predisposed individuals when a by-product of testosterone called dihydrotestosterone (DHT) causes hair follicles on the scalp to shrink, producing ever thinner hairs, until the follicles eventually lose the capacity to produce hair that protrudes above the surface of the skin.

For the moment, there are few treatment options. The only two approved by the US Food and Drug Administration are minoxidil (Rogaine), a vasodilator thought to prevent or slow follicle miniaturization by increasing nutrient supply, and finasteride (Propecia), which achieves the same goals by blocking the conversion of testosterone into DHT. Research has shown that both can prevent or slow hair loss, and sometimes induce regrowth, by rescuing follicles that have recently begun to miniaturize. But neither can revive totally shrunken follicles. And while relocating healthy follicles to barren patches can solve the problem, hair transplant procedures are expensive and invasive.

The ultimate victory, when it comes to the long-fought battle against baldness, would be to find a way to trick the body into creating brand-new hair follicles.

Researchers first raised the possibility in the 1950s, when they observed new hair follicles forming during wound healing in rabbits and mice, but the work was later discredited. Then, in 2007, George Cotsarelis, a dermatologist at the University of Pennsylvania's Perelman School of Medicine, spotted hairs growing in the middle of small cuts they'd made in the skin of adult mice. "We figured out they were de novo hair follicles formed in a process that looked a lot like embryogenesis," says Cotsarelis.

It turns out that the wound-healing process causes skin cells to dedifferentiate, providing a

limited time window during which those cells can be persuaded to form new hair follicles. Even more intriguingly, the researchers also found that inhibiting Wnt signaling during this window reduced follicle neogenesis, while overexpressing Wnt molecules in the skin increased the number of new follicles (Nature, 447:316-20, 2007). Cotsarelis and his colleagues had discovered a potential way to generate new hair follicles.

PureTech Ventures, a Boston-based venture capital group, snapped up the research even before the paper had come out. PureTech's Daphne Zohar, David Steinberg, and Bernat Olle had previously recruited Cotsarelis to help explore commercial opportunities arising from dermatological research. Having evaluated hundreds of existing patents without finding anything to form a company around, Cotsarelis began to reveal the molecular machinery behind follicular regeneration in mice—a finding with obvious commercial potential. "I thought, gee, this is perfect for PureTech," he recalls. In 2006, Cotsarelis, Zohar, Steinberg, Olle, and several other scientists cofounded a company called Follica to develop new combination therapies to induce follicle neogenesis.

Although Follica has released few details on their proprietary procedure, the general idea is clear: their patented minimally invasive "skin perturbation" device removes the top layers of skin, causing the underlying skin cells to revert to a stem-like state, after which a molecule is applied topically to direct the formation of new hair follicles.

Indeed, Follica has already done preclinical and clinical trials, says Olle, "all of which confirm that we can consistently create new hair follicles in mice and in humans. As far as I know, no other approach has been able to achieve that."

News of the progress has attracted strong interest from the public, with comments piling up below online articles about Follica and serving as de facto message boards for the science-savvy bald community to exchange expressions of hope and skepticism—and to speculate about when the "cure" might hit the market. Earlier this year, Cotsarelis's group sparked another comment frenzy by demonstrating that a protein called fibroblast growth factor 9 (Fgf9), which is secreted by gamma delta (?d) T cells in the dermis, plays a key role in the formation of new follicles during wound healing in adult mice.

Very little is known about the mechanism of hair follicle neogenesis besides the Wnt family, so the discovery of Fgf9 was very important.

When Cotsarelis and his collaborators inhibited Fgf9, fewer new follicles formed compared to controls. And when the researchers induced overexpression of Fgf9, new follicle formation increased 2–3-fold compared with normal expression. That's because Fgf9 initiates a feedback loop in wound fibroblasts that amplifies the signaling factors required for follicle neogenesis, explains Cotsarelis. Importantly, even when the researchers added Fgf9 to wounds in knockout mice engineered to lack ?d T cells (which are rare in humans), they observed increased Fgf9 expression in fibroblasts—and hair regeneration (Nature Medicine, 19:916-23, 2013).

"Very little is known about the mechanism of hair follicle neogenesis besides the Wnt family, so the discovery of Fgf9 was very important," says Luis Garza, a dermatologist at Johns Hopkins School of Medicine who has previously collaborated with Cotsarelis but was not involved in this research. "There are probably a whole panoply of agents which control regeneration," but this study demonstrates Fgf9's potential as a baldness therapy.

The next step is to test the effects of Fgf9 on human skin in xenograft models and then in the clinic. “If results hold up in humans, we could expect a several-fold increase in new follicles beyond what we were already accomplishing,” says Olle.

There is a long way to go, of course, and Garza points out that “there are myriad questions regarding moving Fgf9 to human use.” But the recent advances by Cotsarelis and Follica are raising fresh shoots of hope for people who are losing or have already lost their hair. For Cotsarelis, that means more e-mails from interested members of the public, something he’s gotten used to over the last 5 years.

“I’ve learned to accept that I’m the baldness guy,” he says. “Everybody asks about it, but I don’t get sick of it. It’s nice to work in an area that people care about.”

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http://www.nature.com/nature/journal/v447/n7142/abs/nature05766.html
Nature 447, 316-320 (17 May 2007) | doi:10.1038/nature05766

Wnt-dependent de novo hair follicle regeneration in adult mouse skin after wounding

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The mammalian hair follicle is a complex 'mini-organ' thought to form only during development1; loss of an adult follicle is considered permanent. However, the possibility that hair follicles develop de novo following wounding was raised in studies on rabbits2, 3, mice4 and even humans fifty years ago5. Subsequently, these observations were generally discounted because definitive evidence for follicular neogenesis was not presented6. Here we show that, after wounding, hair follicles form de novo in genetically normal adult mice. The regenerated hair follicles establish a stem cell population, express known molecular markers of follicle differentiation, produce a hair shaft and progress through all stages of the hair follicle cycle. Lineage analysis demonstrated that the nascent follicles arise from epithelial cells outside of the hair follicle stem cell niche, suggesting that epidermal cells in the wound assume a hair follicle stem cell phenotype. Inhibition of Wnt signalling after re-epithelialization completely abrogates this wounding-induced folliculogenesis, whereas overexpression of Wnt ligand in the epidermis increases the number of regenerated hair follicles. These remarkable regenerative capabilities of the adult support the notion that wounding induces an embryonic phenotype in skin, and that this provides a window for manipulation of hair follicle neogenesis by Wnt proteins. These findings suggest treatments for wounds, hair loss and other degenerative skin disorders.

Methods, Kits, and Compositions for Generating New Hair Follicles and Growing Hair
US2012156228

Description

BACKGROUND OF THE INVENTION

[0001] The invention relates to methods, kits, and compositions for generating new hair follicles and growing hair on a subject.

[0002] Follicular neogenesis is defined as the generation of new hair follicles (HF) after birth. Humans are born with a full complement of HF, which can change in size and growth characteristics as in early baldness or can ultimately degenerate and disappear as in the late stages of baldness or in permanent scarring (cicatricial) alopecias. Therefore, the generation of new HF is desirable in the treatment of common baldness as well as less common hair loss conditions, such as discoid lupus erythematosis, congenital hypotrichosis, lichen planopilaris, and other scarring alopecias.

SUMMARY OF THE INVENTION

[0004] In one aspect, the invention features a composition including from 0.001% to 0.1% (w/v) of a small molecule EGFR inhibitor formulated for topical administration, wherein the EGFR inhibitor is a non-naturally occurring nitrogen-including heterocycle of less than about 2,000 daltons, or a metabolite thereof...

[0009] The invention features a kit including (i) a composition comprising an EGFR antibody; and (ii) instructions for administering the antibody to a subject in need of generating a hair follicle or stimulating a hair growth. In one embodiment, the antibody is selected from zalutumumab, cetuximab, IMC 11F8, matuzumab, SC 100, ALT 110, PX 1032, BMS599626, MDX 214, and PX 1041...

[0023] In yet another particular embodiment of the methods, kits, and compositions of the invention, the EGFR inhibitor (e.g., a small molecule EGFR inhibitor or EGFR antibody) is combined (e.g., administered, formulated, or contained in a kit) with an additional biologically active agent selected from an antihistamine (e.g., mepyramine, diphenhydramine, and antazoline), an anti-inflammatory (e.g., corticosteroids, NTHEs, and COX-2 inhibitors), a retinoid (e.g., 13-cis-retinoic acid, adapalene, all-trans-retinoic acid, and etretinate), an anti-androgen (e.g., finasteride, flutamide, diazoxide, 11alpha-hydroxyprogesterone, ketoconazole, RU58841, dutasteride, fluridil, and QLT-7704), an immunosuppressant (e.g., cyclosporine, tacrolimus, rapamycin, everolimus, and pimecrolimus), a channel opener (e.g., minoxidil, diazoxide, and phenyloin), an antibiotic, and an antimicrobial (e.g., benzyl benzoate, benzalkonium chloride, benzoic acid, benzyl alcohol, butylparaben, ethylparaben, methylparaben, propylparaben, camphorated metacresol, camphorated phenol, hexylresorcinol, methylbenzethonium chloride, cetrimide, chlorhexidine, chlorobutanol, chlorocresol, cresol, glycerin, imidurea, phenol, phenoxyethanol, phenylethylalcohol, phenylmercuric acetate, phenylmercuric borate, phenylmercuric nitrate, potassium sorbate, sodium benzoate, sodium proprionate, sorbic acid, and thiomersal)...

[0026] In an embodiment of any of the forgoing methods, kits, and compositions, the small molecule EGFR inhibitor is selected from leflunomide, the leflunomide metabolite A771726, gefitinib, erlotinib, lapatinib, canertinib, vandetanib, CL-387785, PKI166, pelitinib, HKI-272, and HKI-357.

[0027] In another embodiment of any of the forgoing methods, kits, and compositions, the EGFR antibody is selected from zalutumumab, cetuximab, IMC 11F8, matuzumab, SC 100, ALT 110, PX 1032, BMS599626, MDX 214, and PX 1041.

METHODS FOR GENERATING NEW HAIR FOLLICLES, TREATING BALDNESS, AND HAIR REMOVAL
US2012121693
AU2012204059

The present invention provides methods of treating baldness in a subject and generating new hair follicles, comprising epidermal disruption and administration of a compound that promotes a differentiation of an uncommitted epidermal cell into a hair follicle cell. The present invention also provides methods for hair removal and inducing hair pigmentation.

FIBROBLAST GROWTH FACTOR-9 PROMOTES HAIR FOLLICLE REGENERATION AFTER WOUNDING
WO2010056759

The present invention provides methods for treating hair loss, treating, inhibiting, or suppressing a degenerative skin disorder, treating androgenetic alopecia (AGA), generating new hair follicles (HF), and increasing the size of existing HF. The methods comprise epidermal disruption or administration of wnt, and administration of a fibroblast growth factor-9 polypeptide or another compound that upregulates sonic hedgehog gene signaling.

METHODS AND COMPOSITIONS FOR INHIBITING OR REDUCING HAIR LOSS, ACNE, ROSACEA, PROSTATE CANCER, AND BPH
WO2007149312
US2011021599

Abstract

This invention provides methods of treating androgenetic alopecia (AGA), acne, rosacea, prostate cancer, and benign prostatic hypertrophy (BPH), comprising the step of contacting a subject with a compound or composition capable of decreasing prostaglandin D2 (PGD2) level or activity, a downstream signaling or receptor pathway thereof, or prostaglandin D2 synthase level or activity; methods of stimulating hair growth, comprising the step of contacting a subject with a compound or composition capable of increasing or decreasing the activity or level of a target gene of the present invention, or with a protein product of the target gene or an analogue or mimetic thereof; and methods of testing for AGA and

evaluating therapeutic methods thereof, comprising measuring PGD2 levels.

METHODS OF ENHANCING EPITHELIAL CELL PROLIFERATION
WO9632127

Method of identifying and modulating the activity of label retaining cells in hair follicles for diagnostic and therapeutic purposes
US5340744
