FGF9 for baldness

By Lauren Martz, Staff Writer

A **University of Pennsylvania** team has found that increasing fibroblast growth factor 9 levels in wounded skin can promote the growth of hair follicles in mice.[1] **Follica Inc.** has licensed the findings and plans to test the effects of the growth factor in hair growth indications.

Male pattern baldness, or androgenic alopecia, occurs when circulating hormones cause hair follicles to shrink and eventually stop producing hair. Treatments include Rogaine minoxidil from **Johnson & Johnson**, a vasodilator thought to increase nutrient supply to the follicles and prevent miniaturization, and Propecia finasteride from **Merck & Co. Inc.**, which converts testosterone to dihydrotestosterone.

Minoxidil needs to be applied twice a day and can actually cause hair loss in some patients. Finasteride's effects on hormone balance can lead to side effects such as loss of libido. Both molecules are indicated to prevent future hair loss but do not regrow lost hair.

An alternative to therapeutically inhibiting hair loss is hair transplantation, which involves relocating a patient's healthy follicles to sites of baldness. The procedure is the only approved method that actually replaces lost hair, but it is invasive and requires that a patient have some hair to transplant.

Also, the transplanted hairs remain subject to the same factors that caused follicle miniaturization in the first place, suggesting the solution is not permanent.

In a search for alternatives, George Cotsarelis and colleagues at the University of Pennsylvania have been studying the process in mice. In 2007, the team found that skin wounds in mice initiated the formation of new hair follicles, a process called hair follicle neogenesis, through upregulation of the wingless-type MMTV integration site (Wnt) pathway.[2]

Now, the researchers have zeroed in on fibroblast growth factor 9 (FGF9; GAF) as a key player in the process.

The group injured healthy adult mice and saw that new hair follicles began to form around day 14 post-injury. Gene expression profiling during the wound healing process showed that Fgf9 was upregulated just before new follicle formation.

In the same mouse model, injection of an FGF9-neutralizing antibody into the wounded skin decreased the number of new follicles compared with injection of an isotype-matched IgG control antibody. Adenovirus-mediated overexpression of Fgf9 increased new follicle formation compared with normal expression of Fgf9.

The team fluorescently labeled γδ T cells, which are known to produce Fgf9, and found that the immune cells accumulated at the wounds right before Fgf9 upregulation. Knockout of the T cell subset in the mice decreased new follicle growth. The effects were partially reversed by administration of exogenous Fgf9.

Finally, the group found that mouse fibroblasts at the wound sites expressed two receptors for Fgf9—the keratinocyte growth factor receptor (Kgfr; Fgfr2; Cd332) and fibroblast growth factor receptor 3 (Fgfr3; Cd333).

When activated by Fgf9, the receptors increased Wnt activity and transcript levels. The higher Wnt activation in turn increased Fgf9 expression on fibroblasts.

These studies suggest FGF9 produced by γδ T cells initiates a feedback loop in wound fibroblasts that amplifies the signaling components required for follicle neogenesis (*see* **Figure 1, "Wound-induced hair follicle neogenesis"**).

In human dermal samples, the γδ T cells required to initiate the process were scarce, unlike in mouse skin. This finding potentially explains why humans do not undergo hair follicle neogenesis when wounded.

> **"FGF9 modulation could be used in combination with skin disruption alone or in combination with skin disruption and other compounds."**
>
> **—Bernat Olle, Follica Inc.**

Results were published in *Nature Medicine*.

Cotsarelis told *SciBX* that the next steps for this research include testing the effects of FGF9 on human skin in xenograft models and then in the clinic.

Cotsarelis is chairman of dermatology at the **Perelman School of Medicine at the University of Pennsylvania**, director of the program on epithelial regeneration and stem cells at the University of Pennsylvania's Institute for Regenerative Medicine and director of the university's Hair and Scalp Clinic.

The paper also included researchers from the **Seoul National University College of Medicine**, the **New York University Langone Medical Center**, **Chungnam National University**, **Texas A&M University** and the **Washington University in St. Louis School of Medicine**.

Follica advancement

Follica plans to test FGF9 as a potential component of its follicle neogenesis technology.

The technology is a combination of a device that the company says removes the top layers of skin and undisclosed topical molecules that help regenerate hair follicles. The company says that the process is not very painful but the region can easily be numbed.

"Follica's technology platform is based on Cotsarelis' discovery that when skin is perturbed, some cells revert to a more basic state from which they can develop into either skin or hair follicles," said cofounder Bernat Olle. "During a limited time window after the perturbation, these cells can be directed to form new hair follicles by modulating pathways involved in hair neogenesis with exogenous compounds."

In a Phase IIa trial, the device and undisclosed molecules showed

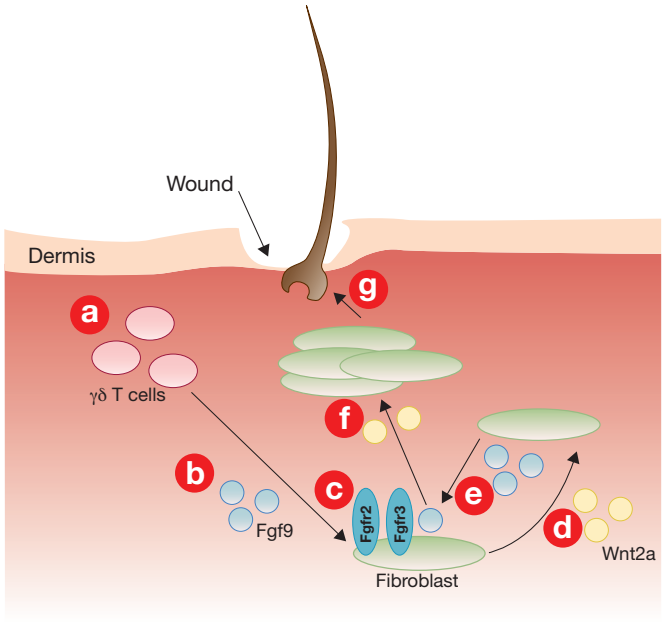

Figure 1. Wound-induced hair follicle neogenesis. In mice, skin wounds create an embryonic-like state in the surrounding cells that allows for the generation of new skin and hair follicles. The wounded dermis causes the recruitment of γδ T cells to the site of injury [**a**]. The T cells produce fibroblast growth factor 9 (Fgf9; Gaf) [**b**], which binds to keratinocyte growth factor receptor (Kgfr; Fgfr2; Cd332) and fibroblast growth factor receptor 3 (Fgfr3; Cd333) [**c**]. This leads to the activation of Fgfr2 and Fgfr3 and production and activation of wingless-type MMTV integration site family member 2a (Wnt2; Wnt2a) [**d**]. The protein stimulates the production of Fgf9 by some fibroblasts to initiate a feedback loop to generate more activated Wnt2a [**e**]. Wnt2a then activates a signaling pathway that causes fibroblast proliferation [**f**] and dermis cell-fate determination to promote development of new hair follicles [**g**].

hair follicle neogenesis, according to the company. Further details were not disclosed.

"FGF9 modulation could be used in combination with skin disruption alone or in combination with skin disruption and other compounds," said Olle.

Basil Hantash, founder, chairman and CEO of **Escape Therapeutics Inc.**, said it is still unclear whether the mouse studies of Fgf9 will translate to humans.

"We know that mouse hair cycles differ from humans in numerous ways. The study would have to be performed in a human *ex vivo* hair model or in a human clinical trial," he said.

Escape has human epidermal stem cells with hair growth capacity in preclinical development.

"Topical FGF9 would be catabolized readily in the skin," noted Hantash. "Thus, delivering adequate sustained levels is not a simple task even if FGF9 maintains the same results in humans."

Desmond Tobin, professor of cell biology and director of the Centre for Skin Sciences at the **University of Bradford**, wanted to know about the duration of effect for FGF9 modulation.

Tobin did acknowledge that hormone-induced miniaturization of hair follicles is a long process. Even if the new follicles are susceptible to the same processes, the treatment could be effective for some time, he said.

According to Luis Garza, assistant professor of dermatology at **The Johns Hopkins University School of Medicine**, "FGF9 will not treat the underlying cause of any specific hair disease. Its best use might be in burn scars, for example, where the trauma occurred in the past but is not an ongoing disease."

Cotsarelis told *SciBX* that in the mouse, "new follicles that form behave like neonatal follicles. There may be a period of time when the new follicles do not respond to testosterone. The goal is to regenerate a large follicle and keep it that way."

The University of Pennsylvania has filed a patent application covering the FGF9 work. Follica has licensed the approach and other IP from the group and has filed additional patents to protect the technology.

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