Biotechs target stagnant baldness market

In December, Samumed of San Diego, California announced phase 2 results for its drug for treating hair loss, or androgenetic alopecia, commonly known in men as male-pattern baldness. The drug SM04554, a topically applied small molecule, upregulates WNT activity to stimulate hair growth. The 300-participant trial resulted in increased hair density as quantified by macrophotography and hair quality as assessed by questionnaires, with no serious adverse events, and the company now plans to move SM04554 into phase 3. The hair loss market has been remarkably stagnant, but Samumed and other biotechs are now leveraging molecular insights in hopes of revitalizing it.

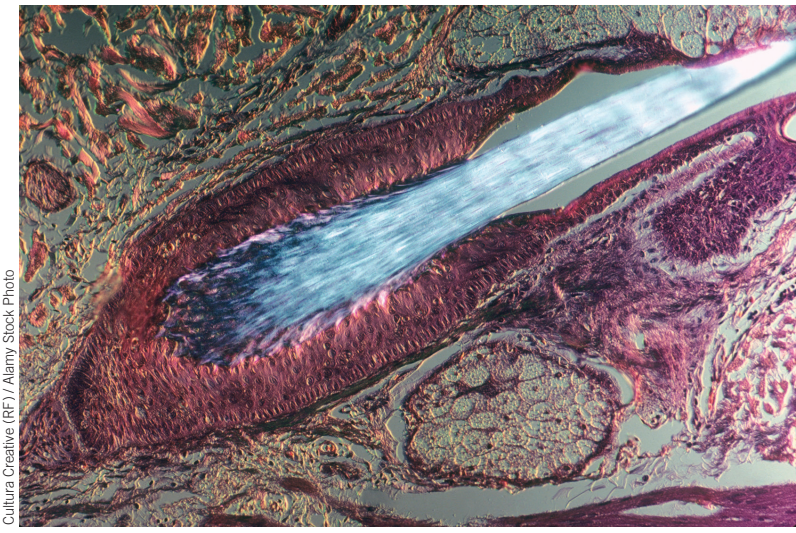
It's been 25 years since Propecia (finasteride), from Merck of Kenilworth, New Jersey, was approved by the US Food and Drug Administration (FDA) in 1992. But although prescription-based Propecia and its over-the-counter competitor, Johnson & Johnson's Rogaine (minoxidil), slow hair loss in about half the people who try them, they're not always well tolerated, and neither drug stimulates new hair growth, "so we clearly need better treatments," says George Cotsarelis, chair of the department of dermatology at the University of Pennsylvania's Perelman School of Medicine, in Philadelphia.

Androgenetic alopecia, also known as 'genetic balding', is the main cause of hair loss in both men and women. In men, the hairline recedes above the temples to form an 'M' shape, and also thins at the crown, often progressing to baldness. In women, the hair becomes thinner all over the head but rarely to the point of baldness.

In both sexes, genetics play a role in androgenetic alopecia, though only a few genes, including *WNT10A* and the androgen receptor gene (*AR*), have been confirmed by scientific studies. WNT signaling activates β-catenin, a protein that in turn regulates the differentiation of skin stem cells into follicular keratinocytes, the skin cells that form the hair follicle. Evidence links androgenetic alopecia most strongly to variations at region chr2q35 on chromosome 2, where *WNT10A* is located.

The extent to which tissues respond to dihydrotestosterone (DHT) and other androgens is regulated by the *AR* gene. Variations in *AR* boost androgen receptor activity in hair follicles in people with androgenetic alopecia. Over time, the hormone DHT acts on the follicles, weakening and shrinking them until the thinning hairs can't penetrate the scalp skin, resulting, ultimately in hair loss.

Androgenetic alopecia affects roughly 50 million men and 30 million women in the US. A better therapy, with fewer side effects, than those currently on offer could be worth billions, according to Brian Silver, partner at Parella Weinberg Partners, in New York. "Because generic products currently dominate the market, more precise estimates are difficult to gauge," he says. "We expect that novel branded products will significantly increase the market's overall value."



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A healthy hair follicle in its shaft.

Samumed's strategy is a radical departure from the anti-androgen approach pursued by Merck. By targeting WNT, Samumed is exploiting a pathway found in virtually all the body's organ systems. WNT signaling helps to regulate stem cell differentiation and tissue regeneration, and aberrations in the pathway have also been linked to various cancers. Researchers have known since the 1990s that WNT-associated pathways prompt hair follicles to shift from a resting to a growing state. Early studies showed that WNT stimulators delivered into abraded skin caused new hairs to emerge during wound healing. But it's only in the last five years that academics and biotechs have begun developing topically absorbed compounds that ideally will trigger WNT pathways in the scalp to stimulate the growth of new hairs.

Citing a pending publication, Samumed's chief executive officer, Osman Kibar, declined to say precisely how SM04554 modulates WNT, saying only that it binds targets in the cell nucleus and "triggers a chain reaction that causes dermal stem cells to differentiate into new hair follicles." The company currently has nearly 20 WNT-based compounds in various stages of development. Cotsarelis cautions that WNT stimulation could have off-target consequences in other tissues, so side effects—including cancers—pose ongoing concerns. "Most companies are more interested in blocking WNT than activating it," he says. Nevertheless, Cotsarelis himself has patented methods for growing new hair by targeting the WNT pathway. And Kibar emphasizes that SM04554 degrades quickly upon reaching the bloodstream. "We've detected no evidence of cancer or other major adverse effects in treated patients," he says. Wilma Bergfeld, a senior dermatologist at the Cleveland Clinic, and principal investigator on the phase 2 study, says the results so far seem encouraging. "SM04554 falls into this proliferative pathway, and that's very exciting," she says. "But having said that, our review of the clinical data is not yet complete."

A serendipitous discovery led Allergan, of Dublin, Ireland, to prostaglandins. The FDA in 2001 approved the small-molecule drug Latisse (bimatoprost) in an eye drop formulation to treat glaucoma. Latisse is a prostamide, a synthetic structural analog of natural prostaglandins, a group of cyclic fatty acids with hormone-like effects. In addition to lowering intraocular pressure to ease glaucoma symptoms, Latisse activates prostaglandin F2—a promoter of hair growth—upon binding to its receptor (*Dermatol. Surg.* **36**, 1361–1371, 2010). After patients who used it reported longer, thicker eyelashes, Allergan sought and obtained FDA approval for eyelash hypotrichosis—or inadequate eyelashes—in 2008. Allergan subsequently developed a topical formulation to deliver Latisse to the base of the hair follicle for alopecia treatment. But results from phase 2 trials were unsatisfactory, according to Gurpeet Ahluwalia, Allergan's director of clinical dermatology. "We have good evidence that bimatoprost [Latisse] stimulates hair growth, but skin absorption with our formulation was less than 1% so most of it was wasted," he says. Allergan has since developed a new formulation with increased scalp penetrance, which will enter phase 1 safety testing in February.

Allergan has a second compound in its pipeline that targets prostaglandins. The key discovery took place three years ago, in

Table 1 Selected hair loss treatments in development

Company	Compound	Mechanism	Status
Merck	Propecia (finasteride)	Steroid 5a-reductase inhibitor; blocks conversion of testosterone to dihydrotestosterone (DHT)	Approved
GlaxoSmithKline	Avodart (dutasteride)	Steroid 5a-reductase inhibitor; blocks conversion of testosterone to DHT	Phase 3
Allergan	Latisse (bimatoprost)	Prostaglandin F receptor/PGF2α receptor	Phase 3
Cosmo	CB-03-01	Androgen receptor antagonist derived from 11-deoxycortisone; blocks testosterone and DHT from binding receptor	Phase 2
Samumed	SM04554	WNT pathway stimulator	Phase 2
Allergan	Setipiprant (ACT-129968)	An oral antagonist of chemoattractant receptor-homologous molecule CRTH2, expressed on T helper 2 cells, and a cognate receptor for prostaglandin D2.	IND
Tetralogic Pharmaceuticals	SHAPE (suberohydroxamic acid phenyl ester)	Histone deacetylase inhibitor	IND

IND, investigational new drug.

Cotsarelis' laboratory at the University of Pennsylvania. Cotsarelis' team found that prostaglandin PGD2 is upregulated in the follicular epithelial cells of balding scalps, and that inhibiting its activity triggers hair growth in isolated follicles (*Sci. Transl. Med.* **4**, 126–134, 2012). The University of Pennsylvania patented rights to PGD2 receptor antagonists for the treatment of hair loss and licensed that technology to Kythera Biopharmaceuticals of Westlake Village, California, which was acquired last October by Allergan in a cash deal worth $2.1 billion. The deal gave Allergan rights to Kythera's oral PGD2 inhibitor, setipiprant, which binds to PGD2's receptor. Kythera had licensed setipiprant from its initial developer, Actelion of Allschwil, Switzerland. The Swiss biotech had tested the drug in patients with allergic and inflammatory conditions, but it had proved ineffective.

Drug developers are still pursuing better compounds to stop DHT from miniaturizing hair follicles than those currently on the market. The oral DHT inhibitor Propecia, also used in a higher dose for treating enlarged prostates, slows hair loss but has potential side effects that include impotence and dizziness. Moreover, the drug is approved only for men, since exposures during pregnancy can harm the fetus.

Instead, Cassiopea of Milan, Italy is developing a topical DHT antagonist called Breezula for alopecia treatment. According to the company's chief executive officer, Diana Harbort, the drug breaks down into harmless byproducts on entering circulation. If approved, Breezula would be the first anti-DHT compound available for use in both men and women. Currently a boutique firm specializing in dermatology, Cassiopeia was spun off by its parent company, Cosmo Pharmaceuticals, in January 2015. It's now publicly traded on the Swiss stock exchange and retains the rights to Breezula, but Cosmo owns nearly half the company's stock.

Breezula's active ingredient, cortexelone 17α-propionate, binds the DHT receptor while also reducing PGD2 production in the skin. In a phase 1 study, 18 men and 2 women were exposed to the drug twice daily for 28 days. Researchers used electrophoresis to open skin pores during the study, which generated no evidence of systemic side effects. Breezula is currently being tested against Rogaine and placebo in a 26-week proof of concept study with two primary endpoints: scalp darkness and patient satisfaction. Ken Washenik, a dermatologist and medical director of the Bosley Medical Center, a private practice in Beverly Hills, California, says that unlike Propecia—which cuts the production of DHT—Breezula has the more beneficial effect of blocking the hormone's receptor. That way, he says, "no matter where in the body DHT is produced, its miniaturizing activity is blocked once it reaches the follicle."

Cotsarelis says that in gauging future prospects for alopecia treatment, it's important to have realistic expectations. "I'd hate to use the word cure, because I don't think male-pattern baldness can be completely reversed," he says. "Instead, we'll develop different treatments, and as with other personalized therapies in medicine, some will work better in various subgroups than others." To illustrate, Cotsarelis cites evidence from his lab showing that PGD2 inhibitors work in only about two-thirds of the cultured hair follicles obtained from various donors. What that suggests, he says, is that some people are innately immune to the effects of PGD2 treatment, probably for genetic reasons. One day, he says, "we'll be looking at genomic screening results to predict who responds to a given treatment and who doesn't."

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CRISPR patents to go on trial

The dispute over who owns the intellectual property rights to the game-changing genome editing system CRISPR-Cas heated up in January after the US Patent and Trademark Office's Patent Trial and Appeal Board said it would decide the fate of the patents in a trial-like procedure called an interference proceeding. The first patent for the CRISPR-Cas system was granted in April 2014 to Feng Zhang, a bioengineer at the Broad Institute and founder of Editas Medicine, both in Cambridge, Massachusetts (*Nat. Biotechnol.* **32**, 599–601, 2014). Zhang's patent application was preceded by one submitted by Jennifer Doudna, a biochemist at the University of California, Berkeley, and her co-inventors. Attorneys for both parties have been battling ever since. Their arguments center on who first demonstrated a method for editing a mammalian genome using CRISPR-Cas. The US patent office operates under a first-to-file system for granting patents, but Zhang and Doudna's applications are being judged under the old first-to-invent rules owing to their filing and priority dates. Doudna's attorneys in April 2015 requested the interference proceeding against Zhang's patent, number 8697359, and nine other CRISPR-related patents he has since filed. The contest was recommended by a patent office examiner on December 21, 2015. The Patent Trial and Appeal Board on January 11, 2016 gave the go-ahead for the interference proceeding in a way that evens the playing field for both parties. Such contests are often lengthy and can involve testimony from inventors.

Bayer joins CRISPR

Bayer's LifeScience Center has selected Basel- and Cambridge, Massachusetts-based CRISPR Therapeutics to be its first investment. The newly established strategic innovation unit, which reports directly to Bayer management in Leverkusen, Germany, is forming a 50-50 joint venture with CRISPR to develop systemic *in vivo* therapies for blood disorders, blindness and congenital heart disease. Bayer will provide at least $300 million in research and development funding to the endeavor over the next five years. It is also acquiring a minority stake in the gene editing specialist for an additional $35 million. Know-how derived from the collaboration's efforts using the CRISPR-Cas9 endonuclease system outside of the three disease areas, including target delivery technologies, will exclusively be made available to CRISPR Therapeutics for human use and to Bayer for non-human uses such as agricultural applications. The joint venture will be based in London with operations in Cambridge. Last October, Boston-based Vertex paid $105 million up front, including a $30 equity investment, to set up a research collaboration with CRISPR that includes programs aimed at mutations and genes known to cause and contribute to cystic fibrosis and sickle cell disease. In January 2015, fellow gene editing specialist Intellia Therapeutics, also in Cambridge, partnered with Basel-based Novartis to engineer chimeric antigen receptor T (CAR-T) cells and hematopoietic stem cells using gene editing, marking the first biotech-pharma deal for a CRISPR-Cas9 technology.