

Biotech at the beauty counter

A small cadre of biotech companies is finding an easy entry into the consumer marketplace through the relatively unregulated field of cosmeceuticals. Barbara Nasto investigates.

Recombinant proteins, growth factors and cytokines—these may all sound like components of a drug development strategy. But each represents an approach taken by biotech companies trying to cash in on society's ubiquitous desire to look younger and more beautiful. Expensive cosmetics to treat acne, or to reduce the wrinkles and dryness that accompany age and too much sun, enjoy widespread consumer appeal and help make skin care the largest sector of the global cosmetics and toiletries market.

Last year, the cosmetics and toiletries sector reported the highest growth rate in five years, up 10% to over \$253 billion in global sales, according to market intelligence from Euromonitor International¹. Such numbers leave little room to wonder why both an abundance and variety of companies ranging from small biotech startups (Table 1) to global cosmetic players have leaped onto the so-called cosmeceutical bandwagon.

What's in a cosmeceutical?

'Cosmeceutical', a portmanteau of the words 'cosmetic' and 'pharmaceutical', refers to cosmetic products that claim to have drug-like benefits. Typically, anti-aging creams and moisturizers enjoy the label. An extreme example of just how much some people are willing to spend to maintain a youthful glow is Crème de La Mer. A concentrated serum, marketed by Estée Lauder of New York to an exclusive segment of their clientele, it costs \$100 per day (\$2,100 for a 21-day supply).

Max Huber, an aerospace physicist, devoted years of research to developing the skin-care formula (which serves as the foundation for an entire product line) to treat chemical burn wounds he acquired during an experiment gone awry. In 1995, Estée Lauder purchased Crème de la Mer and brought it to the mass market with great success. According to Estée Lauder senior vice president of global research and development Harvey Gedeon, there is a waiting list for the serum. However, prestige brands do not normally cost \$100 per day; customers can pay from \$100 to \$200 for a three-month supply of skin moisturizer. Of course, an abundant supply of other such products as cleansers, eye balm, night cream and sunscreen are also available for a more complete skin-care regimen.



What will biotech bring to the age-old business of cosmetics?

To those within the industry, 'cosmeceutical' serves as a marketing buzzword that lends a level of credibility to help sell a product at a premium price. For nontraditional players, such as biotech startups, this marketing-misnomer represents an easy entrée into a potentially lucrative commercial market. In addition to the promise of profits, companies introducing a skin-care product line or developing ingredients for skin care are spared the costs of conducting large-scale clinical trials necessary when proving the efficacy of a drug. Among the hundreds of skin creams on the market, only two possess US Food and Drug Administration (FDA) approval: Renova (T-retinoin) developed by healthcare manufacturer Johnson & Johnson (J&J) of New Brunswick, New Jersey, and Avage (tazarotene) developed by Allergan of Irvine, California—both vitamin A precursors. Vitamin A precursors are popular skin-care ingredients because they are thought to stimulate collagen production in the skin, a process that slows as humans age, exacerbated by exposure to the sun. Some companies choose to go through the approval process so that they can make therapeutic claims.

The line between a cosmeceutical and a pharmaceutical is a fine one. For example, Ortho

Dermatological (the arm of J&J that markets Renova) claims the product reduces fine facial wrinkles associated with chronic sun exposure and the natural aging process. Unlike Renova, other skin-care products do not make outright claims to actually reduce wrinkles. Instead, the label will state something like "it helps to reduce the appearance of fine lines." Creative phrasing is enough to keep skin-care products out of the purview of the regulatory agencies on both sides of the Atlantic (Box 1)—meaning double-blind placebo controls trials, if conducted at all, are voluntary—unless the product proves to be unsafe after it reaches the market.

"There is no motivation for companies to conduct large-scale, double-blind placebo control trials," explains Alexa Boer Kimball, director of the Clinical Unit for Research Trials in Skin (CURTIS) at Massachusetts General and Brigham and Women's Hospitals in Boston.

Recently, Kimball authored a study examining the impact of green tea extracts on the skin². The double-blind placebo control study included 40 patients observed for over a two-month period. "These studies are needed to clarify product claims for both dermatologists and the general public."

Kimball's discriminating posture toward high-end product claims is also evident in the advice she offers to patients who inquire "what can I do about wrinkles." She weighs in on the low end of the skin-care spectrum as she suggests the product Oil of Olay, a moisturizer that can be purchased for about \$10 or less at a local health and beauty store or the supermarket.

Daniel Maes, vice president of R&D for Estée Lauder, explains that competition and safety are what drive and determine the clinical testing that companies choose to conduct. "J&J and Procter & Gamble [P&G] are making serious claims supported by good science and this pushes us to come up with more innovative ideas." J&J and Cincinnati-based P&G market products including Oil of Olay and Neutrogena, respectively, which are about one-third the price of Estée Lauder's Hydra Complete Moisture Cream. Estée Lauder tests their moisturizer using a technique known as ballistometry, in which a pendulum is released onto the skin's surface and the resultant bouncing pattern of the pendulum is analyzed by a computer to determine skin firmness.

"If you want to compete, clinical trials are a great differentiator," affirms Dan Yarosh, president of AGI Dermatics of Freeport, New York, a biopharmaceutical company that develops and sells skin-care ingredients and prestige products as well as topical prescription drugs. Burt Ensley, director and CEO of Sedona, Arizona-based NuLastin, a company developing biomaterials for the cosmeceutical and

Table 1 Biotech companies in the beauty business

Company/location	Business focus	Products	Funding sources
AGI Dermatics http://www.agiderm.com/	DNA repair enzymes with liposome delivery, marketed through the internet and through dermatologists	Remergent skin-care line Nine cosmetic ingredients	\$5.5 million in Series A (Trevi Health Ventures, New York, WHI Group) and revenues from products
avVaa World Healthcare Lumby, British Columbia http://www.avvaa.com/	Promotes skin healing with salicylic acid and other natural ingredients, used for skin irritations (eczema, psoriasis, acne, dermatitis) marketed direct to consumer and through trade distributors	Neuroskin spray Dermac Neuroskin (FDA compliant)	Nasdaq: AVVV
DermaPlus New York http://www.dermalastyl.com/	Products based on tropo-elastin (precursor to elastin), marketed through the internet	DermaLastyl line of products	Privately funded Revenues from products
DermaGenetics, a GeneLink company Jersey City, New Jersey http://www.bankdna.com/	Customized skin care using SNP analysis, marketed through the internet and at doctors' offices and spas	Dermagenetics Genetic profiles for oxidative stress, skin health and aging	Nasdaq: GNLK.OB
Greentech Saint-Beauzire, France http://www.greentech.fr/	Extracts molecules from natural sources for cosmetics Maintains database Patented extraction processes	Thousands of molecules from natural sources	Privately held
Helix Biomedix http://www.helixbiomedix.com	Bioactive peptides, licensed out	Natural Results Acne Treatment System	Nasdaq: HXBM
ProtoMedix Jamesburg, New Jersey	Novel botanical therapeutics	Peptide-based nanoparticles	Series A: Inventages Venture Capital GmbH, Burrill & Co.
SkinMedica http://www.skinmedica.com/	Promotes wound healing with fibroblast growth factor, marketed through dermatologists	Nuricel-MD (TNS) product line	Privately held

personal care market, claims he is bringing his trials in line with the recommendations of Amy Newberger, a dermatologist and advisor to the FDA. Among Newberger's suggestions are: the inclusion of 25 individuals over at least a three-month period and the use of profilometry, a method for assessing three-dimensional shape. Skin models and patch tests are also used by the industry to predict the occurrence of skin irritation or allergic reactions.

Peptides, proteins and growth factors

According to Maes, the modern day skin-care consumer is more scientifically literate than 15 years ago. "Science sells," he explains. Consequently, the technology or innovation behind the product becomes an endorsement when marketing the product.

Nature Bisse, a Spanish company started by Ricardo Fisas, actually markets a 'cytokine line'—the term 'cytokine' used seemingly for its scientific cachet. This line includes an ingredient referred to as skin-growth factor, but as its exact chemical nature is not disclosed, skin-growth factor could be any protein (or mixture of proteins). Before founding the company (which is family owned and run) in 1979, Fisas served as managing director of a Barcelona laboratory that researched and developed new ingredients for the cosmetics industry. He noticed that the hands of warehouse workers who handled the laboratory's products were smooth and wrinkle free and deduced that the process used by the manufacturer permitted these proteins to pen-

etrate the skin of the workers. Fisas enlisted the help of a dermatologist and chemist to develop a manufacturing process for a skin cream. These days, Nature Bisse offers about 300 products sold at exclusive US department stores such as Bergdorf Goodman's or Neiman Marcus. Theirs are among the top-selling prestige brands.

Nature Bisse is not the only company mixing growth factors into skin-care products. A genetically engineered form of epidermal growth factor (EGF) is a key ingredient in RéVive, a brand developed and marketed by plastic surgeon Gregory Bays-Brown. In 1994, he patented an EGF he found while conducting research into wound healing³ and launched RéVive (the name of the company and the brand) in 1997. Insulin-like growth factor and keratinocyte growth factor are also featured in RéVive.

The process of wound healing has also served as the starting point for three biotech companies that have launched products or provided ingredients to the skin-care industry: Helix BioMedix of Bothell, Washington, NuLastin and Skin Medica in Carlsbad, California.

"Anti-aging and anti-wrinkling sits on the same continuum with the more medically oriented applications we investigate, such as wound healing and anti-inflammation," says Timothy Falla, vice president and CSO of Helix Biomedix. The company now has an extensive proprietary library of bioactive peptides drawn from a class of innate immunity elements. The company intends to develop and commercialize bioactive peptides with antimicrobial and wound-healing

properties and qualify them for inclusion in both pharmaceutical and consumer products. The appointment to COO of Lori H. Bush, who has worked on the well-known Neutrogena brand, demonstrates the company's current emphasis on cosmetics. Out-licensing and collaboration are integral to the company's business model. Helix BioMedix succeeded in out-licensing one ingredient, the HB64 peptide (marketed as Oligopeptide-10). Oligopeptide-10, which can be found in Chatsworth, California-based Nature's Gate Organics Natural Results Acne Treatment System, has anti-bacterial properties and is paired with salicylic acid (an ingredient commonly used in acne remedies) to control outbreaks.

Three years ago, when NuLastin's Ensley founded his company, he set out to explore the use of proteins in wound healing, tissue regeneration and organ regeneration. "In the meantime, we realized we had a dynamic topical skin care ingredient," Ensley says, referring to tropo-elastin, an elastin precursor. He says it took two years to clone and express the gene and develop a system to generate quantities at the purity level necessary for developing a skin-care cream. The application of the elastin precursor theoretically would slow or stop the loss of elastin.

NuLastin markets Dermalastyl- β , a skin cream that includes the recombinant tropo-elastin and other skin-care ingredients, directly to consumers over the internet.

Ensley says that the direct-to-consumer aspect of the business required learning "the discipline

Box 1 Cosmetic oversight?

Most skin-care products are considered cosmetics. In the interest of trade, the member states of the EU decided to harmonize their national cosmetic regulations in the early 1970s. As a result, cosmetics in Europe are primarily regulated through European Cosmetics Directive, 76/768/EC and its many amendments. The main objective of the European Cosmetics Directive (first adopted in 1976) is to safeguard public health. And the Directive primarily places this responsibility on the cosmetic manufacturer.

In 2005, the EU introduced additional labeling regulations for cosmetic products. The updated regulation identifies 26 allergens (ingredients that may cause an allergic reaction in the skin) that must be listed on the label if there is a greater than 0.01% concentration in the product.

Similarly, in the US, the Federal Food, Drug, and Cosmetic Act of 1938 requires that every cosmetic product and its individual ingredients be safe, and that the product's labeling be truthful and not misleading. Again, the responsibility rests with the manufacturer to ensure that its products comply with the law before they are marketed.

The Fair Packaging and Labeling Act of 1966 provides the FDA with additional authority to require ingredient labeling of cosmetic products sold to consumers. FDA regulations detail where and how ingredients must be listed on the package. In both the EU and in the USA, cosmetic manufacturers are required to print the product's ingredients on the packaging. The ingredients have to be listed in descending order of weight.

of selling science directly to the consumer. This is a very different thing for a biotech company," He says the feedback from customers has helped the company refine their product.

He is also aware that tissue and organ regeneration has proven risky business in the past, citing the demise of Advance Tissue Sciences (ATS) and Organogenesis as examples (*Nat. Biotechnol.* **20**, 1072, 2002). He notes that although the management at ATS did look to the cosmetics industry as a source of revenue, it was too late to save the company from insolvency. "We turned the business model upside down," Ensley explains. In other words, he can use profits generated from the company's skin-care product to finance the company's more "esoteric and long-term goals," such as exploring ways of using elastin in preventing wound contraction, as a matrix for healing and eventually in the development of organs.

In contrast to Helix BioMedix and NuLastin, Carlsbad, California-based SkinMedica develops cosmeceutical products and markets them to dermatologists, who in turn sell them to their patients. According to SkinMedica CEO Rex Bright, the company markets its own product line (named TNS), which incorporates growth factors associated with wound healing. Fibroblast growth factor (FGF) is a prominent ingredient, which augments production of collagen synthesized by fibroblasts and compensates in part for the increased rate of collagen breakdown that occurs as skin ages. Recombinant FGF produced by human cell lines is combined with additional key ingredients (e.g., anti-oxidants) to create the company's TNF skin-care products. The pharmaceutical arm of the company has four drug products on the market: NeoBenz Micro, indicated for treating hyperpigmentation, a condition in which patches of skin become darker than surrounding skin; Vaniqua, which eliminates unwanted facial hair; EpiQuin Micro for acne; and Desonate (desonide), a gel for treating atopic dermatitis.

Exploiting DNA

The iconic status of DNA means that it is often exploited in itself as a selling point in cosmetic products. But AGI Dermatics' Yarosh, who founded the company in 1985, focuses on DNA damage and repair pathways that are linked to photoaging. His firm's products deliver to the skin DNA repair enzymes via a 'proprietary' liposomal delivery system. Products developed by AGI Dermatics are featured both in their own skin-care line, called Remergent, and several prestige skin-care brands such as Aveda. According to Yarosh, the repair enzymes have potential in the pharmaceutical indication of preventing of skin cancer as well.

By marketing Remergent either directly to consumers through the internet or participating dermatologist offices, the company is riding the trend of dermatologist brands. "We are asking consumers to take the next step and asking them to go to the source. Buy us because we are scientists," says Yarosh.

AGI Dermatics is the source for nine different ingredients that appear in prestige brands. The ingredients address different aspects of skin care, such as protection from the sun's harmful rays, oxidative damage, improving the skin barrier and reducing inflammation and employing an innovative liposomal delivery system.

AGI Dermatics also has a product, Dimericine (T4 endonuclease V in a liposome coat) in phase 3 clinical trials for treating xeroderma pigmentosum, a rare genetic disease that produces high rates of skin cancer at a young age.

Elsewhere, among its wide array of traditional genetic profiling tests, Margate, New Jersey-based GeneLink is also claiming to provide a more individualized approach to skin care based on its single nucleotide polymorphisms (SNPs) assay. Clients are asked to swab the inside of their cheek and send the sample off to Dermagenetics, a wholly owned subsidiary of GeneLink.

Monte Taylor, director of business development for GeneLink, explains that the test profiles SNPs and identifies an individual's "particular deficiencies," by rating five parameters: collagen breakdown, environmental pollutants, two oxidative-stress parameters, inflammation and irritation as either green (basic support needed), yellow (added support necessary) or red (maximum support required). On the basis of this analysis, a 'DNA Ultra Custom formula', comprising such antioxidants as coenzyme Q, α -lipoic acid and vitamin B or C, is created for a customer and his or her formula number is kept on file. The product is marketed through spas and online.

Cosmetic crossover?

According to Alan Clapp, vice president of business development for Galderma, a joint venture of L'Oreal and Nestle that consultant IMS Health calls the number one dermatology company in the world, "Biotech companies serve as an important a source of innovation." Many biotech firms that are developing therapies for major indications, such as cancer and cardiovascular disease, are also starting studies in psoriasis and atopic dermatitis, he adds. That could mean new products that cross over into the cosmetic market.

Whether the strategy is direct to consumer or direct to industry, one thing is clear: biotech companies are increasingly recognizing that large cosmetics companies are potential customers in the same way that pharmaceutical firms have been traditional customers in the healthcare arena. In doing so, they have the potential to tap into a whole new source of corporate funding.

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