Healing beauty?

More biotechnology cosmetic products that claim drug-like properties reach the market

Beauty—as the saying goes—is in the eye of the beholder, though this relativistic insight has not stopped humans from spending more than 6,000 years striving to artificially enhance their looks. From Ancient Egypt and Sumer until today, the quest for beauty is recorded in our literature, music and art. Even today, many women and men devote considerable amounts of time and money to selecting and applying the right combination of cosmetic products, and thus drive a huge—and still growing—cosmetics industry. In turn, cosmetics companies, in bids to outdo their competitors, are increasingly using the results of basic research in the biological and chemical sciences to create more sophisticated products that promise little less than everlasting beauty.

The latest wave of cosmetics are based on advanced research that includes the use of biotechnology-derived ingredients, genetic profiling for individual skin-care or nutritional regimes, stem-cell-based products and therapies to regenerate ageing tissues, or cell and tissue engineering for cosmetic purposes. “Cosmetics will take advantage from those technologies that will allow one to achieve observable results upon topical application,” commented Paolo Giacomoni, the head of research at a large cosmetics company. “Stabilized enzymes used in topical applications will help to repair [damage] after exposure to solar radiation, or to digest pigments in age spots. Appropriate polymers will tighten the skin and reduce the appearance of lines and wrinkles, or prolong moisturization.”

As a consequence of this increasing application of science to beauty, the line between cosmetic and medical research is becoming blurred; the laboratories of major cosmetic companies perform cutting-edge research in areas such as matrix biology, antioxidants and ageing processes. In addition to the goal of making women and men look younger, this research also benefits the development of therapies against a range of serious disorders.

Vice versa, various biotechnology companies—such as those that are investigating methods to boost DNA repair or wound healing—have licensed some of their molecules to the cosmetic industry, or have even entered the market with a proprietary line of beauty products themselves (Nasto, 2007). Helix Biomedix, for example, a biotechnology company based in Bothell (WA, USA) has recently patented more than 80 proprietary peptides for use in cosmetic and skin-care applications and products. According to the company, there are now more than 20 products on the market that contain Helix’s peptides (www.helixbiomedix.com).

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One of the main impetuses for researching cosmetics is that they are not required to undergo the clinical trials for efficacy to which drugs are subject. In the case of biotechnology companies, this provides a new source of income to finance their basic research; however, the blurred line between drugs and cosmetics creates a complex regulatory situation. Many beauty products—which often sell at a high retail price—come with claims that the product is based on advanced scientific research, giving consumers the impression that they are as effective—and as tested—as drugs. Conversely, the cosmetics industry does not want its products to be regulated in a similar manner to drugs as this would involve extensive, lengthy and costly clinical trials for efficacy. It therefore falls to the regulatory agencies to decide whether a product—despite its claims—is a cosmetic, or whether it should be classed as a drug because it has a therapeutic effect.

Credit: Timur Suleymanov/Dreamstime.com

The treatment of damaged or ageing skin is an important area in which the interests of medicine and cosmetics collimate most obviously, and one where the line between cosmetics and medicine is most evanescent (Giacomoni, 2005). As our knowledge about the structure of the skin and its underlying repair and maintenance processes improves (Fig 1), scientists are increasingly able to intervene to stop ageing or improve healing. Renovo—a biopharmaceutical company based in Manchester, UK—is approaching phase III of clinical development of a candidate drug that reduces scarring after surgery or injury. Their product, Juvista, is based on a recombinant form of human transforming growth factor- β 3 (TGF- β 3), which is normally present at high levels in developing embryonic skin and in embryonic wounds that heal without a scar, but is almost absent in adult wounds. The intradermal injection of Juvista to the wound margins before or after surgery improves subsequent skin appearance, as scars are less noticeable and resemble normal skin more closely. The

product would benefit consumers who seek to remove small scars and patients with seriously disfiguring scars.

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The cosmetics and pharmaceutical industries have also expended considerable effort to understand the ageing processes of the skin and to devise countermeasures. The fragmentation of the collagen matrix in the dermis—the inner layer of skin—is caused by metalloproteinases and is an important characteristic of aged skin; various treatments, supported by clinical evidence, therefore aim to reduce collagen collapse and to stimulate its renewal. Topical retinoic acid, carbon dioxide laser resurfacing and intradermal injection of cross-linked hyaluronic acid—such as Restylane® and

Perlane® (Medicis; Scottsdale, AZ, USA)—are all known to stimulate the production of collagen, and to improve the appearance and health of the skin (Fisher *et al*, 2008). SkinMedica (Carlsbad, CA, USA) is another example of a biotechnology company that has entered this lucrative market with an anti-ageing product that contains soluble collagen, various growth factors and antioxidants among its ingredients to enhance skin texture and elasticity.

Howard Chang's team at Stanford University (CA, USA) are looking at ageing processes from a more systematic point of view, which might open the way for new interventions and further blur the line between cosmetics and drugs. By applying a bioinformatics approach to pinpoint regulators of age-dependent gene expression in humans and mice, Chang's team have identified the transcription factor NF- κ B (nuclear factor- κ B) as a crucial regulator of gene expression programmes associated with mammalian ageing (Adler *et al*, 2007). Blocking NF- κ B activity in the

epidermis of aged mice reverted tissue characteristics and the global gene expression programme to those of young mice (Fig 2). However, the authors note in a related paper that, “it is unclear whether NF- κ B blockade can become the much sought-after ‘fountain of youth’. The reversal of age-related phenotypes in mouse skin was only short-term; thus we do not know whether long-term reversal of aging is possible or whether tissue longevity has been extended” (Adler *et al*, 2008).

“Work by us and others is showing that the aging process is plastic and potentially amenable to intervention. Even temporary blockade of the aging programme may achieve healthful benefits,” Chang said of the possible implications of their discovery. However, he warned that the “long-term consequences of manipulating genes associated with ageing are not fully understood; these would certainly be a concern for applications in humans.” For example, Chang and colleagues pointed out that blocking NF- κ B in the presence of additional oncogenes might theoretically allow cancerous growth (Adler *et al*, 2008).

The research division of L’Oreal (Paris, France), the world’s largest cosmetics and beauty company, uses similarly advanced tools. While looking for a treatment to restore the hair’s natural appearance and health after excessive exposure to environmental and other stresses—such as chemical products or repeated washing and drying—L’Oreal’s researchers focused on the hair’s cuticle, its external protective sheath. Under the electronic microscope, the scales that make up the cuticle appear to be firmly held together by a cement rich in lipids, in particular, ceramides. Subsequent research confirmed that damaged hair is deprived of ceramides and L’Oreal developed a synthetic ceramide, Ceramide R, which is now incorporated into various products that the company claims will “genuinely repair damaged hair” (www.hair-science.com/).

More recently, L’Oreal developed its so-called ‘Episkin’ model—a human epidermis reconstructed on collagen (www.invitroskin.com). Episkin is not only a good research tool, but was also validated by the European Centre for the Validation of Alternative Methods (Ispra, Italy) as a potential replacement for current methods to assess the skin-irritancy potential of cosmetic ingredients and products, without using animals.

Fig 1 | Three-dimensional reconstruction of a human skin cell using cryo-electron tomography. The image shows organelles in various colours: regions of cell-cell contact (sandy brown), nucleus and nuclear envelope (blue) with pores (red), microtubules (green), mitochondria (purple), and endoplasmic reticulum (steel blue). Credit: Achilleas Frangakis, European Molecular Biology Laboratory, Heidelberg, Germany. Reproduced with permission from Nature Publishing Group; Al-Amoudi *et al*, (2007) *Nature* **450**: 832–837.

Stem cells have attracted similar interest from the cosmetics industry and various companies are already exploring their potential for skin-care products. Proteonomix, a biotechnology company in Mountainside (NJ, USA), for example, has recently launched a line of anti-ageing products that contain proteins derived from specialized stem-cell lines. The inspiration came from the apparently ‘glowing’ appearance of pregnant women. “During pregnancy, a woman’s body increases the production of specific proteins in response to secretions produced by the embryo. These specific proteins affect specific receptors in both fibroblasts and keratinocytes that increase the production of collagen,” explained Proteonomix’s CEO Michael Cohen in a white paper (Cohen, 2008). The company now produces these proteins in human stem-cell derivatives as a treatment for various dermatological conditions, including the adverse consequences of ageing, wrinkling, altered pigmentation, altered viscoelasticity and altered thickness.

Similarly, RNL Bio, a South Korean biotechnology company based in Seoul, which made the headlines earlier this year for undertaking the world’s first commercial

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pet cloning, is developing a stem-cell-based cream for cosmetic applications. According to press reports, the new product will exploit the anti-ageing properties attributed to the human placenta (Wohn, 2008). The active ingredients of RNL Bio’s rejuvenation booster are proteins from cultured placenta stem cells, rather than directly extracted from the placenta. This approach, the company claims, produces more active and stable compounds, thus assuring the faster regeneration of skin cells. RNL Bio and Seoul National University are also investigating whether intravenous injections of stem cells might mitigate the degenerative effects of ageing processes.

Giacomoni, however, remains critical of the role of stem cells in cosmetics. “Stem cell technology is still far from biomedical applications, let alone cosmetic ones,” he said.

Fig 2 | NF-κB action in ageing. (A) NF-κB (shown as a p50–p65 heterodimer) is an ideal integrator of ageing signals: NF-κB is activated by stressors that shorten lifespan (blue text), and it can be repressed by signals that extend lifespan (orange text). (B) Many age-specific functions of NF-κB are revealed as its activity accumulates with chronological age. Continual NF-κB activity seems to be required for age-associated phenotypes (in the skin), as transient blockade of NF-κB reverses multiple ageing phenotypes to that of young phenotypes. FOXO, forkhead box class O transcription factor; NF-κB, nuclear factor-κB; SIRT1, sirtuin 1. Redrawn with permission from Landes Bioscience; Adler *et al*, (2007) *Cell Cycle* 7: 556–559.

As the cosmetics industry and its research laboratories perform increasingly cutting-edge research, the difference between some cosmetic products and some pharmaceutical products is shrinking further—a development that will inevitably attract the attention of the regulatory agencies, such as the increasing scrutiny of Botox (see Sidebar A). Current legislations generally require that cosmetics must not cause harm to human health with normal or reasonably foreseeable use, and that the product itself and its ingredients must have been tested for safety. In addition, health claims made on the label and in commercials must be substantiated, which is the main problem for so-called cosmeceuticals—products that are claimed to have drug-like benefits.

In its 2007 survey, the UK Advertising Standards Authority (ASA; London, UK) classified several medicinal claims for cosmetic

products as breaches of the British codes of advertising and sales promotion. They spotted misleading or unsubstantiated anti-ageing and regenerating claims made for skin creams; claims of skin repair achieved through increased collagen production; claims of the ability to neutralize environmental damage through the use of anti-oxidants; and promises that moisturisers can strengthen immunity and improve circulation (ASA, 2008). Although the overall compliance rate for cosmetics to advertising standards was as high as 93%, “the greatest cause for concern was the relatively poor compliance rate for skin cream ads; 19% were found to breach the Code,” the ASA concluded. “The Compliance team considers that future problems with skin creams could revolve around claims referring to DNA stress, environmental damage, the delaying of wrinkles, cell renewal, cell regeneration and stem-cell-derived

products. Ads for new products seen since the survey have included such claims.”

Given that the cosmetic industry in Europe has an estimated market size of €65 billion, and creates half a million direct and indirect jobs, the European Union takes such problems seriously. The main regulatory framework to regulate the trade and safety of cosmetic products is the Council Directive 76/768 of 27 July 1976, and various guidance documents help regulators to decide on the exact nature of ‘borderline’ products that can fall under a different regulation, especially the one pertaining to medicinal products. “As a general rule a particular product cannot be regulated by both the Cosmetics Directive and the Medicinal Products Directive at the same time. The two regulatory frameworks are mutually exclusive. However, it is recognised that some products may fulfil at the same time the definition of a cosmetic product as well as the definition of a medicinal product. In these cases the question may arise as to which regulatory framework should apply,” explains a European Commission guidance document (EC, 2004). In these cases a ‘non-cumulation principle’ provides that the Medicinal Products Directive is applied (EC, 2004). The demarcation between the two directives—and thus between cosmetics and medicinal products—therefore remains unclear, and decisions are taken on a case-by-case basis by competent authorities as high as the European Court of Justice in Luxembourg.

The European Commission has proposed to recast the European laws on cosmetics and to simplify more than 3,500 pages of legal text from national legislations and the EU Cosmetics Directive with its 55 amendments into a new, single regulation. The aim is to strengthen product safety while reducing costs for businesses and enhancing consumer confidence. Linked to this is the recent launch of ‘Cosing’ (COSmetic INGredients; <http://ec.europa.eu/enterprise/cosmetics/cosing/>), a new online database of more than 15,000 ingredients used in the production of cosmetics—with details of current and past regulation since 1976—which will make it easier for producers to ensure that new formulations comply with existing regulations.

The US Food and Drug Administration (FDA; Bethesda, MD, USA) is facing the same problem of drawing the line between cosmetic and medicinal products, but the outcome differs to

Sidebar A | A blurry future for Botox?

The cosmetic use of botulinum neurotoxins (BoNTs) to remove wrinkles might face an uncertain future. Produced by the bacterium *Clostridium botulinum*, BoNTs are among the most deadly natural toxins known; they interfere with the release of neurotransmitters—mainly acetylcholine—at the junction of nerves and muscles. These paralyzing properties have been exploited to treat a range of serious pathological conditions such as cervical dystonia (severe neck muscle spasms), facial spasticity and strabismus (abnormal aligning of the eyes), and, more recently, to reduce facial wrinkles.

Until now, the use of BoNTs for cosmetic purposes—under the brand and popular name Botox—had been considered safe, in large part because it was assumed that the toxin remained confined to the injection site. However, an Italian research team at the National Research Council's Institute of Neuroscience in Pisa recently showed that this assumption might be wrong. To study the potential use of BoNT type A to block epilepsy, these researchers injected the toxin at various points in the face and brain of rats, including the whisker muscles and hippocampus. Days later, they found that the substance had unexpectedly spread from the whisker pad to the brain stem and crossed from one side of the brain to the other in the hippocampus, blocking hippocampal activity in the untreated hemisphere (Antonucci *et al*, 2008). This should raise some concerns about the safety of BoNT injections as it revealed the ability of the toxin to travel along nerve cells while remaining active.

Earlier this year, the US Food and Drug Administration (FDA) had already warned that it had “received reports of systemic adverse reactions including respiratory compromise and death following the use of botulinum toxins [...] The reactions reported are suggestive of botulism, which occurs when botulinum toxin spreads in the body beyond the site where it was injected” (FDA, 2008). The question is whether this is enough evidence to ban the cosmetic use of BoNTs. “I don’t think that fear is warranted. Thousands of people have already taken the drug for cosmetic purposes, with few reports of side effects”, said Matteo Caleo, the study’s lead author. “At the same time, I believe that the issue of BoNT/A trafficking should be further investigated. It is important to characterize completely the spectrum of actions of a drug that is so widely used.”

Botulinum neurotoxin (see image) hijacks synaptic vesicle recycling at neuromuscular junctions. The toxin first docks to the active zone (blue) by binding to two membrane-anchored receptors, synaptotagmin (red) and ganglioside (yellow). The toxin–receptor complexes are then internalized by endocytosis. Credit: Axel Brunger/HHMI at Stanford University, California, USA.

some extent. As the FDA does not apply the non-cumulation principle, a product can have intended uses as both a cosmetic and as a drug. According to the FDA, the intended use might be established in several ways, including “[c]laims stated on the product labeling, in advertising, on the Internet, or in other promotional materials; [c]onsumer perception, which may be established through the product’s reputation; [i]ngredients that may cause a product to be considered a drug because they have a well known (to the public and industry)

therapeutic use” (FDA, 2002). Such products must comply with the requirements for both cosmetics and drugs.

In the end, cosmetics are not primarily about science, but about the age-old promise of beauty. “Cosmetics will take more advantage from socio-psychology than from biotech,” concluded Giacomoni. “The psychology of the elderly, the social games of children, the well-being resulting from skin care, make up and fragrances will be pointed out and will help to create new concepts and claims for cosmetic products.”

However, the lure of products with ‘scientific’ names such as ‘DNAge’ and ‘Nuvectin’, which invoke the idea of defeating ageing with the help of science, will remain irresistible for many consumers because they sound like they should work. Conversely, the increasing use of scientific research in the development of new cosmetics should ultimately benefit the consumer, as it contributes to the next generation of safer and more efficient beauty products.

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