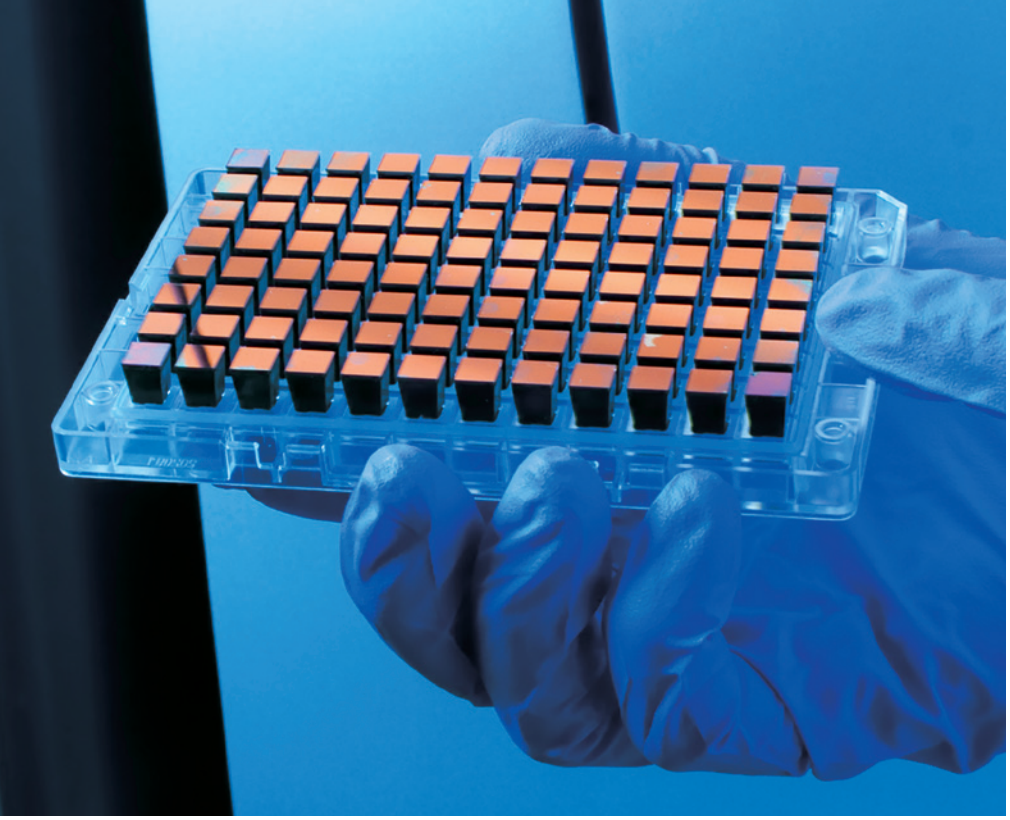

Gene-expression analysis is allowing researchers to define the pathways associated with ageing.

COSMETICS

# Molecular beauty

*The rise of genomic and other technologies in cosmetic skincare is leading to products that might improve skin health.*

BY ALLA KATSNELSON

As scientists raced towards the finish line of the Human Genome Project at the turn of the twentieth century, a New York-based university spin-off called Lab21 set out to apply genetic-sequencing technology to skincare. Using a 'skin DNA test' that assessed mutations in five genes, the company claimed to have designed personalized skincare concoctions that would moisturize, plump and de-wrinkle any individual's face — at a cost of US$250 for a month's supply. "We have taken the guesswork out of the skincare equation," the company's president proclaimed in a 2003 press release. Upscale department stores eagerly signed on.

Geneticists and dermatologists scoffed at Lab21's researchers, saying that too little was known about the genes involved and about how a cream's active ingredients might supplement genetic failings. They turned out to be right. Lab21 fizzled out after a few years, but it was not the last cosmetics company to grab on to the coat-tails of scientific advancements.

Claims of scientific efficacy are so common for today's skincare products that they elicit eye-rolls from the sceptical. But such claims were not always the norm: until a couple of decades ago, "the beauty industry was almost allergic to science", says Barbara Gilchrest, a dermatologist at Massachusetts General Hospital in Boston. The common perception, she says, was that consumers were scared of and uninterested in science, so companies did not want the word associated with their products. That aversion started to melt with the advent of genomics, which not only revolutionized research but — as the enthusiasm for Lab21's product suggested — also captured the public's imagination. Of course, outsized interest has fuelled some "rather flagrant pseudoscience", Gilchrest points out. But alongside the flood of dicey assertions, the field is finally getting onto firmer scientific ground, she says, laying the foundation for formulas that may have the power to legitimately reverse skin ageing.

Over the past decade, cosmetics companies have invested heavily in molecular and genomic research into what causes skin cells to age, with the hope of pinpointing ways to interfere with that process. Researchers are applying these tools from the other direction to determine whether already available treatments that seem to work cosmetically also improve the functional qualities of the skin. "Over the years, we've converged on an understanding that we should be doing really deep biology on the skin-ageing process and on products that can be used to improve skin health," says molecular biologist Jay Tiesman, who works on the beauty brand Olay at consumer-goods company Procter & Gamble. "It's just like any other biological endpoint that a pharmaceutical company would go after."

PROCTER & GAMBLE

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## PROVEN REJUVENATORS

As skin ages and is exposed to ultraviolet light, collagen — the key protein in maintaining skin's elasticity and structural integrity — begins to fragment. Meanwhile, skin cells called dermal fibroblasts that normally produce collagen become less efficient at doing so. Wrinkles, sagging and uneven pigmentation are the result. The first substance demonstrated to treat wrinkles was a vitamin A derivative cream called tretinoin, co-invented by dermatologist Albert Kligman, who was also the first to show that ultraviolet light causes wrinkles. Marketed as Retin-A, the cream was approved to treat acne in 1971, but soon gained a reputation as a wrinkle-buster, and physicians began prescribing it off-label. A small, but influential clinical trial in 1988 demonstrated its efficacy, whipping consumers into a tretinoin frenzy[1]. "It really blew open the translational research field for the reversal of skin ageing," says Sewon Kang, a dermatologist at Johns Hopkins University in Baltimore, Maryland. "Up until then, most physicians thought that if the skin starts to sag, you go and find a good plastic surgeon."

Since then, researchers have found that tretinoin cream (and its related compounds) stimulates fibroblasts to make procollagen (collagen's precursor) and supports the skin's extracellular matrix, countering some of the destructive effects of ultraviolet light. But how exactly this happens — and whether it reverses the degradation that occurs with skin ageing — is unknown. Anne Lynn S. Chang, a dermatologist at Stanford University School of Medicine in California, recently embarked on a project to examine how commonly used topical skin products such as tretinoin might change gene-expression signatures and other molecular markers, and to determine whether those treatments have real benefits for skin health, not just appearance. Chang hopes the project will be as productive as a pilot study she conducted, which examined the efficacy of another widely used dermatological procedure called broadband light (BBL) treatment[2].

To administer BBL, a clinician passes a wand that pulses high-intensity visible and infrared light over a person's skin in a series of sessions weeks apart. The technique has been approved by the US Food and Drug Administration to treat skin discolouration; dermatologists also use it off-label for skin rejuvenation. Chang and her colleagues found that when they used

BBL on people who had substantial sun damage more than half of the genes whose expression had been altered by age were restored to expression levels similar to those of skin from younger individuals.

In a similar vein, Frank Wang at the University of Michigan in Ann Arbor and his colleagues have explored the efficacy of injecting 'dermal fillers' — specifically, those containing hyaluronic acid. This naturally occurring substance is a key component of the extracellular matrix. Skin researchers have surmised that injecting such fillers tightens sagging skin and smooths wrinkles simply by physically adding volume to the skin, but Wang's group found that the effects go much deeper. Hyaluronic acid injections boost gene and protein expression of type I collagen (the most abundant collagen in human skin) within four weeks[3]. In further explorations, they reported that this filler — by providing structural support to the extracellular matrix — activates dermal fibroblast cells and stretches them out. This stretching switches on a signalling pathway that stimulates the skin to rev up its own collagen production. Because newly formed dermal collagen persists for many years, the treatment provides long-lasting effects[4]. "That's telling us that fibroblasts don't inherently lose their function with age," says Wang.

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**Broadband light therapy involves passing high-intensity light over the skin to treat skin discolouration.**

## A PERSONAL TOUCH

These lines of study point to biological ageing processes that are, at least to some extent, reversible. Pinning down the molecular signalling that drives these processes should unveil approaches for designing new products, says Chang. Large-scale gene studies are beginning to tease out the key pathways that are involved in skin ageing — an approach that is old hat in the pharmaceutical industry, but that has more recently infiltrated the skin-health and cosmetics world. In a study of 428 centenarians, 6 gene mutations were found to correlate with youthful skin appearance. But the mutated genes, it turned out, were not the same ones that are associated with longevity[5]. "One of the significant gene variants is near a gene that is found in immune cells in the top layer of skin," Chang says. This observation suggests that individuals with younger appearing skin may have a different immune response than do other people.

Chang is also collaborating with skincare company Nu Skin based in Provo, Utah, to identify gene-expression signatures in the skin of women who naturally have more or less youthful-looking skin. The study, presented at the Annual Meeting of the Society for Investigative Dermatology in May, identified several hundred genes that differed — many of which are involved in known ageing pathways[6].

Other companies are hot on the same trail. Alexandra Kimball, a dermatologist at Massachusetts General Hospital, is collaborating with Procter & Gamble and is thick in the middle of what Tiesman calls "the Manhattan Project of skin ageing". Kimball and her colleagues examined gene-expression patterns in 3,700 samples from a total of 225 African American and white women in different decades of their lives, as well as microbial composition, proteomes and metabolomes in a smaller subset; they looked at skin from exposed parts of the body as well as from the usually shaded buttock area.

At the World Congress of Dermatology in June, the researchers reported distinct patterns of gene activity that are characteristic of each decade, as well as the expression pattern signatures of people whose skin aged especially well or especially poorly. One insight the study revealed is that timing and patterns of molecular changes correspond to known broadly age-related alterations — cell senescence begins to appear in the 40s, and the skin's ability to maintain moisture levels starts to wane in the 50s. "With these data," Kimball says, "we can certainly anticipate skincare products personalized for people by decade."

*"The beauty industry was almost allergic to science."*

And, coming full circle to the Lab21's offerings of a decade ago, a handful of boutique skincare manufacturers are again offering personalized creams based on DNA testing. One of these is GeneU, founded by Imperial College London engineer Christofer Toumazou. In its London store, GeneU offers microarray tests that assess three variants in each of two genes: *MMP1*, with variants indicating whether a person is a fast, medium or slow degrader of collagen; and *NQO1*, with variants pointing to cells' capacity to fight oxidative stress. Based on the results and on a lifestyle survey of factors such as sun exposure, smoking habits and stress levels, customers receive one of 18 formulations of the cream. (The initial test plus a 2-week supply costs £600, US$930; a subsequent supply is £250 per month.) Toumazou says that users experienced a 24–29% reduction in different types of wrinkles, as assessed by dermatologists in a 12-week placebo-controlled, double-blind study.

Those results have not been published, however, and many researchers do not buy the company's claims. "These endpoints have a lot of 'kitchen logic' to them; collagen breakdown is an important part of skin ageing," says Tiesman. But no specific variants in the genes have been explicitly linked to skin health, so it is unclear what actionable information the tests provide.

There is no telling whether the current wave of research will yield cosmetic skincare products that are proven to truly halt or even reverse the ageing clock. Differences in gene expression and other markers are just a start; they must be followed up with studies that explore the underlying biology of the skin, assays of active ingredients and numerous other steps. Just as in drug discovery, dead ends will abound. But these first stabs at building a comprehensive picture of skin ageing have already brought the cosmetics field to a point at which products backed by science, as much as by marketing, seem like a realistic possibility. "It better pay out in the end," says Tiesman, "because it has cost us a lot to execute." ■

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