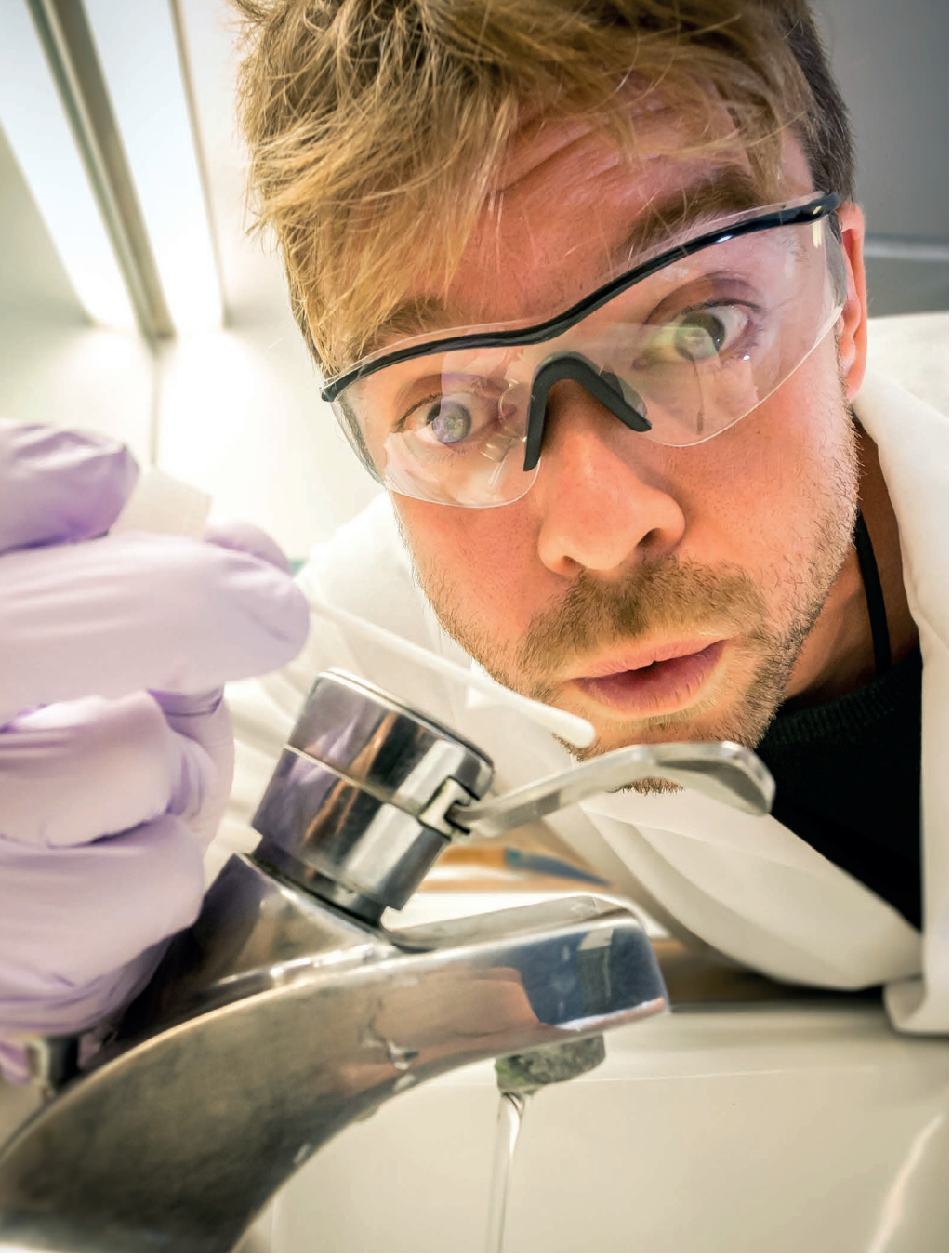


Jack Gilbert investigates the movement of microbes between skin and the environment.

ARGONNE NATIONAL LABORATORY

MICROBIOME

Community effort

Each person's skin carries a unique population of microbes that might help to protect skin, or increase its vulnerability.

BY EMILY SOHN

In December 2012, two months before the opening of a new, ten-storey hospital building in Chicago, Illinois, Jack Gilbert and his team descended with cotton swabs. In ten seemingly empty hospital rooms and at two nurse stations, they took samples from bed rails, floors and other surfaces to test for microbial life that had already moved in. After the building opened, the team returned again and again, taking samples — including from hands, armpits and other body parts of patients — as often as once a day.

After a year of sampling, Gilbert, a microbiologist at the University of Chicago, had enough information to build up a picture of how microorganisms move between the environment and people's skin in a hospital setting. As soon as patients arrived, communities of microbes on the hospital surfaces began to reflect the groups that tend to live on skin, including species of bacteria from the genera *Staphylococcus* and *Streptococcus*. But that wasn't surprising to Gilbert. Each hour, people shed around 37 million bacteria and 7 million fungi into the air.

More intriguing was how the microbial communities changed as patients came and went. Each person's skin carries a unique combination of microbes, known as a microbiota, the collective genomes of which are called a microbiome. During the first day of their stay, patients picked up microbes that had been left behind by the room's previous occupant. Soon, however, their own microbes took over[1]. "Within 24 hours, the old patient's microbiome signature in the room completely disappeared," Gilbert says. "And it completely disappeared on the new patient's skin."

These findings add to a growing understanding of how communities of bacteria, fungi and viruses form on skin, and their potential for affecting health — particularly in hospitals, where drug-resistant bacteria are of increasing concern. In the past decade, researchers have characterized the types of microbe that thrive on skin and have investigated how those microbes colonize people early in life. They have also linked specific species of microbe to infections and skin conditions such as eczema and acne vulgaris — connections that could be more than simple associations, especially as skin-dwelling microbes might both cause skin disorders and prevent them.

Such tantalizing discoveries conjure up ideas of a fresh generation of treatments that improve health by adjusting the skin microbiota. Although the research is less than conclusive, both established and start-up cosmetics companies are enlisting scientific advisers to develop microbe-specific products to improve health and beauty. Many skin researchers, however, urge caution. "Long-term, I do see promise," says Julie Segre, a geneticist at the US National Human Genome Research Institute in Bethesda, Maryland. But, she adds, "We're really at the beginning stages."

TAKING ATTENDANCE

Millions of microbes cover the surface of skin. But studies of the skin microbiota have lagged behind research on gut microbes, Segre says. The reason is partly historical: initial research on microbiotas focused on the gut, which hosts the body's largest community of microbes — with potential implications for nutrition, digestion and immunity.

But as the body's first line of defence against pathogenic agents, skin is also an important gateway to the immune system. Gradually, research on the skin microbiota is catching up. So far, the bulk has focused on working out which microbes are present and how microbial communities form. Using next-generation genome sequencing, scientists have shown that a couple of hundred species of microbes, belonging to several main genera, thrive on the skin's surface — the epidermis. Microbes

© 2018 Springer Nature Limited. All rights reserved.

have also been found to reside in the dermis, a deep layer of skin — a finding that challenges a long-held assumption that the dermis is sterile and protected from bacteria.

The make-up of the body's microbial communities varies by body part. Researchers have defined four basic environments using factors such as pH, moisture levels and temperature. Species of the genus *Propionibacterium* dominate oily sites such as the forehead. Moist sites such as elbow creases have fewer *Propionibacterium* and relatively more species belonging to the genus *Staphylococcus*. Feet are dominated by *Staphylococcus*. Fungi, mainly of the genus *Malassezia*, live all over the body but are most common in oily areas such as the face and back. Hair follicles are especially resource-rich environments for fungi and bacteria.

Such regional variations are consistent between people but, as Gilbert confirmed in his hospital study, each person's skin microbiota is unique enough to be identified from a swab taken from any part of their skin[1]. Like that of the gut microbiota, the composition of the skin microbiota is remarkably consistent over time. For skin, this is probably because microbes that live in the dermis replenish the surface population as skin flakes off.

Over the course of about two years, Segre and her colleagues repeatedly sampled skin microbiotas at 17 sites on the bodies of 12 people[2]. The team's findings showed that there were plenty of transient species of microbe, especially on the feet. But the dominant types tended to stay the same. "Even though our skin is the most exposed organ in our body — we're constantly bathing it, applying creams to it, touching things, being exposed to different people and environments — it's largely stable over time," says Julia Oh, a microbial geneticist at the Jackson Laboratory in Farmington, Connecticut, who worked with Segre on the study.

The microbiota's consistency has implications for drug development. When Oh and her collaborators bathed mice in "tons and tons of human skin microbes" three times a week for 30 weeks, they found that there was little colonization of the animals' skin. But as soon as a mouse received a cut to the skin, the microbes from human skin took over. These results are yet to be published and Oh acknowledges that the outcomes of transferring microbes from mouse to mouse, or from person to person, could differ. However, if a breach in the epidermis is necessary to alter the skin microbiota, Oh says, future therapeutics might need to agitate skin to have an effect.

The initial few months and years of a person's life seem to be a crucial time for the skin microbiota. In one of the first studies to scrutinize the interaction between the skin microbiota and the immune system in infancy, Tiffany Scharschmidt, a dermatologist at the University of California, San Francisco, found that adult mice were tolerant to *Staphylococcus epidermidis*, a skin bacterium found commonly in people, when the microbes were allowed to colonize their skin soon after birth[3]. The immune systems of the mice did not react when *S. epidermidis* was applied to skin abrasions. Although not usually pathogenic, this bacterium can sometimes cause infections.

> ***"It speaks to a window of opportunity for establishing a healthy relationship with skin bacteria."***

But when mice encountered *S. epidermidis* for the first time as adults, their immune systems mounted an inflammatory response, which can impede wound healing, Scharschmidt says. This suggests that there is a period in early life in which it is beneficial for organisms to be exposed to the microbes that they will continue to encounter. In people, the first few years might therefore be a key time for intervention, either by adding important microbes to the skin or by creating an environment that favours ideal microbiotas. "It speaks to a window of opportunity for establishing a healthy relationship with skin bacteria," Scharschmidt says. During that crucial time, she notes, "We don't want to limit exposure to healthy microbes."

MICROBES FOR ECZEMA

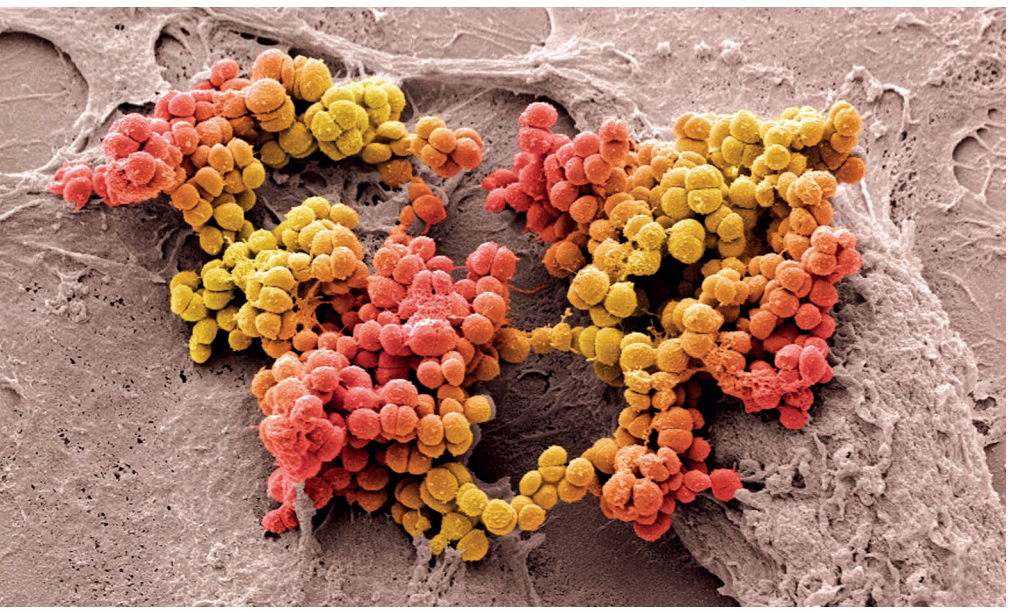
In 2009, around the time that researchers began to decipher the ecology of the skin microbiota, immunologist and dermatologist Richard Gallo and his team at the University of California, San Diego, in La Jolla, published a landmark study that hinted at potential treatments for inflammatory skin conditions. *S. epidermidis*, they found, produces a substance that suppresses inflammation — both in human skin cells in the laboratory and in the skin of mice[4].

Gallo's team has since discovered at least 14 strains of *S. epidermidis* that produce antimicrobial compounds, which kill microbes that trigger inflammation. Some of those compounds inhibit the growth of *S. aureus*, a species of *Staphylococcus* that can cause serious infections. Certain strains of *S. aureus*, including methicillin-resistant *S. aureus*, have become resistant to multiple antibiotics.

The discovery that species of *Staphylococcus* could offer protection from others holds particular promise for treating, or even preventing, atopic dermatitis, the most common form of eczema. The condition, which affects more than 18 million people in the United States and up to 30% of children in industrialized countries, causes itchy, red patches on the skin that have an impact on quality of life and increase the risk of infection. Eczema is also thought to have a bacterial component: when patches develop, the number of *S. aureus* bacteria on affected regions increases, and there is a decline in the overall diversity of the skin microbiota. People with more severe cases of eczema experience larger increases in the number of *S. aureus* bacteria on their skin.

That rise might, in part, be responsible for exacerbating eczema flare-ups. In 2017, Segre, Heidi Kong at the US National Cancer Institute in Bethesda, Maryland, and their colleagues isolated *S. aureus* from the skin of 18 children with or without eczema[5]. The team then allowed bacteria from both groups to colonize healthy mice. Mice that received *S. aureus* from children with eczema went on to develop eczema-like inflammation and thickening of the skin.

If *S. aureus* does cause flare-ups, then fighting that microbe might help to treat eczema. Gallo has developed a cream that incorporates strains of *Staphylococcus* found on human skin that inhibit *S. aureus* by producing an antimicrobial compound. In a randomized, double-blind trial of the cream in 11 people with eczema, all of whom were deficient in the inhibiting bacteria before receiving Gallo's intervention, a single application led to a more than 90% reduction in the number of *S. aureus*



STEVE GSCHMEISSNER/SPL

The bacterium *Staphylococcus aureus* (red and yellow) is found on human skin.

© 2018 Springer Nature Limited. All rights reserved.

ALEX VALM/NHGRI

on the skin of all participants. "It worked fantastically," Gallo says. "It was basically the first time in humans that a microbial transplant on the skin was therapeutically useful."

Gallo says his latest results show that applying the cream twice a day, every day for a week reduces *S. aureus* numbers by more than 99%, with symptoms declining in severity by 20–30%. MatriSys Bioscience in La Jolla, California, a company co-founded by Gallo, is aiming to bring the cream to market in two to three years.

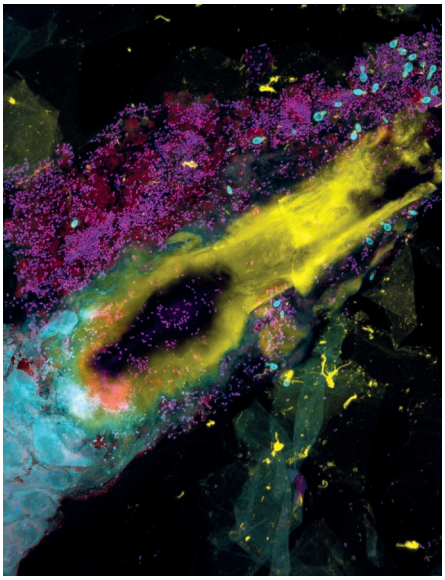
Such treatments could help to tackle more than just skin conditions. People with eczema often develop asthma and allergies — previously thought to be a sign of overall immune-system dysfunction. Some researchers now suspect that microbes living on shed skin cells — a major component of dust in the home — exacerbate these allergic reactions. If this hypothesis is correct, it might be possible to alter the skin microbiota in a way that could ease eczema while also making flaked-off skin less likely to trigger the immune system when inhaled. Or, Segre adds, it might be possible to predict which treatment will work best or when someone might be about to experience an eczema flare-up.

There are hints that fungi might also help to protect skin from eczema, says Thomas Dawson, a pharmacologist and chief executive of skin-product consultancy Beauty Care Strategics in Singapore, who previously spent more than 15 years using skin-microbiome research to develop anti-dandruff products. One clue lies in the point at which certain fungi colonize skin: *Malassezia*, comprising 17 species, peaks in babies, who tend to have greasy skin, and again at puberty — a time when skin becomes oilier and eczema becomes less common. Another clue comes from a 2016 study by researchers in Singapore, China and the United States, who found that the *Malassezia* population decreases as *S. aureus* numbers rise during eczema flare-ups[6]. In 2018, Dawson and his colleagues found a potential mechanism for this relationship, in which some types of the fungus secrete enzymes that digest *S. aureus* biofilms[7].

The role of *Malassezia* in skin health is far from certain; however, there is evidence to suggest that fungi also cause certain other skin conditions. Clarifying the details could lead to the development of strain-specific anti-fungal treatments, or probiotics (live microbes) that when applied to skin help to engineer a health-promoting balance of fungi. "By no means is the hypothesis proven" that skin fungi can be protective, says Dawson, who is also president of the Skin Research Society Singapore. "But the picture is starting to become more clear."

ACNE ACME

Work on eczema is at the forefront of research on the skin microbiota, but other skin conditions such as acne could also benefit from a growing understanding of skin microbes. For decades, scientists have known that the bacterium *Cutibacterium acnes* (formerly *Propionibacterium acnes*) thrives on the skin



Hair follicles host bacteria (pink) and yeast (teal).

of people with acne, which affects up to 85% of teenagers. Antibiotics that target *C. acnes* have therefore long been an effective treatment for the skin disorder.

But initial attempts to solidify a link between acne and the skin microbiota were disappointing, says Huiying Li, a bioinformaticist at the University of California, Los Angeles. When she used next-generation sequencing to compare the microbial make-up of healthy and acne-prone skin, both tended to have similar relative abundances of *C. acnes* bacteria, which suggested that the microbiota might not play a part in acne after all.

However, Li found population-level differences in strain composition that distinguish skin with acne from healthy skin[8]. So far, her team has sequenced 70 of more than 120 known strains of *C. acnes*, revealing genes that are key to the bacterium's virulence, as well as potential explanations for why some strains are associated with acne. Such strains, she suggests, produce much greater amounts of porphyrins, which are molecules that can trigger inflammation in skin cells. Li predicts the development of medications that could help people with acne by eliminating virulent strains of *C. acnes* or by targeting porphyrins. Some companies are already selling products that claim to tackle acne by killing *C. acnes* and restoring balance to the skin microbiota, even though evidence to support the approach is limited.

Researchers also hope to use skin microbiota therapies to target a potentially life-threatening disease: skin cancer. Earlier this year, Gallo and his colleagues reported that certain strains of *S. epidermidis* produce a molecule called 6-*N*-hydroxyaminopurine (6-HAP) that has anti-tumour properties in mice[9]. Injections of 6-HAP slowed the growth of aggressive melanomas in the animals. And the application of *S. epidermidis* that produce 6-HAP to mouse skin reduced the number of tumours that formed in response to ultraviolet radiation. The researchers also found that some people carry 6-HAP-producing strains of *S. epidermidis*. These people might have some natural protection against skin cancer, raising the possibility that doctors could identify people without such bacteria, who might be at higher risk, to take preventive measures.

Researchers speculate that, in the next five years, altering the skin microbiota might become part of routine interventions such as those that aim to protect people from skin infections, especially in hospitals, where drug-resistant *S. aureus* is a growing problem. To understand more about how *S. aureus* infections are acquired, researchers injected mice and zebrafish with *S. aureus* and common, non-pathogenic types of skin bacteria[10]. Those bacteria made the animals more susceptible to *S. aureus*, reducing the number of bacteria that were required to cause an infection. According to Oh, this means that a person's probability of picking up a *Staphylococcus* infection might depend on the composition of their skin microbiota. "That could explain why some individuals are more susceptible," Oh says. "They have different commensal microbes surrounding the context of the pathogens."

In her lab, Oh has been systematically putting together combinations of bacteria that live on skin, to see how various species fare when trying to colonize particular microbiota. It is one of many basic questions that scientists need to address before they can safely and effectively alter the skin microbiota to improve health.

Looking beyond bacteria to fungi and other microbes will also be important. Segre and her colleagues have already published a study on the often underestimated amount of viruses that are found on skin and that could affect a person's vulnerability to warts and other skin conditions[11].

As hype builds, researchers are casting a wide net in their studies of skin microbes. As a follow-up to his hospital microbiota project, Gilbert has been working with NASA to study communities of microbes on the International Space Station. His findings suggest that bacteria there act much like those in hospitals on Earth, moving from people to their environment, and back. Such insights — combined with other, ongoing research on the microscopic life that lives upon us — could help to transform health care, on Earth and beyond. ■

Emily Sohn *is a freelance journalist in Minneapolis, Minnesota.*

1. Lax, S. *et al. Sci. Transl. Med.* **9**, eaah6500 (2017).
2. Oh, J. *et al. Cell* **165**, 854–866 (2016).
3. Scharschmidt, T. C. *et al. Immunity* **43**, 1011–1021 (2015).
4. Lai, Y. *et al. Nature Med.* **15**, 1377–1382 (2009).
5. Byrd, A. L. *et al. Sci Transl Med.* **9**, eaal4651 (2017).
6. Chng, K. R. *et al. Nature Microbiol.* **1**, 16106 (2016).
7. Li, H. *et al. J. Invest. Dermatol.* **138**, 1137–1145 (2018).
8. Fitz-Gibbon, S. *et al. J. Invest. Dermatol.* **133**, 2152–2160 (2013).
9. Nakatsuji, T. *et al. Sci. Adv.* **4**, eaao4502 (2018).
10. Boldock, E. *et al. Nature Microbiol.* **3**, 881–890 (2018).
11. Tirosh, O. *et al. Nature Med.* https://doi.org/10.1038/s41591-018-0211-7 (2018).

© 2018 Springer Nature Limited. All rights reserved.