Interviews

In this issue, we present two insightful interviews with renowned dermatology researchers. First, Richard Gallo discusses the intricate relationship between the skin microbiome, immune system, and emerging microbiome-based therapies. Keith Choate delves into groundbreaking discoveries in dermatogenetics, from rare inherited disorders to gene-based therapies. These conversations highlight the evolving landscape of dermatology, from bench to bedside.

Featuring: Richard Gallo & Keith Choate

Richard Gallo

Professor and Chair,
Department of Dermatology,
University of California
San Diego, USA

Citation: Dermatol AMJ. 2025;2[1]:42-45.
https://doi.org/10.33590/dermatolamj/WXKH5693

Q1 Given the complex interplay between the skin, microbiome, and immune system, how do you envision the future of dermatology in terms of personalized medicine approaches that consider the unique microbial profile of each patient?

The speed and cost for accurately assessing the microbiomes of skin and gut are becoming less of a barrier. At present, many groups are making good progress at identifying microbes that are potentially beneficial or capable of promoting disease. Currently, we are not quite at the place in knowledge or technology that would compel microbiome profiling as an important diagnostic test, but I think we will get there.

Q2 Could you elaborate on the specific characteristics that define a "healthy" skin microbiome and how we can measure and assess this in individual patients?

The gut microbiome produces many factors with varying functions. Some microbes enable absorption of nutrients or drugs, others produce factors that kill pathogens, and still others change the functions of cells in the intestine. On the skin some microbes dampen inflammation, protect against environmental damage, strengthen the skin barrier, and fight other bacteria that could cause infection. There's a wide variety of different organisms that participate in those functions, and there are likely other functions that have yet to be discovered. A healthy microbiome should have a variety of these, and this varies between different individuals.

> **"Even within a single individual, the skin microbiome can differ considerably between various locations on the skin"**

One way to define a healthy microbiome is to understand the genes and metabolic pathways that confer those beneficial behaviors and then measure them using metagenomic or metabolomic approaches.

On the other side of the coin, there's organisms that harm the skin, especially when they're over abundant. We know a lot about those already. Some of those are classic pathogens like *Staphylococcus aureus* or its drug-resistant strain, methicillin-resistant *Staphylococcus aureus*. When these bacteria colonize the skin, it indicates an unhealthy microbiome, and that can be measured as well. Essentially, both beneficial and harmful microorganisms can be studied and measured by knowing how they work.

Even within a single individual, the skin microbiome can differ considerably between various locations on the skin, but there are certain characteristics of beneficial functions and negative functions, and the better we understand that the better we will be able to intervene and promote skin health, prevent disease, and develop targeted therapies for skin conditions.

Q3 Your research has highlighted the role of antimicrobial peptides (AMP) in skin health. Can you discuss the potential for developing novel therapeutic strategies that modulate AMP production or activity to treat skin diseases?

There are hundreds of different AMPs, some are inflammatory and some are regulatory, and they can be influenced by many factors. AMPs benefit us by protecting against infection, but when AMPs are in excess, they can drive inflammation and also contribute to inflammatory diseases.

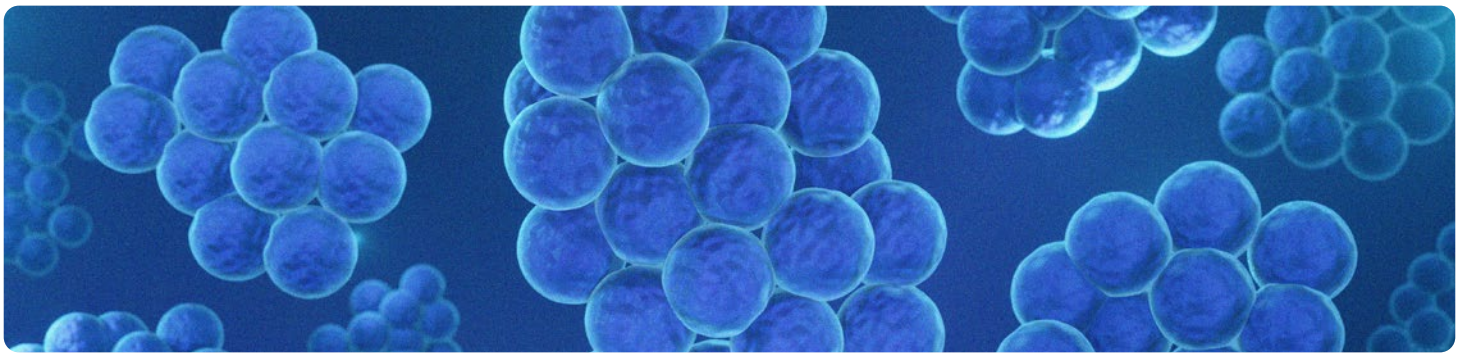
We know that some diseases occur because AMPs are too low (e.g., atopic dermatitis), while in other diseases (e.g., rosacea, and psoriasis), AMPs are too high and either drive disease manifestations or make complications worse. Several current therapeutics seem to work by correcting these AMP defects. We continue to look for strategies to influence AMP production specifically.

A good example of AMP modulation in therapy is a drug we use for eczema that blocks the IL-4 receptor. One of the consequences of doing that is that AMP levels increase when they are abnormally low.

This shows that we are already influencing AMP expression therapeutically, although not intentionally. What we haven't done a very good job of yet is developing drugs that specifically target AMPs alone. While some strategies have been explored, they are still in the early stages. One of the interesting observations several years ago was that vitamin D helps improve AMP expression in humans, and there was some interest in looking at that at one point, but we are still a long way away from being able to intervene directly.

Q4 How do you see the role of bacteriotherapy evolving in the treatment of skin diseases, and what do you believe are the key challenges and opportunities in developing safe and effective bacteriotherapy approaches?

The goal of bacteriotherapy is to identify specific bacteria that help us and the genes responsible for beneficial functions, then use bacteria that express these genes to restore functions that are essential to skin health. As you probably know, we're involved in bacterial therapy trials now and have published on that. We have identified many beneficial organisms and, more importantly, the genes within these organisms



that provide those beneficial effects. By understanding these genes, we can then deliver them back to the skin, especially in situations like eczema, where those bacteria are missing.

This approach is somewhat like stem cell replacement therapy, where we restore something essential by reintroducing it in a living cell. However, one of the biggest challenges in this field has been misleading claims by some in the probiotic market. Many products make bold, often unbelievable statements without a clear understanding of how or if they actually work. And although some consumers have had good experiences with currently available probiotics, many have minimal activity or no activity at all. This has led to growing skepticism about the microbiome and probiotic field. That is probably the major obstacle right now, the exploitation of the probiotic market by false claims, leading to skepticism that has hindered investment and further progress.

Overall, I believe bacteriotherapy will revolutionize the treatment of several skin disorders. They are very safe and are not immunosuppressive, so this provides a whole new tool for therapy.

Q5 Given the growing concern about antibiotic resistance, how can we develop microbiome-based therapies that minimize the risk of antibiotic resistance while effectively treating skin conditions?

One of the remarkable things about the evolution of these genes is that many of them are very carefully regulated, they're not expressed when we don't need them and are also very selective.

The natural antimicrobials often specifically target one pathogenic species of bacteria while leaving many other microbes unharmed. This selectivity and careful regulation are a hallmark of the natural anti-microbial functions.

Antibiotics are not like that, they're very potent, but they're over-prescribed, which puts pressure on the pathogens to develop resistance. Antibiotics also have widespread activity, so they kill both pathogens and non-pathogens alike, somewhat weakening the immune system by killing beneficial bacteria. By learning from the strategies used by the microbiome and our host genome to fight infections, we may be able to adopt a more strategic approach. With microbiome-based therapies as a first-line approach, we can reserve pharmaceutical antibiotics for situations when they are most needed, therefore resisting the development of antibiotic resistance.

Therefore, microbiome-based therapies deploy strategies that have worked on an evolutionary timescale throughout nature. It is a perfect way to decrease antibiotic use and minimize resistance.

“Microbiome-based therapies deploy strategies that have worked on an evolutionary timescale throughout nature”

Q6 Your research has highlighted the importance of understanding skin microbiome in the context of disease. How can we better integrate this knowledge into clinical practice and patient care?

It is a very complicated system with a lot of factors, including metabolic factors produced by the microbiome. We need to understand if they're missing or if they're overabundant. Knowing that would provide valuable insights for physicians and lead to better therapeutic strategies for patients. The problem is that we are still learning. The other problem is it can be quite expensive and slow to measure. We need technology that works quickly and accurately with reasonable expense, and the knowledge to know what to measure. Overall, I think it is important to continue to focus on research, education, and communication, but with a key goal to show scientific justification and demonstration of true efficacy.

Q7 How can we leverage advances in genomics, metabolomics, and other "omics" technologies to further our understanding of the skin microbiome and its role in skin health and disease?

These tools let us look more closely at the microbiome, but they need to be applied in ways that are relevant to disease pathophysiology. There has been too much microbiome analysis for the sake of analysis alone without any clear hypothesis-driven questions. This has changed in the last few years, and the future is bright for this field.

Ideally, we will reach a situation that allows us to utilize various “omics” approaches, such as metabolomics, genomics, and proteomics, quickly and affordably. When this is combined with bioinformatics, particularly through the use of machine learning, the highly complex information of the microbiome can be decoded and used diagnostically and therapeutically.