BEYOND BALANCE:

UNVEILING THE FLAWS IN TRADITIONAL SKIN MICROBIOME CLAIMS

A WHITE PAPER BY

OxiProteomics

OXIPROTEOMICS
2, RUE ANTOINE ETEX
4ÈME ÉTAGE
94 000 CRÉTEIL, FRANCE
–
WWW.OXIPROTEOMICS.FR

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CONTACT@OXIPROTEOMICS.FR
+33 (0)1 43 39 00 95

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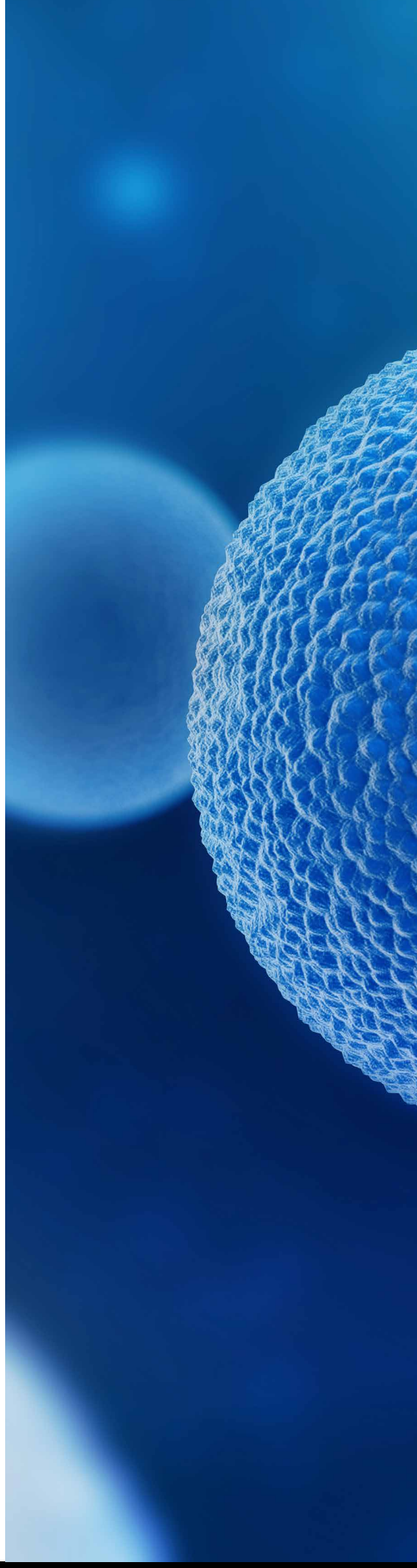


AN INTRODUCTION TO THE SKIN MICROBIOME

A bustling ecosystem of microorganisms, has become a focal point for skincare innovation

The skin microbiome, a bustling ecosystem of microorganisms, has become a focal point for skincare innovation. Yet, the current paradigm, dominated by claims of restoring microbial "balance" and boosting "good" bacteria, is fundamentally flawed. These claims, rooted in an oversimplified understanding of microbial interactions, ignore the dynamic nature of the skin and the nuanced role of pathogenic bacteria. A more refined model, centered on dybiosis – the disruption of microbial harmony – and the destructive potential of proteases released by pathogenic bacteria, offers a more nuanced framework for developing targeted and effective skincare solutions.

A brief introduction to the Skin Microbiome

The human skin, the body's largest organ, is not merely a physical barrier; it is a dynamic ecosystem teeming with trillions of microorganisms, collectively known as the skin microbiome. Recent scientific advancements have revolutionized our understanding of this intricate microbial community, revealing its profound impact on skin health, overall well-being, and even the development of various diseases.

The skin microbiome comprises a diverse array of bacteria, fungi, viruses, and archaea, each playing a distinct role in

maintaining skin health. This delicate balance of microbes acts as a first line of defense against harmful pathogens, aids in wound healing, regulates immune responses, and contributes to the skin's barrier function.

Up until now, claims of "microbiome balance" or “microbiome friendly” in skincare have been most prevalent but often fall short due to their oversimplified view of a complex and dynamic ecosystem. The skin microbiome is not a static entity but rather a diverse community of microorganisms that fluctuates in response to various factors, such as environmental exposures, hygiene practices, and underlying skin conditions.[1,2] Thus, the pursuit of a single "balanced" state for the skin microbiome is not only unrealistic but may also misrepresent the dynamic nature of this ecosystem.[3]

A focus on dysbiosis, characterized by microbial imbalances and functional disruptions, provides a more comprehensive approach to skincare development than the simplistic notion of "balance" or promoting only "friendly" bacteria. By recognizing the dynamic and individualized nature of the skin microbiome, research and product development can move beyond general claims to targeted solutions that address the root causes of skin conditions and promote genuine skin health.

TRADITIONAL MICROBIOME CLAIMS: A SCIENTIFIC PERSPECTIVE

The skin microbiome is highly individualized, varying significantly between individuals based on many factors.

The burgeoning interest in the skin microbiome has led to a surge in skincare products touting benefits related to "microbiome balance" or being "microbiome-friendly." While these claims may resonate with consumers seeking healthier skin, they fall short from a scientific and efficacy standpoint due to several key reasons:

The Myth of a Universal "Balance":

- The skin microbiome is highly individualized, varying significantly between individuals based on genetics, age, environment, lifestyle, and other factors.[4]
- There is no single, universally applicable "balanced" microbiome state. What is

healthy for one person may not be for another.[5]

- Claims suggesting a product can universally restore "balance" are misleading and oversimplify the complexity of the skin ecosystem.

The Dynamic Nature of the Microbiome:

- The skin microbiome is not static; it constantly fluctuates in response to internal and external factors, such as hormonal changes, diet, and topical product use.[6]
- A product's impact on the microbiome may be temporary or vary depending on individual circumstances, making claims of sustained "balance" unrealistic.

The Limitations of "Friendly" Bacteria:

- Labeling certain bacteria as "friendly" or "good" ignores the complex interactions within the microbiome. A microbe considered beneficial in one context may become problematic under different conditions.[7]
- Focusing solely on promoting "friendly" bacteria may overlook the importance of maintaining overall microbial diversity and ecological balance.

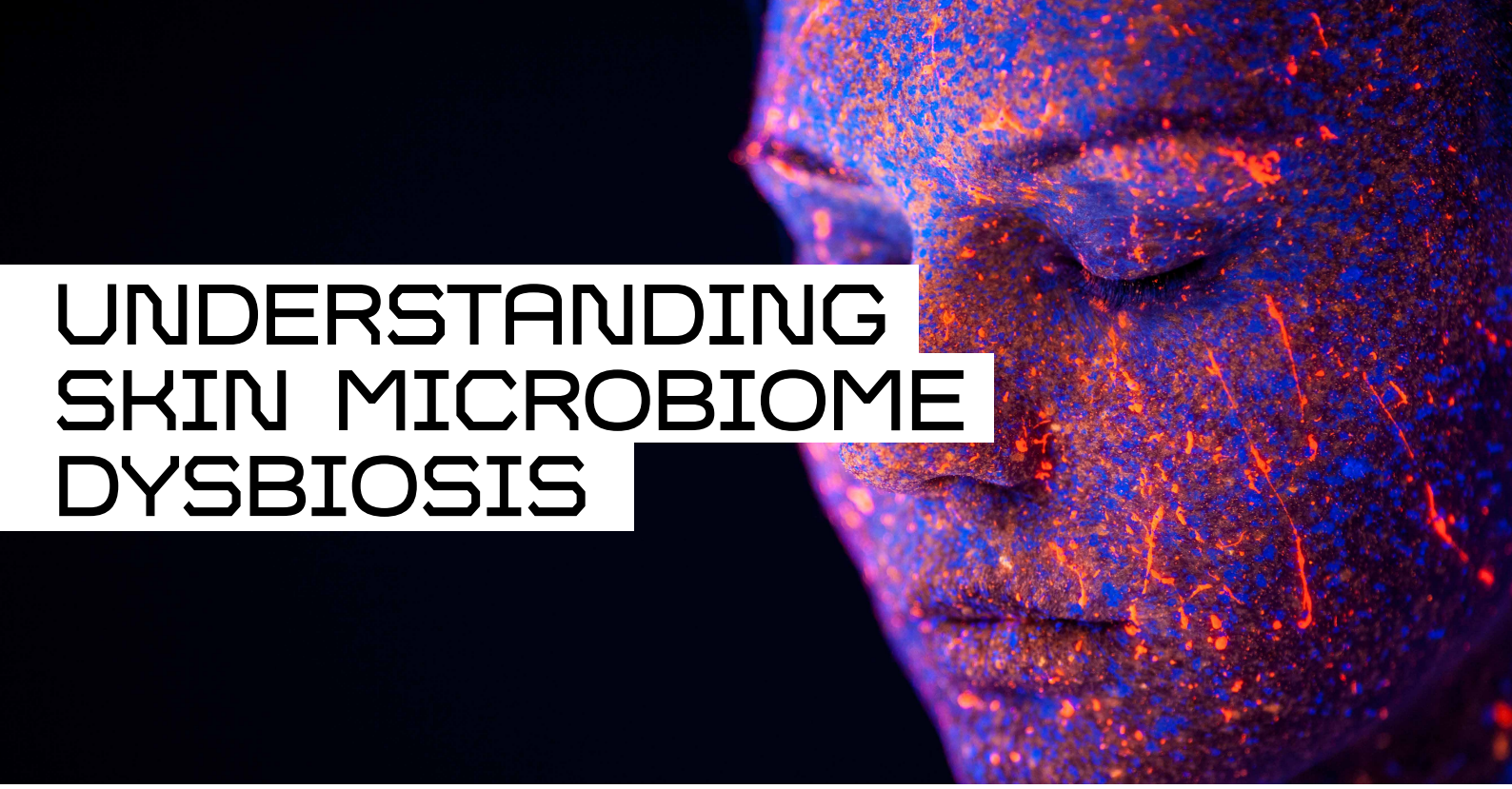
Lack of Standardized Testing and Definitions:

- There is currently no consensus on standardized methods for measuring microbiome balance or defining "microbiome-friendly" products. This lack of standardization makes it difficult to compare product claims and assess their true impact on the skin microbiome.[8]

Focusing on the Absence of Harm Rather Than Active Benefit:

- Many "microbiome-friendly" claims center on the idea that a product does not disrupt the microbiome, rather than actively improving its health or function.[9]
- While avoiding harm is important, consumers increasingly seek products that offer tangible benefits beyond simply maintaining the status quo.

In conclusion, traditional claims of "microbiome balance" and "microbiome-friendly" oversimplify the complexity of the skin microbiome and may not accurately reflect a product's true impact. A more nuanced approach that focuses on understanding and addressing specific dysbiosis patterns, while considering individual variations, is necessary to develop effective skincare solutions and provide consumers with accurate information.



UNDERSTANDING SKIN MICROBIOME DYSBIOSIS

Dysbiosis is used to describe a disruption in the skin microbiome.

A disruption in the skin microbiome, often termed "dysbiosis," refers to a state of imbalance or disruption in the normal composition and function of the microbial communities residing on the skin. This can manifest in several ways:

1. Loss of diversity
A reduction in the variety of microbial species present on the skin. A healthy skin microbiome typically boasts a rich diversity of microorganisms, each contributing to overall skin health.[10]

2. Overgrowth of certain species
While some bacteria are beneficial to the skin, an overabundance of specific strains can lead to dysbiosis. For instance, an excess of Cutibacterium acnes (formerly Propionibacterium acnes) has been linked to acne vulgaris.[11]

3. Changes in microbial function
Even without major shifts in species composition, dysbiosis can occur when the normal functions of skin microbes are disrupted. This can involve alterations in metabolic pathways, immune interactions, or the production of beneficial molecules.[12]

Factors Contributing to Skin Dysbiosis

Several factors can contribute to skin microbiome dysbiosis, including:

Overuse of harsh skincare products

Excessive cleansing, exfoliation, or use of antibacterial products can strip the skin of its natural oils and beneficial microbes, creating an environment conducive to dysbiosis.[13]

Environmental factors

Exposure to pollutants, allergens, and UV radiation can disrupt the delicate balance of the skin microbiome.[14]

Genetics

Individual genetic predispositions can influence the composition and susceptibility of the skin microbiome to dysbiosis.[15]

Underlying health conditions

Certain diseases, such as atopic dermatitis, psoriasis, and diabetes, have been linked to altered skin microbiome profiles.[16]

Consequences of Skin Dysbiosis

Skin dysbiosis has been implicated in various skin disorders, including:

Atopic dermatitis (eczema)

Reduced microbial diversity and an increase in Staphylococcus aureus are associated with atopic dermatitis.[17]

Psoriasis

Although the exact role of the microbiome is still under investigation, dysbiosis has been linked to the development and severity of psoriasis.[18]

Acne vulgaris

An overgrowth of C. acnes is a key factor in the development of acne.[11]

Rosacea

Changes in the skin microbiome, particularly involving Demodex mites, have been observed in rosacea patients.[19]

Dysbiosis of the Scalp

Microbial dysbiosis within the scalp microbiome, characterized by an imbalance in beneficial and potentially harmful microorganisms, can lead to various scalp disorders. One prominent player in scalp dysbiosis is Malassezia, a lipophilic yeast commonly found on the scalp. While Malassezia is a normal inhabitant, its overgrowth can disrupt the delicate microbial balance, triggering inflammation and contributing to conditions like dandruff and seborrheic dermatitis.[20, 21]

Malassezia dysbiosis has also been linked to other scalp issues, including scalp psoriasis, folliculitis, and even hair loss.[22, 23, 24] The mechanisms by which Malassezia contributes to these conditions are complex and involve interactions with the host immune system, alteration of lipid metabolism, and potential disruption of the scalp barrier function.[25]

Vaginal Dysbiosis

Microbial dysbiosis within the vaginal microbiome, characterized by an imbalance in beneficial and potentially harmful microorganisms, can arise from an overgrowth of Malassezia species. While these yeasts are commonly found in the vaginal microbiota, their excessive proliferation can disrupt the delicate balance, leading to various gynecological issues.[26] Studies have linked Malassezia dysbiosis to an increased risk of bacterial vaginosis (BV), a common vaginal infection associated with discomfort, abnormal discharge, and unpleasant odor.[27] Moreover, Malassezia overgrowth may exacerbate existing conditions like vulvovaginal candidiasis (yeast infection) and contribute to chronic vaginal inflammation.[28]

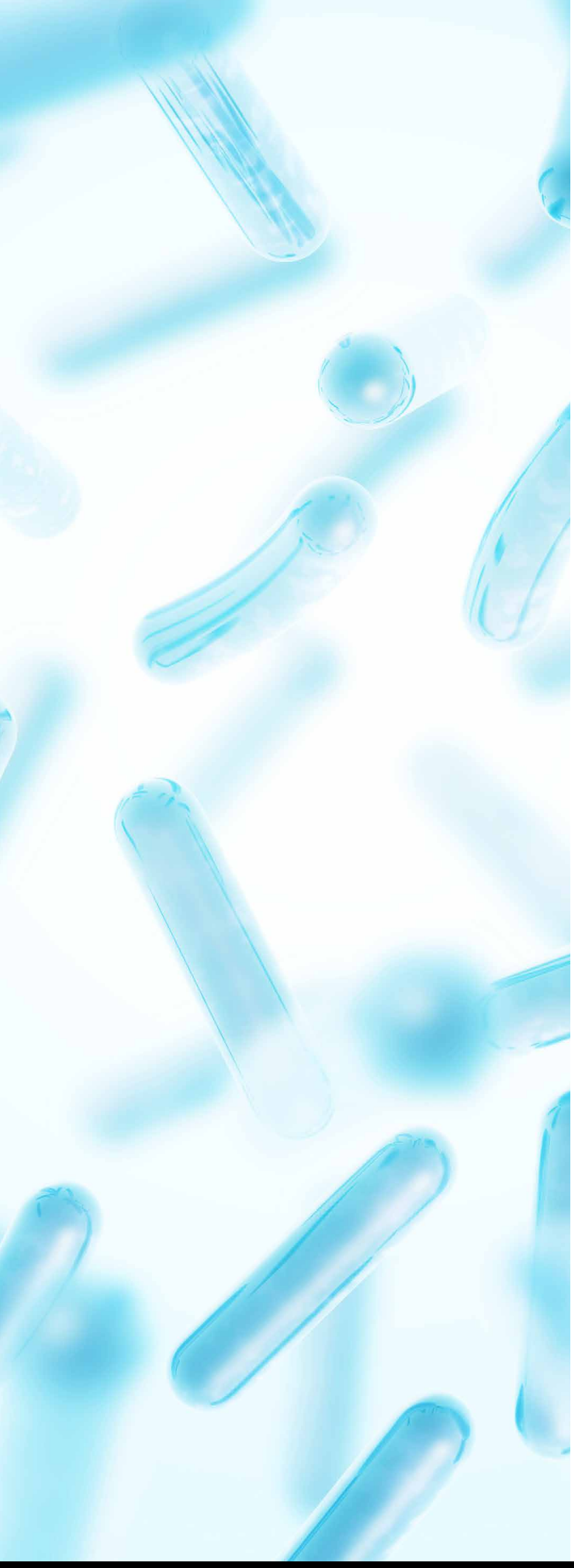
The potential consequences of Malassezia dysbiosis underscore the importance of maintaining a healthy vaginal microbiome through proper feminine hygiene practices and targeted interventions. It is crucial to avoid practices that disrupt the natural balance, such as douching or using harsh soaps, and to prioritize products that promote the growth of beneficial bacteria, such as those containing probiotics.[29] Further research into the role of Malassezia in the vaginal microbiome can aid in developing effective treatments and preventive measures for these common gynecological concerns.

Other Concerns

Skin microbiome dysbiosis can have far-reaching consequences for skin health, potentially contributing to a range of clinical manifestations. Disruptions in the microbial balance can accelerate skin aging through several mechanisms. For instance, dysbiosis-associated inflammation can trigger oxidative stress, leading to the degradation of collagen and elastin, key structural proteins responsible for skin firmness and elasticity.[32]

Additionally, dysbiosis can impair the skin barrier function, resulting in increased transepidermal water loss (TEWL) and subsequent xerosis (dry skin).[33] This compromised barrier also hinders the normal wound healing process, as it becomes more susceptible to infections and delays tissue repair.[34] Moreover, certain microbes associated with dysbiosis, such as Staphylococcus aureus, can release proteases that activate sensory neurons, triggering itching and further exacerbating skin inflammation.[35]

In order to study and understand this complex area, we need solutions which are reproducible and powerful but also simple and elegant in their design.



MOVING TOWARDS TARGETED DYSBIOSIS SOLUTIONS (LEAKY SKIN MODEL)

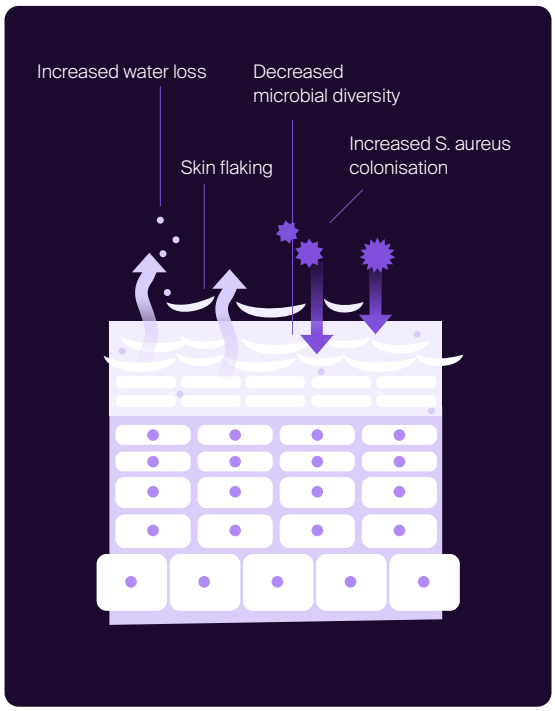
"Leaky skin" is characterized by impaired barrier function and increased transepidermal water loss (TEWL).

Currently, the association between microbiome dysbiosis and skin dysfunction offers limited intervention options, often focusing on re-establishing microbial balance.

However, developing new skin and scalp models that target the early cellular and molecular impacts of opportunistic microorganisms could unlock novel therapeutic avenues, including dermo-cosmetics, dietary supplements, and pharmaceuticals.

In order to understand the new types of claims and studies that can be performed, it is necessary to understand microbiome dysbiosis and its associated consequences.

One of those consequences, “leaky skin” which is characterized by impaired barrier function and increased transepidermal water loss (TEWL), parallels the phenomenon of "leaky gut" in the context of gut dysbiosis. This disrupted barrier not only allows for greater penetration of irritants and allergens, potentially triggering inflammation and sensitivity, but may also be interconnected with gut health through the gut-skin axis.[30, 31]



Rationale

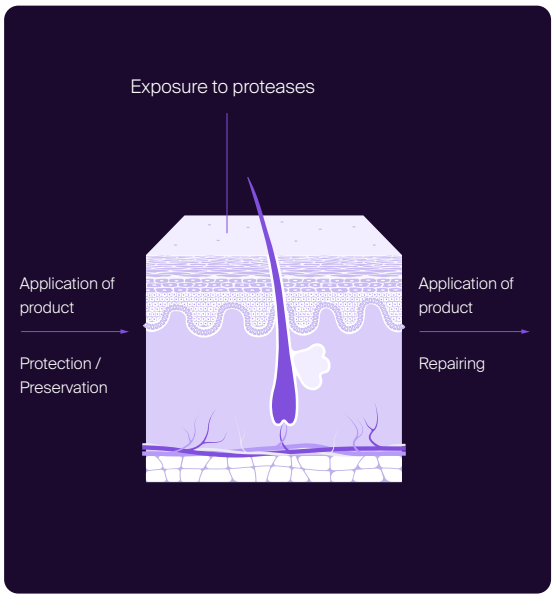
At OxiProteomics we have designed a model which focuses on imbalance rather than balance, using proteases associated with pathogenic bacteria we can see the effect both on the compromised skin barrier without the added complexity of culturing live bacteria, making the model more efficient and predictable.

The microbes and their secreted proteases are confined to the stratum corneum, which is the outermost layer of the skin, and their potentially harmful effects are mitigated by skin turnover, skin/microbial interactions.

In a context of microbiota dysbiosis, the epidermal barrier is breached or compromised by these secretory proteases that can also reach the deeper layers of the epidermis and dermis, resulting in skin tissue damage and inflammation.

Experimental Design

Proteases from pathogenic bacteria, such as S. aureus, are utilized in this model due to their well-established association with skin conditions like atopic dermatitis.



Products can be evaluated for their ability to protect against protease damage when applied beforehand, or to repair existing damage when applied afterward.

Impaired Skin Barrier Function

When the skin's barrier function is compromised due to microbiome dysbiosis, it becomes more permeable to harmful substances and microbes. This heightened permeability can trigger inflammation, damage skin tissue, and increase the risk of infections and various dermatological conditions.

This breakdown in the skin's defenses often presents as dryness, irritation, redness, and other visible signs of skin distress.

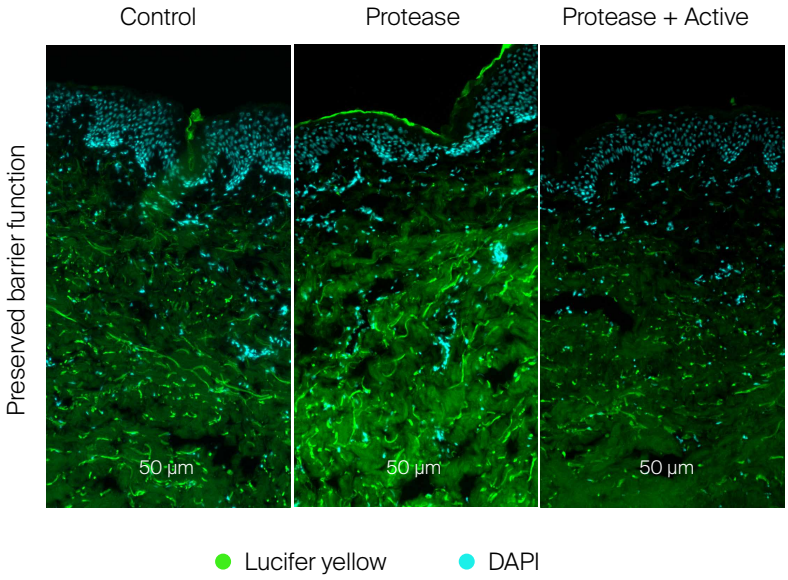
Consequences of barrier impairment

Our models can help to identify and show the effects on the skin barrier through the study of various biomarkers such as Claudin-1 and DSG1.

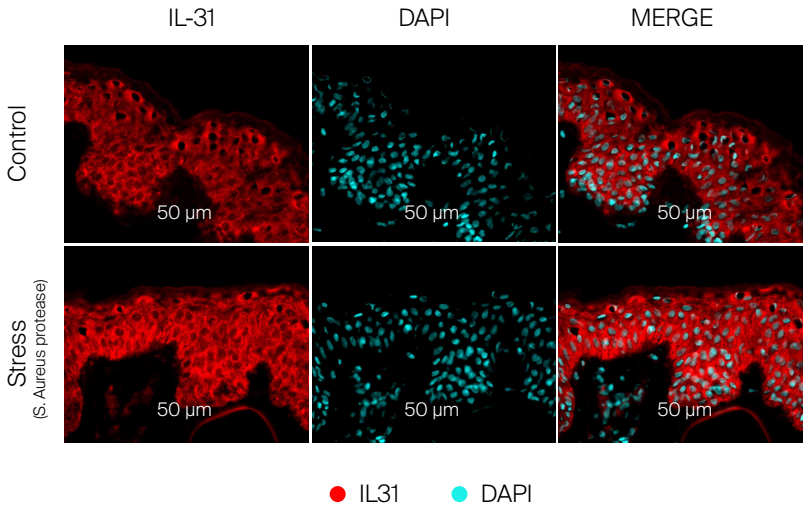
Claudin-1 (a tight junction protein) helps maintain the skin's BARRIER FUNCTION by INTER-CELLULAR COHESION, preventing the loss of moisture, blocking the entry of pathogens or harmful substances.

DSG1 (a desmosomal cadherin) contributes to CELL-CELL ADHESION, playing a key role in maintaining the INTEGRITY and STRENGTH OF THE SKIN.

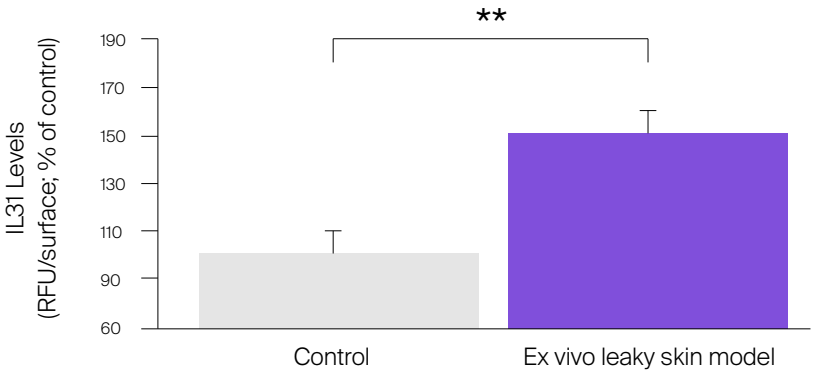
Efficacy of postbiotic active

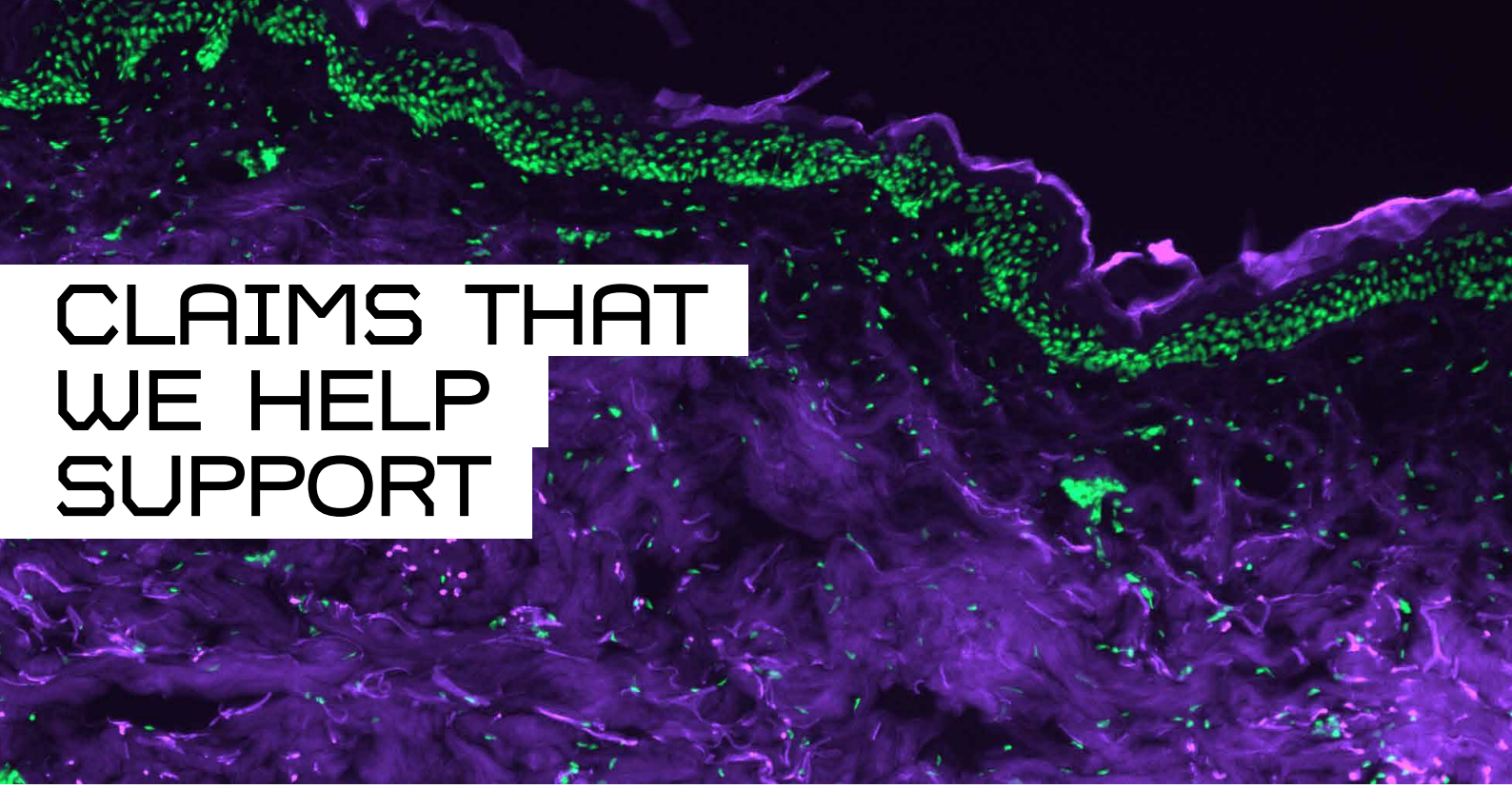


Leaky skin_Annex: In situ visualization of IL31 levels



Student test binary comparison





CLAIMS THAT WE HELP SUPPORT

A biotech CRO specialized in biomakers discovery / assessment on biological samples.

Common claims associated with skin barrier function often include:

Strengthening/Repairing the Skin Barrier
Products claim to reinforce the skin's natural protective layer, making it more resilient to environmental stressors and preventing moisture loss.

Reducing Transepidermal Water Loss
Products may claim to decrease the amount of water that evaporates from the skin's surface, thus preventing dehydration.

Protecting Against Environmental Damage
Claims highlight the ability of products to shield the skin from pollutants, UV radiation, and other external aggressors that can damage the skin barrier.

Soothing and Calming Irritated Skin
Products often claim to alleviate inflammation and irritation caused by a compromised skin barrier, restoring comfort and balance.

Improving Skin Texture and Elasticity
By strengthening the skin barrier, products may claim to improve overall skin texture, making it appear smoother, firmer, and

more youthful.

Improving Hydration

Claims focus on the ability of products to enhance the skin's ability to retain moisture, leading to softer, smoother, and more hydrated skin.

Filaggrin, essential for skin hydration and barrier function. It aggregates keratin fibers in skin cells, which helps form the skin's outer layer. Filaggrin also breaks down into amino acids and derivatives that act as natural moisturizing factors (NMF), maintaining the skin's hydration and pH balance.

Associated Claims

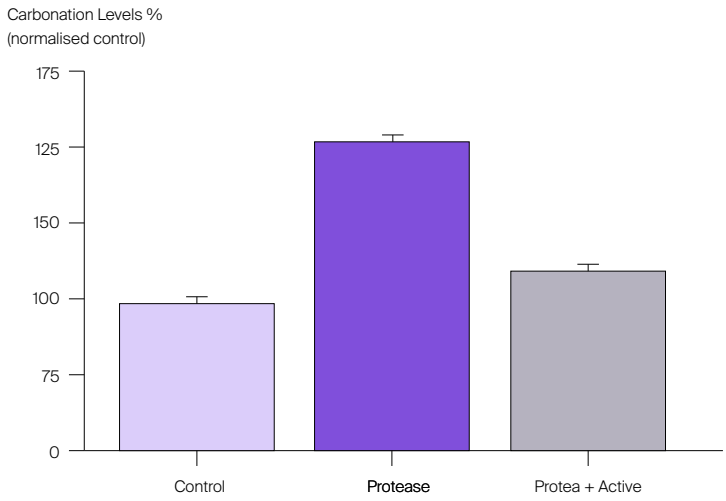
- Hydration
- Protection of Skin Hydration
- Enhances Skin Hydration
- Restores Skin Hydration

Anti-Ageing Claims

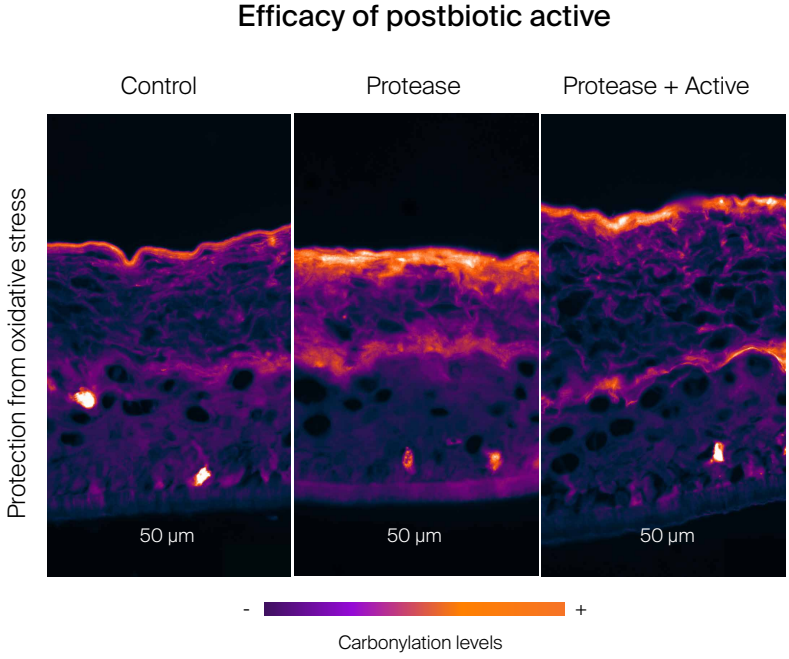
The aging process is intrinsically linked to an increase in oxidative stress, a state of cellular imbalance where harmful free radicals accumulate.

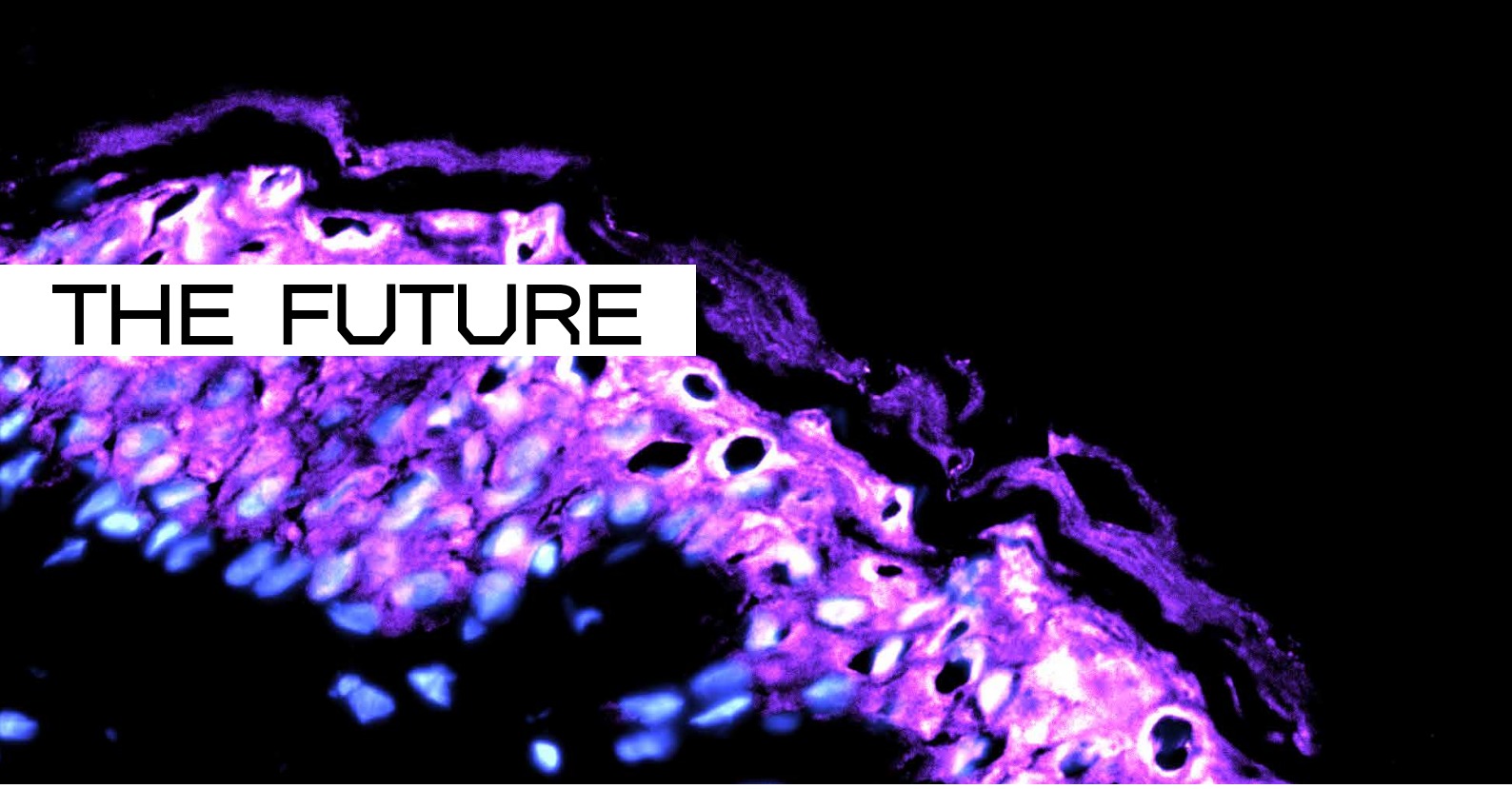
This oxidative stress can disrupt the delicate equilibrium of the skin microbiome, leading to dysbiosis – a state of microbial imbalance characterized by a decrease in beneficial bacteria and a rise in potentially harmful ones. This dysbiotic shift can further exacerbate oxidative stress, creating a vicious cycle that accelerates skin aging, manifesting in wrinkles, fine lines, and loss of elasticity.

A deeper understanding of this intricate relationship between aging, oxidative stress, and microbiome dysbiosis can pave the way for innovative skincare solutions that not only address the visible signs of aging but also target its root causes.



Efficacy of postbiotic active





THE FUTURE

The future of microbiome claims lies in moving away from simplistic promises

As research into the skin microbiome continues to evolve, so too will the claims associated with it. The future of microbiome claims lies in moving away from simplistic promises of restoring "balance" or boosting "good" bacteria. Instead, a more nuanced and scientifically grounded approach will focus on addressing dysbiosis – the disruption of the microbial community's equilibrium.

This shift will lead to claims that highlight:

Targeted Interventions
Instead of generic claims of "balancing" the microbiome, future products will target specific dysbiotic states. For example, a product might claim to reduce the abundance of Staphylococcus aureus in individuals with atopic dermatitis, based on evidence of its association with disease flares and severity.

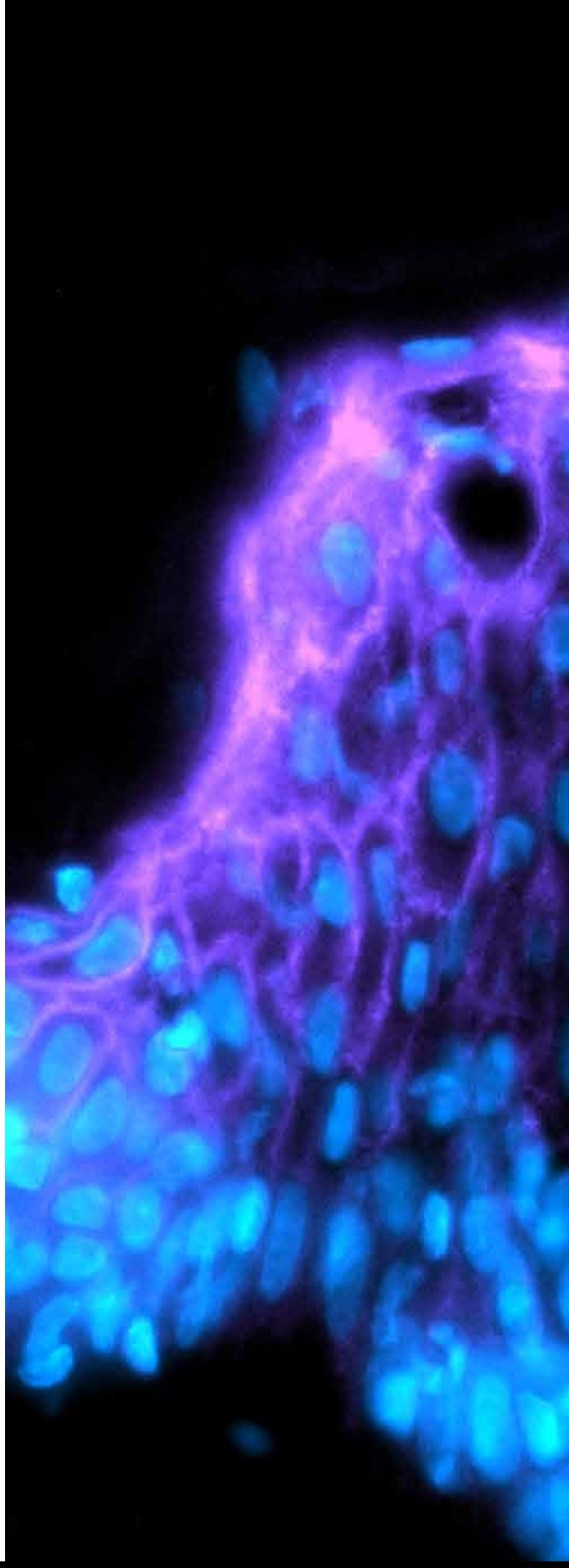
Protease Inhibition
Given the growing understanding of the role of proteases in skin damage, claims may focus on the ability of a product to inhibit protease activity from specific pathogenic bacteria. This could translate into claims of reducing inflammation, improving barrier function, or even preventing premature aging.

Personalized Solutions

With advances in microbiome testing, personalized skincare recommendations based on an individual's unique microbial profile will become increasingly common. Products might claim to be formulated for specific dysbiotic states, or to be suitable for individuals with certain genetic predispositions.

Crucially, the substantiation of these claims will necessitate rigorous scientific evidence. This involves not only well-designed clinical trials on human subjects but also the utilization of advanced in vitro skin models. These models, which closely mimic the complex structure and function of human skin, provide a controlled environment to assess the impact of products on the skin microbiome, measure changes in microbial composition and protease activity, and evaluate various skin health parameters without the ethical concerns and variability associated with human testing.

By integrating in vitro testing alongside clinical trials, a comprehensive and robust body of evidence can be built to support the safety and efficacy claims of microbiome-targeted skincare products.



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OXIPROTEOMICS
2, RUE ANTOINE ETEX
4ÈME ÉTAGE
94 000 CRÉTEIL, FRANCE

–

WWW.OXIPROTEOMICS.FR
+33 (0)1 43 39 00 95
CONTACT@OXIPROTEOMICS.FR