Current Clinical Solutions

March 2022

What's New from La Roche-Posay?

Peter Lio MD FAAD
Assistant Professor, Clinical Dermatology and Pediatrics
Northwestern University
Feinberg School of Medicine

Kavita Mariwalla MD FAAD
Founder, Mariwalla Dermatology

Distributed by
JOURNAL OF DRUGS IN DERMATOLOGY
JDD

JO00322

The following is a behind-the-scenes look at development, formulation, and design of skin treatments from La-Roche Posay based on a recent webinar hosted by Next Steps in Derm *with Dr. Peter Lio and Dr. Kavita Mariwalla.*

Background
The La Roche-Posay dermatology clinic in France treats up to 8,000 patients a year for various skin conditions, including atopic dermatitis, rosacea, and burn wounds, and has the largest and fastest growing patient base for those seeking relief for skin problems due to cancer treatment. The water has been studied extensively and shown to have therapeutic properties, and is used at the clinic for balneotherapy, which are water-based treatments, including high-pressure baths, showers, facial mists, and oral irrigation. The water is also used in all La Roche-Posay products.

The Discovery of the Microbiome
Dr. Peter Lio began by explaining the concept of the microbiome, which he called one of the most exciting and interesting areas currently in all medicine, in particular, dermatology. There are a couple different ways to interpret the term *microbiome*, but one way is that it is the actual genetic component of the biome. The other is a broader concept that the biome is the "host of life," so the microbiome can be more than just microbiota, which refer to the specific organisms, but instead defined as all the microorganisms, including bacteria but also fungi and viruses, that inhabit the human body outside and inside and what these organisms produce and cause to be produced in and on the body. Given the role the microbiome plays, it can be thought of as virtually an additional organ system.

The Human Genome Project and the Human Microbiome Project
The Human Genome Project aimed to map the entirety of the human genome—the blueprint for the human structure and function. It was anticipated that about 2 million genes would be found, but only 20,000 were mapped, only one-fifth of what was expected.

A search began to discover the missing pieces to account for the discrepancy. It was surprising to learn that, in addition to the genes, there also are many other organisms that make up a functional human being. The Human Microbiome Project had the goal of identifying all bacteria in and on the human body associated with health and disease. All DNA, both human and microbial life, were sequenced, and effectively the missing 2 million were found, implying that humans' function is driven more by our resident microbes than by our own genes.

The human body contains 10 times more bacteria than human cells ($10^6/cm^2$ of skin) and expresses more than 2 millions genes (20,000 human genes), which is tantamount to finding a new organ in the body. The 500 different healthy bacterial species on normal skin constitute about 5 pounds on each person, working together with our bodies to form, in effect, a superorganism.[1]

Healthy Skin Bacteria
The microbiome is part of the functional aspect of our skin barrier, and for that to work well, we need to make sure there's optimization of some of the other parts of the skin barrier, such as the chemical skin barrier, which includes the optimal skin pH, good fats and lipids, and a healthy immune system. These are critically important for a healthy harmony to keep the water in and keep all other harmful substances out, including everything from allergens, irritants, pathogens, and pollutants. When the barrier is weak, what Dr. Lio refers to as "leaky skin," we start to lose water very quickly. We know we only must lose about 10% of our moisture from the stratum corneum to start to feel itch, so healthy skin barrier is critical not just in preventing or in controlling atopic dermatitis, but also in acne and in rosacea and probably in psoriasis and any skin disease where there is inflammation. Damage to the skin barrier results in an immune response—actions by way of inflammatory cytokines and mediators—that directly affects the appearance of the skin. The microbiome contributes to normal barrier function of the skin. A lack of diversity in the microbiome is a sign of disease. In fact, the definition of an infection is the absence of diversity.

The skin microbiota has an autonomous role in controlling the local inflammatory milieu and tuning resident T-lymphocyte function. Protective immunity to a cutaneous pathogen was found to be critically dependent on the skin microbiota but not the gut microbiota. Furthermore, skin commensals tuned the function of local T cells in a manner dependent on signaling downstream of the interleukin-1 receptor.[2] These findings underscore the importance of the microbiota as a distinctive feature of tissue compartmentalization and provide insight into mechanisms of immune system regulation by resident commensal niches in health and disease.

Can a Healthy Microbiome Contribute to a Reduced Inflammatory Environment?
When the skin barrier functions well, it keeps harmful substances out, keeps moisture in, prevents inflammation, and promotes effective innate immune functions. Dr. Lio suggested that we need to rethink the skin barrier as a living barrier since bacteria are essential to its function. When we have dysbiosis, we have barrier dysfunction. Dysbiosis is linked to atopic dermatitis flares, often resulting in excessive growth of *S. aureus.*

Several skin diseases are associated with alterations in the skin microbiome. Research shows atopic dermatitis and psoriasis have decreased bacterial diversity and an abundance of *S. aureus.*[1] Healthy skin is related to a healthy, diverse microbiome, which in turn helps support skin barrier function, control pathogenic bacteria, and helps prevent inflammation and infection. An unbalanced skin microbiome is associated with skin barrier dysfunction. It also reduces the skin's ability to detect and respond to pathogens such as *S. aureus*, which can lead to flare-ups and cause skin reactions such as itchiness and visible redness.

Intervention With Probiotics, Prebiotics, and Postbiotics
What can we do? Can we directly influence our microbiome? The answer is yes, and there are three general things we can think about. First, we have probiotics, which are supplements or foods that contain *live* microorganisms. They are composed of healthy live bacteria. These include yogurts and kefir. Prebiotics are the food that essentially feed and support the healthy bacteria. They are supplements or foods that selectively stimulate the growth and/or activity of the bacteria. Then, there are postbiotics, which are the bacterial products or metabolic byproducts that have biologic activity in the host: for instance, gut bacteria metabolize food into vitamins. The good bacteria on the skin are making many metabolic byproducts that support the healthy bacteria or the host.

Water Is a Prebiotic
What can be used as a prebiotic or postbiotic on the skin? Water itself is actually a prebiotic, and water is crucial for microbial growth. Dry skin promotes the development of *S. aureus* (as in atopic dermatitis). Skin that is too wet promotes the development of fungi on the feet and bacteria in the axilla. There does need to be a balance, but there is no doubt that water is playing an important role for supporting our skin.

Does the kind of water matter, and what do we know about water? In La Roche-Posay, the water contains a high concentration of Xanthomonas, which acts as a probiotic and has been shown to be effective in the treatment of both psoriasis and atopic dermatitis. In the products that are sold in the U.S., the Xanthomonas have been killed, so, in effect, form a kind of *post-biotic* (sometimes called a *parabiotic*) substance.

In La Roche-Posay water, there are several minerals, including selenium, that make an enriched water that may have some effects on biology not only of the microbiome, but may also for us. Some of these trace elements like strontium and selenium have anti-inflammatory properties. The pH is a bit acidic, which may help the skin since it normally has an acid mantle, and when you use something like deionized water, you lose all that, and anyone who's ever had a sip of deionized water or distilled water knows it tastes flat, because the minerals that are normally in the water, which have been removed, not only make it feel better in the mouth but also give it a familiar taste and also may have some health benefits.

What Would a Skin Postbiotic Look Like?

Because using living bacteria as a probiotic may lead to questions and present challenges, postbiotic treatments utilizing material from bacteria offer an alternative. For example, *Vitreoscilla filiformis*, a gram-negative, nonpathogenic filamentous bacteria found in the hydrothermal vents and spa waters are known for prebiotic beneficial effects on the skin and have been shown in vitro to reduce free-radicals and have anti-inflammatory effects. Farmed in a factory outside La Roche-Posay in France, *Vitreoscilla filiformis* is grown in prebiotic thermal spring water and heat-killed and concentrated to be used as both an emollient and as a postbiotic in some treatments, including the Lipikar Balm AP+. Furthermore, research shows that combining prebiotic thermal water with postbiotic *Aqua Pose filiformis* and a biomass of *Vitreo filiformis* may help patients by restoring homeostasis of the skin, repopulating the diversity of the microbiome, encouraging the commensal bacteria growth, and improving skin-barrier function and atopic dermatitis symptoms. Although not a cure, these results may make help patients avoid more invasive treatments, such as systemic immunosuppressants.

What Could Help Prevent Biofilm Formation?

We have learned that certain components may block the ability of *Staphylococcus* from forming biofilms that are nearly impervious to antibiotics. For example, Microrésyl comes from the Ophiopogon japonicum tuberous root that is used in traditional Chinese medicine and has anti-inflammatory and antioxidant, or antimicrobial, properties, and seems to not only strengthen the skin barrier but also improve skin hydration and limit *Staph* resistance by preventing biofilm formation, as shown in electron microscopic images of skin treated with Lipikar Balm AP+M with Microrésyl.

Furthermore, there was a significant reduction found in disease severity in patients who were treated for atopic dermatitis with Lipikar Balm AP+M. As illustrated in the graph below, after 3+ months' use, a microbiome analysis showed that there was a measurable difference in the population of their skin microbiome: the *Staphylococcus* genus decreased, while the Xanthomonas bacteria increased, a marker of improved microbial diversity in the microbiome, and an indicator of overall healthier skin.

Additional microbiome analysis shows that compared to patients who used a competitive moisturizer, the patients using Lipikar Balm AP+M experienced a significantly greater increase in Xanthomonas and a greater decrease in *Staphylococcus.* Also, after discontinuation of the prescription, patients who used

Figure 1. Skin Microbiome in Patients with AD Treated with LB AP+M.

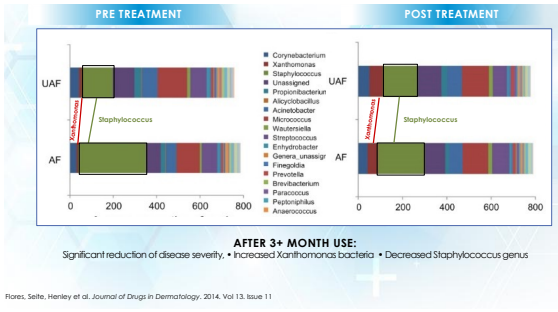
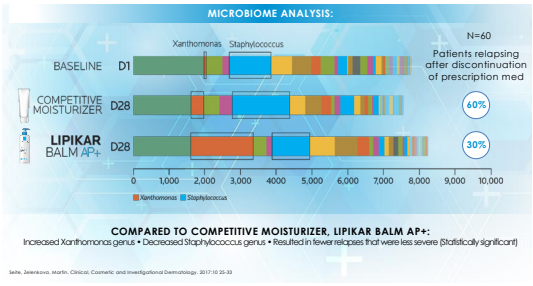


Figure 2. Skin Microbiome in patients with AD treated with LIPIKAR BALM AP+M.



Lipikar Balm AP+M experience a lower percentage of relapses, which were also less severe.

Furthermore, the same research shows that Lipikar Balm AP+M has been shown to provide a 39% improvement in itch relief in patients with atopic dermatitis by day 7 and a 47% improvement in itch relief by day 42, and given that hard data on over-the-counter moisturizers are few and far between, physicians seeking an easy to use, affordable, paraben- and fragrance-free product that has been tested by both dermatologists and pediatricians may want to consider adding Lipikar to their short list of treatments for their patients suffering from atopic dermatitis and sensitive skin.

Anti-Aging Serums

Dr. Mariwalla turned the discussion to the new line of serums by La Roche-Posay. The serum line contains dermatologically tested and proven-therapeutic ingredients, including hyaluronic acid, vitamin C, and retinol. The formulation is designed for optimal efficacy and safety with an appropriate concentration of active ingredients. The products are tested on sensitive skin so can be used post-procedure, which should not be surprising, since, as Dr. Mariwalla pointed out, the La Roche-Posay brand philosophy is to always keep patients and those with sensitive skin in mind when they do all their testing, since it is known that post-procedure, a patient's skin barrier may be slightly compromised, and during the healing phase, one must be careful about what products to use.

The Glycolic B5 is a Dark Spot Corrector for exfoliating and brightening that helps with wound repair and skin hydration, and it is meant for normal to oily skin and nonirritating. Together with glycolic and the other ingredients in the formulation, it is intended to decrease irritation and help to brighten the skin.

One of Dr. Mariwalla's favorites in the line, she noted, is the Hyalu B5 Serum, which, has pleasant after-feel that is silky and smooth. The Hyalu B5 anti-aging concentrate is meant for repairing and re-plumping to help with fine lines, elasticity, and dehydration.

The Vitamin C Serum is intended as a rejuvenating antioxidant featuring vitamin C, which is well known for its antioxidant effects on the skin. Although it is not uncommon for patients to report that vitamin C serums give them acne or blackhead breakouts or make them feel oily, keep in mind that unlike most vitamin C serums, the La Roche-Posay Vitamin C Serum is formulated at a pH of about 5.5, so it is meant for the sensitive-skin patient who breaks out potentially with other vitamin C serums.

Finally, the Retinol B3 Serum works well on oily-prone skin and acne-prone skin. Why have B5 in one formulation and B3 in another? B3 is known to be effective on sensitive skin, so this again shows how La Roche-Posay has given significant thought to these formulations.

The Glycolic B5 Serum is an anti-aging correction that is meant to be applied under a moisturizer on the face and neck, and specifically targets visible dark spots, age spots, and discolorations, enhancing or improving skin color and tone and targeting uneven skin. It is fragrance-free and has been allergy tested, and it contains the La Roche-Posay thermal spring water, which as Dr. Lio explained, the benefits of conditioning agents in these formulations will help calm the skin. The addition of B5 and thermal spring water helps tremendously to reduce the dryness or irritation or the stinging that are common complaints for those who are using multiple products to target dark spots or uneven skin tone. The formulation also contains 10% glycolic acid, which helps increase cell turnover, plus 1.5% tranexamic acid, a new "it" ingredient in the treatment of discoloration, that may act as a tyrosinase inactivator reducing melasma and hyperpigmentation[3,4]; and 1% kojic acid, which acts as a melanin synthesis inhibitor; and finally, .04% lipo-hydroxy acid provides surface exfoliation. Together, these ingredients may bring about skin renewal, an improvement in skin tone, and a release of pigment to the surface so that it can exfoliate.

Dr. Mariwalla further noted that while many formulations are now using tranexamic acid by itself, many patients will experience dryness and irritation when using it in this manner. In contrast, research shows that kojic acid, glycolic acid, and tranexamic acid combined may avoid such issues.

Overview of the Glycolic B5 Clinical Study

The Glycolic B5 clinical study included 51 aging female subjects, aged 25–50, and Fitzpatrick III–VI. Fifty percent of the subjects self-reported having sensitive skin, which is consistent with the patient population who self-perceive sensitive skin. The subjects were rated mild to moderate (scores 3–6 on a 10-point scale; n=25) for dark spot intensity, PIH (n>25), overall hyperpigmentation, uneven skin, and dull skin. The study design was to evaluate at different time points: baseline, morning after the first use, week 2, week 4, and week 8. The outcome measurements were evaluated with clinical grading using objective tolerance and consumer self-assessment. Subjects were instructed to use the facial serum once every night and then SPF 30 sunscreen applied during the daytime to their face.

In terms of dark spot intensity, the data shows that with prolonged use, in weeks 2, 4, and 8, there were statistically significant reported improvements in dark spots, hyperpigmentation, skin-tone evenness, radiance, post-inflammatory hyperpigmentation, and then overall appearance. At 4 weeks, patients on average report a 20% improvement in radiance, a 15% improvement in skin tone, and hyperpigmentation, both significant P values.

Similarly, research looking at patients with type Fitzpatrick skin type III–VI among females, ages 25–55, with mild to moderate dark-spot intensity (scores 3–6 on a 10-point scale; n=25), PIH (n>25), overall hyperpigmentation, uneven skin, and dull skin, found after 2 weeks, a statistical and clinically significant self-reported improvement in skin radiance/brightness, and after 4 weeks, a statical and clinically significant self-reported improvement not only in radiance, but also in dark-spot intensity, skin tone evenness, and overall appearance, and after 8 weeks, a statical and clinically significant self-reported improvement in all these, as well as an improvement in overall hyperpigmentation.

Table 1. Glycolic B5 Serum Clinical Data.

Assessment	Time Point	n	Mean ± SD	Mean Change from Baseline (±SD)	Mean % Change from Baseline	p-value
Dark Spot Intensity	BL	52	4.21 ± 0.67			
	Week 2	49	4.07 ± 0.73	-0.15 ± 0.23	-3.69	<0.001
	Week 4	49	3.78 ± 0.71	-0.39 ± 0.39	-9.35	<0.001
	Week 8	51	3.62 ± 0.75	-0.60 ± 0.40	-14.36	<0.001
Overall Hyperpigmentation	BL	52	4.20 ± 0.78			
	Week 2	49	4.05 ± 0.81	-0.19 ± 0.25	-4.64	<0.001
	Week 4	49	3.59 ± 0.65	-0.56 ± 0.44	-13.07	<0.001
	Week 8	51	3.43 ± 0.66	-0.78 ± 0.49	-18.09	<0.001
Skin Tone Evenness	BL	52	4.19 ± 0.62			
	Week 2	49	4.01 ± 0.62	-0.21 ± 0.29	-4.93	<0.001
	Week 4	49	3.51 ± 0.55	-0.64 ± 0.40	-15.29	<0.001
	Week 8	51	3.37 ± 0.65	-0.83 ± 0.45	-19.75	<0.001
Radiance / Brightness	BL	52	4.13 ± 0.58			
	Week 2	49	3.70 ± 0.64	-0.47 ± 0.33	-11.41	<0.001
	Week 4	49	3.23 ± 0.61	-0.89 ± 0.49	-21.34	<0.001
	Week 8	51	3.12 ± 0.60	-1.03 ± 0.48	-24.68	<0.001
Post Inflammation Hyperpigmentation	BL	24	3.63 ± 0.78			
	Week 2	23	3.52 ± 0.67	-0.13 ± 0.27	-2.91	0.070
	Week 4	22	3.23 ± 0.83	-0.34 ± 0.39	-9.65	0.001
	Week 8	51	3.15 ± 0.88	-0.48 ± 0.54	-13.35	<0.001
Overall Appearance of Skin Quality	BL	52	4.07 ± 0.51			
	Week 2	49	3.86 ± 0.54	-0.23 ± 0.27	-5.71	<0.001
	Week 4	49	3.45 ± 0.57	-0.60 ± 0.42	-14.81	<0.001
	Week 8	51	3.29 ± 0.59	-0.78 ± 0.43	-19.28	<0.001

Red/ Bold indicate statistical significance p≤0.05. **Blue** indicates statistically significant improvement.
Negative mean percent change values indicate an improvement for all attributes

Table 2. Glycolic B5 Serum Clinical Data Fitzpatrick Skin Type III–VI.

Claim	Assessment	Week 2	Week 4	Week 8
Dark Spot	Clinical Grading	X	X	X
Overall hyperpigmentation	Clinical Grading	X	X	X
Skin tone evenness	Clinical Grading	X	X	X
Radiance/ Brightness	Clinical Grading	X	X	X
PIH	Clinical Grading		X	X
Overall appearance of skin quality	Clinical Grading	X	X	X

X indicates statistically significant improvement when compared to baseline (p≤0.05).
Red Bold X indicates statistical and clinical significance (minimum change of -0.26) and (p≤0.05).

Conclusion

Prescription medications for some dermatological conditions, such as hyperpigmentation, are not well covered by insurance, and being able to rely on an OTC product as either an adjunct to another treatment or as a step therapy may potentially increase a physician's credibility with patients. While OTC products are usually not covered by insurance, at least not in the United States, they can be for certain conditions, and perhaps more important, many patients may have a flexible health spending account that can be used to pay for OTC products with tax-free dollars. Although OTC moisturizers can be rather expensive, doctors are able to take costs into consideration by being careful to recommend products with relatively affordable prices, like La Roche-Posay's, especially when compared to more expensive competing products that do not necessarily have any hard data or research to support the efficacy of their claims.

References

1. The NIH HMP Working Group. The NIH Human Microbiome Project. *Genome Res.* 2009;19(12):2317–2323. doi: 10/1101/gr.096651.109 PMID: 19819907; PMCID: PMC2792171.
2. Naik S, Bouladoux N, Wilhelm C, Molloy MJ, Salcedo R, Kastenmuller W, Deming C, Quinones M, Koo L, Conlan S, Spencer S, Hall JA, Dzutsev A, Kong H, Campbell DJ, Trinchieri G, Segre JA, Belkaid Y. Compartmentalized control of skin immunity by resident commensals. *Science.* 2012; 31;337(6098):1115–9. doi:10.1126/science.1225152. PMID: 22837383; PMCID: PMC3513834.
3. Chung JY, Lee JH. Topical tranexamic acid as an adjuvant treatment in melasma: Side-by-side comparison clinical study. *J Dermatol Treat.* 2016;27(4):373–377. doi: 10.3109/09546634.2015.1115812. PMID: 26526300.
4. Evan Austin BS, Julie K, Nguyen MD, Jagdeo J. Topical treatments for melasma: A systematic review of randomized controlled trials. *Drugs Dermatol.* 2019;18(11):1156–1171. PMID: 31741361.

To learn more about this topic, please watch the recent webinar on *Next Steps in Derm*, supported by La Roche-Posay:
https://nextstepsinderm.com/webinar/whats-new-from-la-roche-posay/