WHITE PAPER

STOPPING THE CLOCK: UNDERSTANDING MICAH CHEMISTRY

HALLSTAR

For centuries, people of all cultures have sought ways to prevent visible signs of aging—sagging, wrinkles and discoloration. Today, the anti-aging market is poised to reach nearly $200 billion (USD) globally by 2019.[1] And yet, the beauty and personal care market has seen few significant innovations in anti-aging science since the introduction of retinol and broad-spectrum UV protection—both of which present drawbacks alongside the benefits they confer. This paper provides an overview of current challenges and explains a new chemistry based on fused-ring cyanoacrylates that promises an entirely new, breakthrough platform in anti-aging science and product development.

PERSISTENT CHALLENGES IN THE ANTI-AGING MARKET

Competition, Limited Innovation

Today's anti-aging market remains highly fragmented and intensely competitive. Large, established brands face increasing competition from smaller, niche players, while brands outside the category look to diversify their product lines. In fact, not a single beauty and personal care brand can claim more than a small percentage of the anti-aging market.

The lack of brand dominance may be attributed to some extent on the formidable challenges in developing high-performing anti-aging products, as well as limited innovation in the category as a whole. Retinol, a form of Vitamin A on the market for the past few decades, remains the only product clinically proven to repair the signs of aging. However, despite some advances, retinol is known for its harshness (particularly on women's thinner skin) and continues to cause irritation and redness for many consumers. Lack of stabilization can also limit it to a daytime-only product.

The Sunscreen Phenomenon

Products aimed at the prevention of aging have progressed at a somewhat faster pace. Innovative stabilization chemistry has enabled authentic, effective protection from direct damage by the most penetrating, longer wavelength (340 nm and 400 nm) UVA-I rays. However, even some stable chemical sunscreen agents are capable of transferring the energy they absorb into molecular oxygen and causing damage to the skin's DNA, protein and lipids. Antioxidant additives can scavenge for and quench the resulting free radicals and oxidation, but their neutralization capability is limited and complicated by strong color, even at low concentrations. Antioxidants are, at best, a partial and after-the-fact response.

At the same time, even with highly advanced formulations and ideal usage, the effects of the UVA-I region of the light spectrum can never be completely blocked or absorbed—UV photons will always take some kind of toll on the skin whenever exposure occurs. Add to these challenges the growing concern among consumers about synthetic ingredients and perceived toxicity—regardless of product efficacy—and there seems to be no easy path toward better anti-aging products. The current market is one of continual one-upmanship aimed at small, incremental gains in market share.

THE CRITICAL LINK: UV RADIATION AND AGING

Fused-ring cyanoacrylates chemistry (commercial name Project Micah) offers a novel path to skin protection and may enable entirely new anti-aging products or dramatically enhance current products. To appreciate the potential of the new chemistry, it's important to first understand the UV photoreaction. Sun exposure is hardly the only factor that causes accelerated and long-term aging of the skin. Diet, exercise, genetics, stress and lifestyle factors such as smoking all play an important role in the skin's ability to remain elastic, even toned and relatively free of wrinkles and fine lines. However, it is well documented and universally accepted that the most damaging factor is longer UV wavelengths that cause burns, mutations, skin cancer and premature skin aging—linked phenomena tied to the effect of UV radiation on skin cells.

Direct and Molecular Damage

Amino acids, lipids and other endogenous substances in the skin are poor absorbers of radiation above 290 nm and most do not absorb at all; the vast majority of UV photons are directly absorbed by DNA and RNA. Absorption by these molecules causes single-strand breaks or "nicks" in the DNA, an attempt by the body's repair system to excise the DNA and remove the pyrimidine dimers (pre-mutagenic lesions) caused by the photochemical reaction. This process in turn activates enzymes that result in cell death and inflammation and ultimately the degradation of the skin's appearance.

At the molecular level of the skin, endogenous chromophore molecules (melanin, porphyrin and riboflavin) absorb UV photons and enter an "excited" state. At this singlet excited state, these skin photosensitizers must transfer the charge or the energy to oxygen (O_2) or substrate, causing harmful reactive oxygen species ($^1O_2$, or ROS) and free radicals. The light-induced ROS and free radicals lead to oxidative stress, wreaking havoc on proteins, lipids and DNA and causing negative changes to skin structure, function and appearance. Antioxidants may "hunt" the ROS before damage occurs and active ingredients may counteract gene expression, transcription and translation—but their effect is limited and variable.

"[The fused-ring cyanoacrylates chemistry] is important and unique because there is nothing else that kills the aging phenomenon at the beginning …this is a long-awaited breakthrough."

—Paolo Giacomoni, PhD, biochemist, atomic physicist and former director of research at both Estée Lauder and L'Oreal

FUSED-RING CYANOACRYLATES– A NEW PARADIGM

The fused-ring cyanoacrylates family of chemical compounds offers a highly promising, entirely new paradigm within anti-aging chemistry. This chemistry platform eliminates one of the key causes of UV-related aging by stopping the formation of damaging light-induced ROS and free radicals. UV can also directly damage DNA without forming ROS. Early data suggests that DNA bases can be stabilized, but we are still seeking to prove this in skin.

By acting directly on the skin's photosensitizers, e.g., endogenous poryphyrins, the chemistry stabilizes and balances energy conditions within the skin itself, including the potential to stabilize the skin's own retinol:

- The fused-ring cyanoacrylates quench the excited photosensitizers by accepting the energy transfer.
- The quenching then returns the photosensitizer to the ground state, eliminating the possibility that a singlet oxygen molecule and the subsequent ROS and free radicals will be generated.
- No structural or functional changes occur within the extracellular matrix. In this scenario, UV-induced skin aging is not merely stopped or repaired—it simply does not occur.

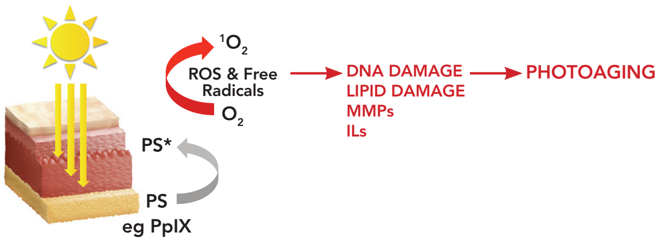
"With this chemistry, the energy among the complex of molecules is changed, and there is no way the porphyria will transfer the energy to make singlet oxygen," says Paolo Giacomoni, PhD, a biochemist, atomic physicist and former director of research at both Estée Lauder and L'Oreal. "This is important and unique because there is nothing else that kills the aging phenomenon at the beginning. For a molecule not to quench but to actually hinder singlet oxygen—this is a long-awaited breakthrough."

Efficacy and Implications

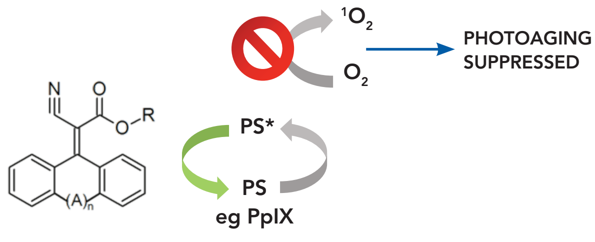
In early testing with blinded analysis, the fused-ring cyanoacrylates chemistry platform prevented 93 percent of light-induced ROS and free radicals from forming in UVA-irradiated *ex-vivo* porcine skin.[2] The choice of a porcine skin test is notable, as it most closely mimics the physiology of human skin. Additional testing is underway to determine whether the chemistry also produces significant improvement in collagen and elastin protection.

Based on a blind market research survey conducted by the Gerson Lehrman Group, the industry response to the potential of the chemistry has been strong: 78 percent of scientists and dermatologists agree there is a need to more effectively prevent oxidative stress in the UVA region, and 88 percent agree there is a need for new topical antioxidants.[3] The chemistry has also proven to be safe based on Hallstar's early testing. The fused-ring cyanoacrylates are negative in Ames, HRIPT and HET-CAM tests, and longer-term clinical trials are expected to provide even more safety data.

"The fused-ring cyanoacrylates do not seem to generate the same harmful side effects as other chemistries and products," says Giacomoni. "The energy must still be dispersed, but it is done through typical channels in ways that do not generate free radicals."



Base Case
Solar radiation excites endogenous photosensitizers (PS) in human skin. The excited photosensitizer (PS*) transfers energy to O_2 to generate $^1O_2$ and the subsequent reactive oxygen species (ROS)/free radicals can lead to photoaged skin.



Fused-ring Cyanoacrylates Case
The chemistry quenches excited states of endogenous photosensitizers, stopping the formation of $^1O_2$ and subsequent ROS/free radicals. It stabilizes by an electron transfer mechanism and will not absorb visible light and impart color onto skin.

MARKET OPPORTUNITIES AND CHALLENGES

Fused-ring cyanoacrylates chemistry has the potential to redefine how the public and the beauty and personal care industry understand and experience UV-induced aging. The new chemistry platform may evolve as a stand-alone, next generation product. It may also dramatically boost anti-aging claims and, when combined with sunscreen, enhance broad-spectrum sun protection well beyond current claims and ratings.

Nonetheless, a stubborn challenge for manufacturers is the continued demand for faster, more visible *repair* products and fixes rather than preventive products. But even within this market dynamic, fused-ring cyanoacrylates chemistry may prove to be a game changer by offering a unique, multifunctional approach:

- Stabilizing endogenous skin receptors for a more effective or less irritating topical retinol
- Coupling with antioxidants for full spectrum oxidative stress reduction
- Addressing skin disorders associated with aging
- Enhancing color correction cosmetics

The market is also ripe for an innovation of this type. In the U.S., the large baby boomer generation shows a greater inclination toward anti-aging products than previous generations. At the same time, Millennials are more attuned to anti-aging than one would expect; the so-called "involved segment" of Millennials is younger, buys branded and adopts anti-aging products earlier.[4]

Even customers who insist on natural ingredients are known to make concessions for effective anti-aging, and the highly innovative technology can command a higher price point within the desirable "prestige" market.

As fused-ring cyanoacrylates chemistry continues to be refined and tested, it will be up to beauty and personal care companies, along with their partners and providers, to create a new anti-aging story that captures the true potential of the chemistry and differentiates it from traditional prevention products.

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HALLSTAR

Hallstar's fused-ring cyanoacrylates chemistry platform, under the commercial name Project Micah, is in the early stages of development with key customers. A general market launch is tentatively slated for 2017. Hallstar is a leading global provider of specialty chemistry solutions. The company takes a collaborative approach to every engagement, delivering technical support, chemistry expertise and industry knowledge that helps its customers make the most of their products, from concepts to the first production batches.

To learn more, contact:

Varun Mathur
Director of Business Development
vmathur@hallstar.com
312-810-1021

Felicia Parks
Technical Director, Beauty & Personal Care
fparks@hallstar.com
708-594-6004

[1] O'Brien, Elizabeth. (2014). Ten secrets of the anti-aging industry. Retrieved from http://marketwatch.com

[2] Gematria Test Lab. Berlin, Germany

[3] Excerpt from blind market research survey conducted by Gerson Lehrman Group. Project Micah–Phase 1 Interim Update. Hallstar. (2014). Chicago, IL.

[4] Anti-aging reports. (2013). Mintel.com