Extrinsic skin aging—which produces coarse wrinkles, irregular pigment spots, and elastosis—is clearly distinguishable from intrinsic skin aging at clinical, histological, and molecular levels. It is commonly—and inaccurately, it now turns out—referred to as *photoaging*. Although long regarded as due exclusively to the interaction between skin and ultraviolet radiation (UVR), recent epidemiologic and mechanistic research has now established that extrinsic aging results from other common environmental stressors as well—stressors that lack a visually obvious connection to skin aging but are no less damaging to exposed human skin. They are the particulate matter (PM) and noxious gases in air pollution. These studies—directed by Jean Krutmann, MD (see box on page 6), Scientific Director of the IUF-Leibniz Research Institute for Environmental Medicine and Professor of Dermatology and Environmental Medicine at Düsseldorf University in Germany—have mapped and begun to characterize this important new landscape. And in doing so, he and his colleagues have also advanced our knowledge of skin biology. They found the molecular mechanism responsible for air pollution-induced skin aging to be the *aryl hydrocarbon receptor* (AHR), a little-known ligand-activated transcription factor (see box on page 8) that turns out to be an important regulatory and protective component of skin cells and melanocytes.

The clinical implications of Dr. Krutmann’s research are significant, as air pollution is a serious problem worldwide. Across the globe, about 90% of the population living in cities is exposed to traffic-related PM in concentrations exceeding WHO air quality guidelines. In some areas, cooking with unclean fuels or inefficient technologies provide our fruits and vegetables with their colors (see box on page 10). Polyphe}nols are abundant micronutrients in our diet, "and one of the interesting things about them," Mukhtar says, "is that they are all antioxidants. Thus they are all equipped to trap the free radicals that are notoriously harmful for our skin." Many of these plant
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pollutes the air indoors. Recognizing the significant aging impact of air pollution on skin enables the institution of protective efforts. And understanding how the underlying signal pathways are initiated provides a meaningful molecular target for the development of preventive and therapeutic agents.

**Focusing the IUF on Aging**

The IUF-Leibniz Research Institute for Environmental Medicine—a joint government and academic venture—was established in 2001 specifically to address environmentally induced disorders, and do so via molecular medical research aimed at the biological effects of air pollution (PM, nonionizing radiation—which includes infrared and near ultraviolet, and chemicals). The IUF was responding to a critical global need, as air pollution—both outdoor and indoor—has become responsible for significant mortality and morbidity worldwide, and the numbers continue to rise. The WHO’s most recent report calls air pollution “the largest single environmental health risk,” which caused an estimated 6.5 million deaths in 2012—11.6% of all global deaths that year, the latest for which figures are available. “Fine particulate matter has the greatest effect on human health,” the WHO states. “And most fine particulate matter comes from fuel combustion.”

Aging and the environment, however, was not yet part of the newly established IUF’s research agenda when Krutmann had been invited to become Scientific Director. He was concerned about the surging growth of the world’s aging population and the pressing need to learn a great deal more about aging and health, and was convinced that this critical need had not been recognized. Here was an exceptional opportunity—thus Krutmann ensured that mapping and understanding the aging impact of chronic air pollution exposure became the IUF’s focus.

Thus the IUF is dedicated to exploring the ways in which air pollution ages the human cardiovascular system, skin, and lungs, and impairs the immune system and brain function. Their investigators represent scientific expertise in toxicology, immunology, molecular aging research, and epidemiology. And the allied goals are improving healthcare and developing preventive strategies.

Krutmann personally looked forward to exploring the environment’s impact on skin aging. “The aging of our skin has medical, psychological, and social consequences because it is the most visible of all our organs and directly impacts an individual’s self-esteem,” he underlines, “and aging from extrinsic factors is far more amenable to intervention than intrinsic aging.” In addition, the skin is “a great model for understanding aging in other organs. So understanding skin aging will enable us to draw many conclusions about the aging of other organs,” Krutmann points out.

**The First Observations—Airborne Particle Exposure Ages Skin**

Many millions of humans worldwide are exposed to rising levels of ambient PM, which have long been shown to increase the risk for cancer and for pulmonary and cardiovascular diseases. More recent evidence has indicated that human skin can be directly affected by ambient PM, as particles in the nanosize range—which are among the most harmful components of ambient PM, and include those from traffic sources—can penetrate skin transepidermally and through hair follicles. Krutmann and his colleagues were the first to assess the effects of long-term ambient PM exposure on human skin, hypothesizing that it might lead to extrinsic skin aging either through oxidative stress generated directly by the particles themselves, or by polycyclic aromatic hydrocarbons (PAHs) that are adsorbed on the surface of particles suspended in the air.

During 2008–2009, they assessed the impact of these nanoparticles in a cohort of 400 Caucasian women 70–80 years old who were participating in a long-term study of pulmonary aging. These women were almost equally distributed between the urban Ruhr region and the villages and farms of rural Borken. Skin aging was assessed with the clinically validated SCINEXA (SCore of INtrinsic and EXtrinsic skin Aging), an instrument Krutmann had developed that differentiates between extrinsic and intrinsic skin aging. Exposure to traffic-related particle emissions in general, to soot in particular, and to background particle concentration was determined at each subject’s place of residence with state-of-the-art technology, and the study design took the necessary measures to ensure that sun exposure could not confound results.

Krutmann et al. not only found significant association between extrinsic skin aging signs and exposures to traffic-produced air pollution and soot—most strongly for lentigines, less so for rhytides (the upper lip and nasolabial fold)—but the skin response appeared to be dose-related. After dividing the range of absorbance values for these nanoparticles into quartiles, each increase from one quartile of soot absorbance to the next, for example, was associated with an additional 22% increase in the number of forehead lentigines and 20% on the cheeks. The composite of traffic-produced nanoparticles produced 16% more lentigines on the forehead and 17% more on the cheeks with each interquartile increase in absorbance. And looking at the impact of
traffic-produced particles for women who lived within 100 meters from a busy road, each interquartile increase in absorbance produced allied increases in lentigines of 35% on the forehead and 15% on the cheeks. Because lentigines had always been considered exclusive to chronic UV radiation exposure, Krutmann was highly intrigued that they showed the strongest association with air pollution’s skin-aging impact, and the strongest of all when soot was involved. He gathered together other observations indicating that lentigines can occur in the absence of UV radiation. “They are the leading extrinsic skin aging symptom in Asians who, in contrast to Caucasians, avoid sun exposure and thus should have fewer rather than more lentigines,” he pointed out at the time. And “of particular interest,” Krutmann says, “we had recently shown that AHR ligands, such as dioxin and PAHs, could induce melanocyte proliferation, and thereby skin tanning, in mice.” PAHs constitute a group of more than 100 different organic compounds released from burning organic matter, including fuels, tobacco, trash, wood, and meat. They frequently bind to the surface of these combustion-derived nanoparticles, with soot carrying an especially high PAH concentration. “And the strongest effect among these women was seen for soot,” Krutmann underlines.

Extending the Outdoor Evidence

When Krutmann and his colleagues decided to expand their focus and see if chronic exposure to nitrogen dioxide (NO₂)—a gaseous component of traffic-related air pollution—induces skin aging, it was the first time that its effects on human skin had been investigated. Krutmann’s research at the IUF had strongly suggested that “environmentally induced lung
and skin aging appear to be closely related,” he says, and NO2 exposure is known to be associated both with low lung function and with lung cancer. To assess the link between chronic exposure to NO2 and lentigo development, Krutmann and his group evaluated women from two geographic areas: an expanded Caucasian cohort (806 subjects) and 1,072 Han women >50 years old from a larger Chinese study. Lentigines were visually evaluated by trained personnel. The results recapitulated what had been found with PM. Exposure to NO2 was significantly associated with more lentigines on the cheeks in both cohorts.

This was the largest epidemiologic study to demonstrate the link between traffic-related air pollution and lentigo formation. And it showed the association not only in Caucasians but in Asians, a population in which lentigo formation is a hallmark of skin aging.

Solar lentigines have been considered the exclusive hallmark of skin exposed to cumulative doses of UVR, the clinical icon of photoaged skin. Photoaging and extrinsic aging have been interchangeable terms. But in light of such powerful evidence that widespread lentigo formation also occurs independently of UVR, Krutmann has recently reformulated the concept and terminology. He proposes the term environment-induced lentigo—or EIL—to replace the “solar” lentigo misnomer.

“We define EILs as acquired pigment spots (PS) of human skin that result from chronic exposure to a variety of environmental noxae,” Krutmann explains (see illustration on front cover). (Noxae are agents capable of exerting a harmful effect on the body.) In addition to UVR, these stressors

Johann Gudjonsson, MD, PhD, Chair of the Dermatology Foundation’s 2017 Medical & Scientific Committee, says he knows just how much a DF research award can mean to a young investigator. “I am actually the poster child for what these grants are capable of.”

This native of Iceland received three DF research awards early in his career that were essential to his becoming an independent investigator. “They were critical because they covered the period right after I finished my dermatology residency training at the University of Michigan, during those difficult early years as a junior investigator” when there were no other sources of support available.

Dr. Gudjonsson was drawn to dermatology out of curiosity about psoriasis, which affected some of his family members. A two- to three-month research project on psoriasis that he had begun at the University of Iceland Medical School “extended into summer and then into full PhD training.” It also led ultimately to the University of Michigan, where the Department of Dermatology was engaged in groundbreaking research delineating the immune system’s active role in psoriasis, and documenting that it is treatable with immunosuppressive drugs. Dr. Gudjonsson is now an Assistant Professor there. His primary research focus has been basic immunologic and genetic research on psoriasis, with projects directed at improving the diagnosis and treatment of this inflammatory disease. He also sees patients and directs the inpatient consultation service.

The new direction that his research has begun to take involves learning why so many more women than men develop autoimmune diseases. Naturally, he has started out by looking at genomic differences, and a paper reporting his initial findings will be in Nature Immunology by the end of the year.

Dr. Gudjonsson, an experienced grant reviewer, has been a member of the Medical & Scientific Committee for the past three years. He profoundly enjoys the great group of people and the collegial discussions, and “I am quite honored to lead it this year.” His goal as Chair is to “move the best science and people forward so we can keep growing the field.” Dr. Gudjonsson stresses that dermatology continues to lose too many talented new investigators because of research funding concerns. “We desperately need more individuals who are dedicated to the intellectual excitement of exploration, discovery, and advancing the state of knowledge.”

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Early DF Research Award Essential to Career as Independent Investigator

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Pollution-induced skin damage. With intact skin, ozone acts superficially on the SC but the organic compounds sticking to nanoparticle PM penetrate skin and affect keratinocytes, melanocytes, and fibroblasts → altered signal pathways → pigmentation and rhytides, plus oxidative stress → skin inflammation. Barrier-deficient skin exacerbates the impact. AHR (aryl hydrocarbon receptor); MIF (microphthahlia-associated transcription factor); O₃ (ozone); PAHs (polyaromatic hydrocarbons); POMC (pro-opiomelanocortin); PM (particulate matter); ROS (reactive oxygen species); VOC (volatile organic compounds). (Reprinted with permission from Japanese Society for Investigative Dermatology; J. Krutmann et al. See “Suggested Readings” for citation.)

include particulate and gaseous constituents of ambient air pollution. It is clear that cumulative UV irradiation is a major contributor, in part because UVB is the most important physiological trigger for skin pigmentation in general, and in part because, in Caucasians, EILs preferentially occur on chronically sun-exposed skin. But the fact that Asian women typically avoid sun exposure, yet develop EILs substantially sooner than do age-matched sun-exposed Caucasians, highlights that there is more than sun exposure at work. Krutmann places the AHR (see box on page 8) front and center. He points to mechanistic studies strongly indicating that lentigines form in human skin as a consequence of disturbed crosstalk between melanocytes on the one hand and keratinocytes and fibroblasts on the other. Krutmann’s earlier research had already shown that the AHR is expressed in both mouse and human skin cells and melanocytes, and that it regulates melanocyte proliferation and melanin synthesis, and thus is central to the tanning response. This altered communication occurs because the keratinocytes and fibroblasts have been stimulated to overproduce pigmentation-relevant soluble factors directly affecting melanocyte behavior and function. These soluble factors are induced by signaling pathways that can be activated by both UVR and air pollution (see illustration at left). "So the common denominator—explaining the fact that these diverse environmental insults are causing similar clinical consequences," Krutmann explains, "is activation of AHR signaling in these skin cells."

Because of its role in tanning, the AHR connection is obvious for UVR-induced lentigines. PAHs—the major harmful components of soot and other PM from ambient and indoor pollution, which are lipophilic and thus easily penetrate the skin—are also AHR ligands. And in addition, AHR activation would explain the wrinkling that occurs with both UVR and chronic air pollution exposure. Krutmann’s research has shown that the AHR can also play a role in collagen breakdown (as well as in photocarcinogenesis and in skin inflammation).

Indoor Air Pollution Also Ages Skin—But Differently

In China, indoor air pollution from the use of solid fuels (such as coal) for cooking is a known risk for significant pulmonary problems—serious respiratory infections, COPD, and lung cancer. Krutmann wanted to see whether it also increases the risk of skin aging in Chinese women. The evaluation used independent study populations living in two geographically different areas. Each was a large cross-sectional group involving women from 30–90 years old, with 405 women from Pingding in northern China and 857 from Taizhou in the south. The SCINEXA was used to assess their skin.

Krutmann’s group found that, independently of age and other influences on skin aging, cooking with solid fuels is significantly associated with a 5–8% increase in severe wrinkling on the face, and a 75% greater risk of having fine wrinkles on the back of the hands. Possible mechanistic explanations for this association come from in vitro studies that have examined the effects of exposing cultured human fibroblasts to tobacco smoke extract, which is a complex mixture of pollutants similar to air pollution. Tobacco smoke induces skin aging—mainly the development of wrinkles—apparently by shifting the balance from collagen production to collagen degradation. And here again the AHR is at work. The PAHs included in tobacco smoke can trigger the AHR signaling pathway, and the result in this case induces fibroblasts to produce the matrix metalloproteinases that break down collagen. The PAHs that attach to the fine particles produced by indoor solid cooking fuels also activate the AHR signaling pathway.

Treatment Attempts

Pycnogenol®. Krutmann carried out a small trial of the nutritional supplement Pycnogenol®, an extract from the bark of the French maritime pine that is standardized to contain a variety of bioactive molecules protective against oxidative stress. It had exerted beneficial effects on skin cells in vitro and in animal studies. Claims had been made for clinical benefit in ameliorating extrinsic aging in human subjects. Krutmann knew that Pycnogenol® has a high physical affinity for extracellular matrix proteins that are rich in hydroxyprolines, such as collagen.
and elastin, “both critically involved in skin aging,” he notes. An earlier clinical trial elsewhere with a multinutrient product containing Pycnogenol® as the leading active ingredient improved visible signs of skin aging as well as skin elasticity and smoothness after 6 weeks. This appears to address at least some of the changes induced or exacerbated by environmental stressors. But in general, molecular evidence substantiating clinical observations of skin benefit is scarce, and there was none for Pycnogenol®. Krutmann used a pure Pycnogenol® product in a 12-week trial, and if he observed similar clinical benefit, he planned to look for evidence of concomitant changes at the molecular level.

His subjects were 20 healthy postmenopausal women who received a daily Pycnogenol® supplement for 12 weeks. The condition of their skin was assessed both by noninvasive biophysical methods and via biopsies used for gene expression analyses related to extracellular matrix homeostasis. The supplement, which was well tolerated by all volunteers, significantly improved skin elasticity (top graphs) and hydration. This improved skin physiology was accompanied by a significant increase in hyaluronic acid synthase-1 (an enzyme critically involved in the synthesis of hyaluronic acid) (left-hand graph below), and an increase in gene expression involved in de novo collagen synthesis (right-hand graph below). This could counteract the collagen degrading effect of chronic exposure to air pollution and the Journal of the American Academy of Dermatology (JAAD) has published seven articles this year in its new “From the Dermatology Foundation” section created in partnership with the DF. Announced in the May issue of the JAAD, it features clinically relevant articles by researchers whose work was supported by DF Career Development Awards. The articles are available online to all JAAD subscribers and also through the DF’s Facebook page. “From the Dermatology Foundation” is a great way to see how DF award recipients are working to further the science of the specialty for the benefit of all dermatologists and the patients in their care.

October, 2016
“Persistence of atopic dermatitis (AD): A systematic review and meta-analysis.” Jooho P. Kim, Lucy X. Chao, Eric L. Simpson**, and Jonathan I. Silverberg*
November, 2016
“Impact of pruritus on quality of life: A systematic review.” Robert Kantor, Prarthana Dalal, David Cella, and Jonathan I. Silverberg*
“Direct-to-Consumer Teledermatology Services for Pediatric Patients: Room for Improvement.” Alexander L. Fogel, Joyce Teng**, and Kavita Y. Sarin*
December, 2016
“Association of atopic dermatitis with smoking: A systematic review and meta-analysis.” Robert Kantor, Ashley Kim, Jacob P. Thyssen, and Jonathan I. Silverberg*
*Recent DF Award Recipient  ** Former DF Award Recipient
**AHR: The Ligand-Activated Aryl Hydrocarbon Receptor**

Poorly understood and thus marginalized until now, the AHR is highly expressed and active in all skin cells and in melanocytes. It is essential for normal cell function and pigmentation as well as for protecting the skin against environmental threats, including UVR. This molecular lymph pin can bind with a variety of activating ligands, both endogenous and exogenous, and it is the particular situation-specific ligand that determines the molecular and clinical outcome.

The AHR had first come to Krutmann’s notice once he began working hands-on at the IUF. “Toxicologists here had been studying dioxin—its effects on liver cells, its effects in mouse models, its ability to impair T-cell development. And they had found all of these effects to be mediated by this almost unknown ligand-activated transcription factor. Then not long after I had begun working here,” he continues, “other roles for these ligand-activated receptors were discovered.” They were found to be important in the embryo for tissue and organ development. And a particularly big breakthrough was finding a significant functional role in the immune system. Treg cells express it, and it is extremely important for their immunosuppressive function.

“But no one had systematically looked at whether, where, and why the AHR is expressed in skin cells,” Krutmann recalls, “so I asked our AHR experts to take a look.” And they hit paydirt. They showed that epidermal keratinocytes express functionally active AHR, that they can be activated by UVB radiation (mediating both skin tanning and immunosuppression), by PM in air pollution, and by the PAHs that attach themselves to these nanoparticles. At this point, Krutmann knows the AHR plays substantial roles in the adaptive responses to environmental challenges (such as UVB exposure and topical chemicals, including those in polluted air and in tobacco smoke), in maintaining skin cell homeostasis, in regulating melanogenesis (by controlling melanocyte proliferation and melanin synthesis), and in skin immunity.

**Infrared A (IRA) Protection.** IRA—part of the spectrum of nonionizing radiation—is also an environmental stressor that accelerates aging, in part by upregulating the expression of collagen-degrading matrix metalloproteinase-1 (MMP-1) in dermal fibroblasts. Krutmann and his colleagues created an enriched sunscreen and assessed its protective capability against IRA exposure. Their hope was to protect human skin against the upregulation of MMP-1 that exposure induces. They compared a standard SPF30 sunscreen to the identical sunscreen supplemented with an antioxidant cocktail containing grape seed extract, vitamin E, ubiquinone, and vitamin C. The antioxidant-enriched formulation was successful. As expected, exposure to IRA radiation significantly upregulated MMP-1 expression compared to nonirradiated skin. Use of the unmodified SPF30 sunscreen did not offer adequate protection against the increased presence of MMP-1, but the antioxidant-amplified product reduced this increased expression significantly. Krutmann and his coworkers concluded that the topical application of specific antioxidants effectively protects human skin against IRA radiation, and that regular sunscreens need to be supplemented with this antioxidant cocktail to be effective.

**AHR Antagonist.** And finally, Krutmann’s group has developed an AHR antagonist—called BDDI—that transiently prevents AHR activation during UBV exposure. The unligated, inactive AHR is trapped in a cytosolic multiprotein complex that rapidly dissociates upon ligand binding, allowing the activated AHR to shuttle into the cell nucleus where it binds to elements in the promoter region of target genes. This initiates transcription of these genes, in turn unleashing the signal pathways that result in much of the damage from UBV exposure. In cultures of normal human epidermal keratinocytes, BDDI temporarily prevented AHR activation. Then a placebo-controlled study was done with 10 healthy volunteers who applied a topical agent containing BDDI to defined skin areas once daily for 4 days. After application on day 4, volunteers were irradiated (or sham-irradiated) with 1.5 MED. Skin biopsies taken 24 hours later clearly showed typical AHR activation in response to placebo-mediated UBV irradiation. But the BDDI-containing cream prevented AHR from activating any of its target genes, thus eliminating the AHR-dependent signal pathways. Krutmann adds that “our in vitro data also indicate that BDDI may protect against the adverse effects of PAHs typically found on airborne particulate matter, and that potentially makes this AHR antagonist relevant as well for protection against the skin aging effects of air pollution indoors and out.”

**Conclusions**

A great deal of research remains to be done to arrive at a full understanding of the aging impact that air pollution components have on human skin, and to develop the most effective preventive and therapeutic agents. One of Krutmann’s additional concerns is the role of sensitive skin. The pathophysiology of sensitive skin, although not yet fully understood, is thought to be associated with disturbed barrier function and increased stratum corneum permeability. Considering that individuals with sensitive skin have a barrier defect, they may represent a subgroup within the population that is particularly sensitive to pollution-induced skin problems. This is an additional question requiring further study, which Krutman has begun to pursue by exploring the involvement of the AHR in skin barrier function.

**Suggested Readings**


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Allison Sutton, MD

NON-PHYSICIAN PROVIDER
Arthur J. Haughey, PA

italics = Young Leaders (Within 5 years of residency)
derived antioxidants are absorbed through the skin, which ensures reaching their target tissue. Determining the absorption capability for any given polyphenol is very straightforward. Apply it to the skin, and if it becomes detectable in the blood, then it has been absorbed and metabolized.

Reaching Out to Botanicals for Treating the Skin

Having grown up in India, Mukhtar had always been personally aware that many plants have medicinal value. India’s traditional health care system—Ayurvedic medicine—includes a sophisticated experience-based understanding and application of regional plant compounds. With a PhD in biochemistry and drawn to drug metabolism, Mukhtar came to the U.S. in the mid-1970s as a postdoctoral fellow, then moved to a pharmacology/toxicology lab at the National Institute of Environmental Sciences to study the cytochrome P450 system of metabolic enzymes. He began some research involving natural products, among others, but not involving their medicinal activity.

Mukhtar’s work there brought him to a basic realization about the skin’s nature and function, and that ultimately led him to the dermatology department at Case Western Reserve. Back at that time the skin was still regarded as simply an inert mechanical barrier, but Mukhtar began to see clear evidence that it is a great deal more. In studying the P450 system, he saw that some agents applied to the skin were ultimately metabolized for excretion by one of these liver enzymes—and this clearly could not occur unless they had first been absorbed through and processed by the skin. This meant that the skin is clearly an active metabolic organ, and Mukhtar wanted to show this. “So I began some work to demonstrate the skin’s true nature,” he recalls, “and that got me so interested in skin that I chose it to be my life’s work.” Once at Case Western Reserve and learning about cutaneous damage and diseases, Mukhtar suddenly realized the value in a partnership between the antioxidant power of botanical polyphenols and caring for the skin.

Green Tea—First on the Menu

Mukhtar began to focus on skin cancers. The first botanical he chose to study in this context was green tea, which Mukhtar and his group eventually put on the map as a dietary constituent with dramatic chemopreventive properties for the skin, among other organs. Green tea is one of the world’s most ancient and popular beverages (grown in about 30 countries) and consumed by the Chinese as a medicine because of its pharmacologic and physiological effects. But no one at that point understood why green tea appeared to have important health benefits, nor had the biological foundation for these benefits been assessed with the tools and techniques of contemporary science. “It was natural for me to see if it has any activity against skin cancer,” Mukhtar says. He and his colleagues concentrated on green tea’s polyphenols, ie, its antioxidant compounds. He parsed them down to the molecules that provide their primary chemopreventive power—the epicatechin familiarly referred to as EGCG (epigallocatechin gallate)—and he established the compelling data that put green tea on the therapeutic map.

Now Mukhtar is working intensely with three additional botanical agents (see box on page 12). He has been studying the juice and fruit of the pomegranate (a fruit with a complex of potent antioxidants) for some time, and more recently has added the individual polyphenols delphinidin and fisetin. He is addressing photodamaged skin, skin cancers (including melanoma), and psoriasis.

Photochemoprevention—One Goal, Multiple Benefits

“Exposure of the skin to UV radiation from the sun—particularly its UVB component, which is in the 280- to 320-nm range—results in erythema, edema, hyperplasia, hyperpigmentation, sunburn cells, immunosuppression, photoaging, and skin cancer,” Mukhtar notes. “And within this spectrum of impact, skin cancer and photoaging are of great concern. In fact, solar UV radiation is the most prominent and ubiquitous physical carcinogen in our natural environment,” Mukhtar points out.

Changes in lifestyle have led to a significant increase in the amount of UVB radiation that people receive, creating a continuing surge in the incidence of both skin cancer and photoaging. “Thus the adverse effects of UVB have become a major human health concern,” Mukhtar states. “And this makes it highly desirable to develop novel strategies to reduce the occurrence of skin cancer and delay the process of photoaging.”

One way to do this is through photochemoprevention—the use of agents capable of ameliorating the adverse effects of UVB on the skin. Using botanical antioxidants that are present in the typical human diet “has gained considerable attention,” Mukhtar points out, and he lists green tea, pomegranate, resveratrol, and genistein as the more commonly encountered options. Accumulating laboratory data indicate that many botanical agents with antioxidant properties exert anti-inflammatory, cancer preventive, and anti-photoaging effects in the skin (see illustration on page 11). “Because UVB radiation plays such an important role in cutaneous damage, agents that can protect against it would simultaneously be photochemoprotective against photoaging and skin cancer. The use of skin care products with sunscreen and supplemented

Focus on Research

Botanical Antioxidants—A Multifunctional Approach to Preventing and Treating Skin Damage and Disease

(Continued from cover)

Polyphenols

These common antioxidants are present in many foods and beverages of plant origin. Their chemical structure involves one or more phenolic groups, which are capable of reducing reactive oxygen species and various organic substrates and minerals. These prominent redox properties explain the considerable interest in their potential for preventing or treating major chronic diseases associated with oxidative stress, especially cardiovascular diseases, cancers, type 2 diabetes, neuro-degenerative diseases, and osteoporosis. Polyphenols come in a great variety, and over 500 different molecules have been identified in foods. A handful of the more well-known ones are the flavonoids and flavonols, ellagic acid, tannic acid, resorcinol, the anthocyanidins, catechins, and epicatechin.
with several effective agents that work through different pathways may be an ideal way to reduce UVB-generated ROS-mediated photoaging and skin cancer in humans.”

To this end, Mukhtar has been putting pomegranate through its paces to prevent both photoaging and skin cancer. He is also studying delphinidin—an important constituent of pomegranate as well as other red- and blue-colored fruits and vegetables—for cancer prevention, and has done a handful of studies now with fisetin specifically in the context of melanoma. He has been providing the strong mechanistic foundation that is laying the ground for further preclinical work and clinical trials.

### Emphasis: Preventing Photoaging

Mukhtar has assessed the photochemopreventive capabilities of pomegranate extracts in two different settings to determine whether it has the potential to protect against the damage that underlies photoaging. His first set of studies used

**Multifunctional botanical antioxidants.** Three simultaneous photochemoprotective modes of action prevent (the changes → photodamage and/or skin cancer), repair (existing changes), and suppress (inflammation and consequent damage). (Reprinted with permission from Blackwell Munksgaard. F. Afaq et al. 2006; Exp. Dermatol. See “Suggested Readings” for citation.)
HaCaT cells, which belong to an immortalized line of keratinocytes widely used for studies of skin biology and cell differentiation. He pretreated some of his cell cultures with a pomegranate fruit extract (PFE) before exposing them, and untreated control cultures, to UVB radiation. Mukhtar found that pretreating cell cultures with PFE reduced oxidative stress and photoaging. It inhibited UVB’s ability to diminish cell viability, to decrease intracellular glutathione, and to increase lipid peroxidation. Using immunoblotting to detect protein synthesis, Mukhtar showed that PFE also inhibited several elements responsible for collagen breakdown. It prevented activation of the MAPK (mitogen-activated protein kinase) pathway, which is largely responsible for stimulating the transcription factor AP-1, which in turn stimulates the transcription of matrix metalloproteins (MMPs) that degrade the extracellular matrix—MMP-1, MMP-2, and MMP-9. Not only did these MMPs not increase, but PFE also maintained the collagen-friendly expression of TIMP-1.

Next, Mukhtar and his coworkers looked at several pomegranate extracts—PFE, juice, and oil—to treat a reconstituted skin model 1 hour before exposing this skin to UVB. After exposure, assessing protein oxidation along with markers of DNA damage and photoaging confirmed the protective profile. Pretreatment with each product had inhibited a variety of UVB-induced alterations and DNA and protein damage. Pretreatment had also minimized cancer-promoting changes in the proto-oncogenes c-Fos and c-Jun.

Mukhtar found these studies to provide a strong basis “for more in-depth investigations to assess the effectiveness of pomegranate fruit and its derived products in preventing UVB-mediated damage and photoaging.”

**Skin Cancer Statistics**

Skin cancer represents a substantial health care burden in the U.S.—and roughly 90% of cases are associated with exposure to UV radiation from the sun. The Skin Cancer Foundation notes that over the past three decades, more people have had skin cancer than all other cancers combined. Each year in the U.S., more than 40 million cases of basal cell carcinoma and more than one million cases of squamous cell carcinoma are diagnosed. The annual cost of treating these skin cancers is estimated at $8.1 million. Melanoma rates doubled between 1982 and 2011, and they are still rising. Although melanoma accounts for less than 1% of all skin cancer cases, it is responsible for the vast majority of skin cancer deaths. An estimated 10,130 people will have died of melanoma in 2016. The new cases of skin cancer identified in the U.S. each year involve considerable morbidity. Mortality becomes a significant concern with more aggressive cancers. Effective photochemoprevention would dramatically improve this landscape.

**Prevention: Nonmelanoma Skin Cancers**

UV-induced responses result in inflammation, oxidative stress, dysregulation of apoptosis (allowing abnormal proliferation of keratinocytes containing DNA damage), acquisition of p53 mutations, alterations in signal transduction pathways, and immunosuppression. All of these changes contribute to the onset of skin cancers. In addition, UV radiation from the sun is a complete carcinogen, which is what makes it particularly dangerous. It causes the DNA damage initiating the carcinogenic process, and later it is equally effective at promoting tumorigenesis by generating clonal expans-
JUBLIA®
(efinaconazole)
Topical Solution 10%

ONYCHOMYCOSIS*
STEALING THE SHOW?

FIGHT IT
AT THE SITE OF INFECTION^1

*For the treatment of onychomycosis of the toenail(s) due to Trichophyton rubrum and Trichophyton mentagrophytes.

JUBLIA allows some patients to have clearer toenails grow back. Individual results may vary.

INDICATION

JUBLIA (efinaconazole) topical solution, 10% is indicated for the topical treatment of onychomycosis (tinea unguium) of the toenail(s) due to Trichophyton rubrum and Trichophyton mentagrophytes.

IMPORTANT SAFETY INFORMATION

• JUBLIA is for topical use only and is not for oral, ophthalmic, or intravaginal use.

• Patients should be instructed to contact their health care professional if a reaction suggesting sensitivity or severe irritation occurs.

• The most common adverse reactions (incidence >1%) were (vs vehicle): ingrown toenail (2.3% vs 0.7%), application-site dermatitis (2.2% vs 0.2%), application-site vesicles (1.6% vs 0%), and application-site pain (1.1% vs 0.2%).

• JUBLIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and should be used with caution in nursing women. The safety and effectiveness in pediatric patients have not been established.

Please see Brief Summary of full Prescribing Information on the adjacent page.


BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use JUBLIA safely and effectively. See full prescribing information for JUBLIA.

JUBLIA® (efinaconazole) topical solution, 10%

For topical use
Initial U.S. Approval: 2014

INDICATIONS AND USAGE
JUBLIA (efinaconazole) topical solution, 10% is an azole antifungal indicated for the topical treatment of onychomycosis of the toenail(s) due to Trichophyton rubrum and Trichophyton mentagrophytes.

DOSAGE AND ADMINISTRATION
Apply JUBLIA to affected toenails once daily for 48 weeks, using the integrated flow-through brush applicator. When applying JUBLIA, ensure the toenail, the toenail folds, toenail bed, hyponychium, and the undersurface of the toenail plate, are completely covered.

JUBLIA is for topical use only and not for oral, ophthalmic, or intravaginal use.

CONTRAINDICATIONS
None.

ADVERSE REACTIONS

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two clinical trials, 1227 subjects were treated with JUBLIA, 1161 for at least 24 weeks and 780 for 48 weeks. Adverse reactions reported within 48 weeks of treatment and in at least 1% of subjects treated with JUBLIA and those reported in subjects treated with the vehicle are presented in Table 1.

In a pre- and post-natal development study in rats, subcutaneous doses of 1, 5 and 25 mg/kg/day efinaconazole were administered from the beginning of organogenesis (gestation day 6) through the end of lactation (lactation day 20). In the presence of maternal toxicity, embryofetal toxicity (increased prenatatal pup mortality, reduced live litter sizes and increased postnatal pup mortality) was noted at 25 mg/kg/day. No embryofetal toxicity was noted at 5 mg/kg/day (17 times the MRHD based on AUC comparisons). No effects on postnatal development were noted at 25 mg/kg/day (89 times the MRHD based on AUC comparisons).

Nursing Mothers
It is not known whether efinaconazole is excreted in human milk. After repeated subcutaneous administration, efinaconazole was detected in milk of nursing rats. Because many drugs are excreted in human milk, caution should be exercised when JUBLIA is administered to nursing women.

Pediatric Use
Safety and effectiveness of JUBLIA in pediatric subjects have not been established.

Geriatric Use
Of the total number of subjects in clinical trials of JUBLIA, 11.3% were 65 and over, while none were 75 and over. No overall differences in safety and effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and the younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility
A 2-year dermal carcinogenicity study in mice was conducted with daily topical administration of 3%, 10% and 30% efinaconazole solution. Severe irritation was noted at the treatment site in all dose groups, which was attributed to the vehicle and confounded the interpretation of skin effects by efinaconazole. The high dose group was terminated at week 34 due to severe skin reactions. No drug-related neoplasms were noted at doses up to 10% efinaconazole solution (248 times the MRHD based on AUC comparisons).

Efinaconazole revealed no evidence of mutagenic or clastogenic potential based on the results of two in vitro genotoxicity tests (Ames assay and Chinese hamster lung cell chromosome aberration assay) and one in vivo genotoxicity test (mouse peripheral reticulocyte micronucleus assay).

No effects on fertility were observed in male and female rats that were administered subcutaneous doses up to 25 mg/kg/day efinaconazole (279 times the MRHD based on AUC comparisons) prior to and during early pregnancy. Efinaconazole delayed the estrous cycle in females at 25 mg/kg/day but not at 5 mg/kg/day (56 times MRHD based on AUC comparisons).

PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Patient Information).

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies with JUBLIA in pregnant women. JUBLIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 2, 10 and 50 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-16) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal deaths, decreased number of live fetuses, and placental effects) was noted at 50 mg/kg/day (559 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons). No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD based on AUC comparisons). No malformations were observed at 50 mg/kg/day (559 times the MRHD based on AUC comparisons).

Subcutaneous doses of 1, 5, and 10 mg/kg/day efinaconazole were administered during the period of organogenesis (gestational days 6-19) to pregnant female rabbits. In the presence of maternal toxicity, there was no embryofetal toxicity or malformations at 10 mg/kg/day (154 times the MRHD based on AUC comparisons).

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PATIENT COUNSELING INFORMATION
See FDA-Approved Patient Labeling (Patient Information).
At the heart of this process is the fact that UV exposure increases the generation of reactive oxygen species to a degree that overwhelms the skin’s antioxidant defense mechanisms, a disequilibrium termed oxidative stress. Mukhtar chose two items to assess for their ability to prevent this oxidative stress. One was pomegranate, well known by then for its antioxidant strengths. The other—based on his earlier assessment—was delphinidin.

When Mukhtar and his coworkers studied delphinidin’s ability to protect against the early changes leading to UVB-induced skin cancer, they looked first at human HaCaT keratinocytes, and then at hairless mice. With HaCaT cell cultures, 24 hours of delphinidin before a 24-hour period of UVB exposure substantially improved the outcome. Delphinidin protected cell viability and survival, reduced lipid peroxidation and DNA damage, maintained the protective presence of proliferating cell nuclear antigen (PCNA), minimized the appearance of important biomarkers of DNA damage, and significantly limited a variety of UVB-induced changes that create an environment favoring the creation and preservation of DNA-damaged cells. Applying delphinidin to the skin of hairless mice both before and after UVB exposure demonstrated its strong antioxidant activity, and showed substantially reduced DNA damage and consequent apoptosis in keratinocytes. The observed benefits translated to a potent photochemopreventive effect.

Mukhtar et al. also looked at the preventive strengths of pomegranate. First they assessed the effect of PFE on early biomarkers of photocarcinogenesis. After mixing it in drinking water and feeding it to hairless mice for 14 days before a single UVB exposure, the treated mice showed only very modest increases in skin edema, hyperplasia, leukocyte infiltration, lipid peroxide and hydrogen peroxide generation (see graph on page 16), among a variety of early markers. PFE pretreatment also increased the elevation of tumor suppressor p53 and its partner, cyclin kinase inhibitor p21. This was convincing evidence that oral feeding of PFE to mice affords them substantial protection from the adverse effects of UVB radiation, intervening right at the start and minimizing the early biomarkers of photocarcinogenesis.

A more recent study involving oral...
feeding of PFE to hairless mice repeated the pretreatment PFE regimen and daily UV dose, but increased this from a single exposure to a total of 7 given on alternating days. This time, Mukhtar et al. looked at PFE’s ability to normalize the activity of signal pathways critical to carcinogenesis. One was the MAPK pathway, which is important in tumorigenesis as well as photoaging. It normally links extracellular signals to the intracellular machinery that controls fundamental existential cellular processes. Tumorigenesis requires deregulation of at least 6 of these cellular processes to enable acquisition of the abilities to proliferate independently, evade apoptosis, ignore anti-growth signals, replicate without limitation, invade and metastasize, stimulate angiogenesis, acquire drug resistance, and avoid induced senescence—and abnormalities in MAPK signaling facilitate most, if not all, of these processes. MAPK abnormalities are activated by UVB exposure. Mukhtar also monitored the inflammatory NF-κB pathway that becomes involved in cell growth and proliferation. “Taken together, our data show that PFE consumption affords protection to mouse skin against the adverse effects of UVB radiation by modulating these signaling pathways,” Mukhtar explains. “And thus it points to PFE’s potential efficacy as a photochemopreventive agent for skin cancer.”

Prevention: Melanoma Skin Cancers

Although the new immunotherapies now helping some patients with advanced or unresectable disease are the first significant improvement in many years, the outlook remains bleak for the large majority. And for those who do respond to these new drugs, side effects can be damaging and the cost for these drugs is monumental. Mukhtar is approaching melanoma with fisetin, a common and potent flavonoid already being investigated for its growth inhibitory properties in other cancer models. He and his coworkers initially found that fisetin inhibits melanoma cell proliferation both in vitro and in vivo. Then they used a 3-D full-thickness melanoma skin model to study the effect of fisetin on melanoma progression. Days 12 and 16 showed a dramatic decrease in melanoma cells versus untreated control skin. Untreated skin contained nests of tumor cells and many invading disseminated cells. (See graph above.) By day 16, melanocytic lesions were barely detectable in fisetin-treated skin tissue, contrasting significantly with untreated controls. Further studies in melanoma cultures and mouse xenografts showed that fisetin-mediated growth inhibition was associated with deactivating several essential proteins, including mTOR.

Mukhtar’s studies characterized, for the first time, the distinctive interactions of a botanical agent with kinases specifically involved in melanoma growth. They demonstrated that fisetin binds directly to mTOR and p70/S6K to achieve inhibition of these critical melanoma pathways, but achieves inhibition of Akt indirectly by targeting pathways that then turn Akt off. Additional study made it clear that fisetin induces cytotoxicity in cultured metastatic human melanoma cells. Looking for the molecular basis of this impact, they discovered that the primary mechanism through which fisetin inhibits melanoma cell growth is apoptosis, and that this impact integrates activation of both extrinsic and intrinsic pathways.

2017 DF Annual Meeting Events: Mark Your Calendar

As you make your plans to travel to Orlando, Florida this next March, please be sure to add the Foundation’s events to your schedule. Join your colleagues at the Annual Meeting of Membership to come up to speed on DF activities, and to recognize this year’s honorary awardees and the recipients of DF research awards.

** Friday, March 3 – Sunday, March 5 **
DF Exhibit Booth #3310
Orange County Convention Center

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<tr>
<th>Day</th>
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<tr>
<td>Fri</td>
<td>Annual Leadership Gala</td>
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<td>Sat</td>
<td>Pre-Gala Young Leaders Reception</td>
<td>6:45 – 7:30 pm</td>
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<td>Sun</td>
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(By invitation only—tickets required)

Treating Psoriasis

The ideal treatment of psoriasis remains elusive. Although patients are now benefiting from dramatic progress in treatment capability stemming from fundamental advances in understanding the underlying immunopathology, the targeted biologic drugs now used are extremely costly and come with significant side effects. Most concerning is the more general
immunosuppression imposed on patients that is currently the price to pay for inhibiting the immune hyperactivity responsible for psoriatic lesions. The goal of finding a way to restrain the signaling abnormalities underlying psoriasis without creating other health vulnerabilities motivated Mukhtar to explore a botanical option.

He had noticed that the PI3K/Akt/mTOR pathway—frequently deregulated in many malignancies—is also clinically relevant in psoriasis. So he decided to use delphinidin, a polyphenol from pigmented fruits and vegetables that had already shown good activity against this pathway in a skin cancer setting, and see what it might possibly do in psoriasis. His first attempt used an experimental system that closely mimics in vivo human skin—and the results were excellent. Treating reconstituted human skin with this extract “increased the expression of caspase-14, which is involved in cornification,” Mukhtar explains. “And it also increases the expression of epidermal differentiation marker proteins.” These observations meant that delphinidin could be a useful agent for dermatoses associated with epidermal barrier defects, including the aberrant keratinization, hyperproliferation, and inflammation that occur in skin diseases like psoriasis and ichthyoses.

Next they used delphinidin in a full-thickness 3-D reconstitution of psoriatic skin as well as in a normal skin equivalent. Applying delphinidin daily for 2–5 days produced highly encouraging changes. It induced differentiation, thickened the stratum corneum (see graph on page 18) and epidermis, and inhibited proliferation. And it minimized the expression of endogenous antimicrobials—such as psoriasin and koebnerisin—that are strongly increased in inflamed psoriatic skin (see photos at right).

Delphinidin minimized the characteristic features of human psoriasis seen in imiquimod-treated mice. 3 groups—control (black), 5% imiquimod cream (red), imiquimod + topical delphinidin (green)—were evaluated regularly. Thickened ear skin, inflammatory erythema, and scales were dramatically minimized with delphinidin. (***P≤0.001; ****P≤0.0001) (Reprinted with permission from Mary Ann Liebert. JC Chamcheu et al. 2016; Antioxidants Redox Sig. See “Suggested Readings” for citation.)

Delphinidin suppresses inflammation in psoriatic skin. This shows the substantial reduction in expression of the proinflammatory alarmins psoriasin (S100A7) and koebnerisin (S100A15) in dose-related fashion. (Reprinted with permission from Karger. JC Chamcheu et al. 2015; Skin Pharmacol Physiol. See “Suggested Readings” for citation.)

A Special Thank You to 2016 Leaders Society Volunteers

The DF Board of Directors offers its profound gratitude to those listed below, who each welcomed at least three (3) new members to the Leaders Society this year. Each of the volunteers recognized here devoted exceptional time and effort to ensure that tomorrow’s leaders have the early DF support they need to conduct the innovative research vital to strengthening the specialty for years to come.

- Misty D. Caudell, MD
- Yvonne E. Chiu, MD
- Robert P. Dellavalle, MD, PhD
- Rebecca L. Euwer, MD
- Eric S. Fromer, MD
- Sherri K. Kaplan, MD
- Carrie L. Kovarik, MD
- John C. Maize, Jr., MD
- Aaron Mangold, MD
- Elizabeth I. McBurney, MD
- John M. Pelachyk, MD
- Jack S. Resneck, Jr, MD
- Vera Y. Soong, MD
- Kathleen S. Stokes, MD
- Ruth A. Yates, MD
In a 3-D full-thickness reconstituted human skin model of psoriasis, delphinidin significantly enhances stratum corneum cornification in dose-related fashion, comparable to vitamin D₃ (Vit-D₃) and significantly more effective than retinoic acid (RA). (**P<0.01; ***P<0.0001). (Reprinted with permission from Karger. JC Chamcheu et al. 2015; Skin Pharmacol Physiol. See “Suggested Readings” for citation.)

Then Mukhtar et al. moved to the flaky skin mouse, a murine model of psoriasis, to see if topically applied delphinidin can minimize pathologic markers of psoriasiform lesions. And it did. Five-week-old mice were divided into 3 groups. Groups 2 and 3 were treated topically with delphinidin 5 times a week until 14 weeks of age. Control mice were treated with vehicle. Treatment “reduced psoriasiform lesion pathogenesis,” Mukhtar says. And he adds that it inhibited keratinocyte proliferation, spared keratinocyte differentiation, and improved the expression of epidermal tight junction proteins. Delphinidin treatment also inhibited proinflammatory cytokines, infiltration of macrophages and neutrophils, and increased the expression of AP-1 proteins,” he adds. Benefits equaled those achieved by vitamin D agents, and were superior to the performance of retinoic acid.

Most recently, Mukhtar and his team studied topically applied delphinidin in a psoriasis mouse model created by imiquimod application. They were highly encouraged to find inhibition of key kinases involved in psoriasis pathogenesis—a number of which are involved in the PI3K/Akt/mTOR pathway—and alleviation of the psoriasis-like disease in these mice (see graphs on page 17). Mukhtar concluded that “a novel PI3K/Akt/mTOR pathway modulator to treat psoriasis can be developed from delphinidin.”

Reviewing these consistently positive results, Mukhtar says that “these promising biological effects, coupled with the relatively low cost and toxicity of natural agents, combine to make delphinidin a highly promising agent for treating psoriasis and other hyperproliferative skin disorders.”

Conclusions

Mukhtar’s in vitro and preclinical studies with these plant-derived antioxidants for photochemoprevention and the treatment of psoriasis have produced results that clearly support the progression to clinical trials. He welcomes the opportunity to partner with interested colleagues.

Suggested Readings


The Dermatology Foundation is grateful to the following corporations for their generous contributions last year. Their support furthers the DF’s mission to develop and retain tomorrow’s leaders in the specialty, enabling advancements in patient care.

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Dr. Mangold was so grateful for the research award he received from the Dermatology Foundation when he was a resident at the Mayo Clinic in Phoenix, that he joined the Leaders Society just as soon as he could. “I wanted to pay it forward,” says Dr. Mangold, Assistant Professor at the Department of Dermatology at Mayo Clinic in Arizona. “It’s the minimum I can contribute, given the current economic environment we have for research. It is really critical that we have an organization like the Dermatology Foundation.” Soon after joining the Leaders Society in 2016, he volunteered to add his energy and enthusiasm to the national campaign and invite his Arizona colleagues to join him in leadership giving.

Dr. Mangold received a DF Medical Dermatology Career Development Award in 2015 for research on the prognostic value of inositol polyphosphate 5-phosphatase in cutaneous squamous cell carcinoma. In addition to his ongoing research, he maintains a busy clinical schedule. A main driver of dermatology’s appeal for him is the unique aspect “that we not only diagnose both common and very rare diseases, we also manage them.” In addition to his DF volunteer role, Dr. Mangold is already actively involved in his state and regional dermatology societies. He feels strongly that new dermatologists need to contribute to the leadership of their local, state and national communities to further the specialty at every level.

Given limited improvement expected in tight federal research funding, Dr. Mangold sees the DF’s work remaining essential to new investigators and becoming even more important to the future of the specialty. “It’s in a league of its own.” As both a volunteer and Leaders Society member, he shares that “the most important thing we can do is encourage young people to get involved—to make a commitment to their field. We need this organization.”