Unravelling Vitiligo’s Secrets—
And the Path to Durable Treatment

John E. Harris, MD, PhD, is dedicated to transforming care for people with vitiligo, the common and highly challenging autoimmune disease of the skin that inspired his passion for dermatology. About 1% of the population worldwide is affected with vitiligo’s disfiguring depigmented macules and patches. There are no FDA-approved medical treatments, and off-label treatments are time-consuming and typically only moderately effective. When treatment does restore pigmentation, it disappears again if treatment stops.

After his residency and initial vitiligo project at the University of Pennsylvania—creating an animal model that would vastly expand the research questions that could be posed—Harris joined the Department of Dermatology at the University of Massachusetts in 2010 and established the Vitiligo Clinic and Research Center. (He is now a tenured associate professor and department vice chair.) Harris and his team began a robust research program that seamlessly integrates basic, translational, and clinical investigations to tease out the cellular and molecular components of the autoimmune response that destroys melanocytes, and thus pigment, in lesional skin—and in severe disease, in hair as well. “We were inspired by the fact that so much progress has been made in psoriasis—a highly inflammatory autoimmune disease—in the past 25 years,” Harris notes. “The cytokines that drive this disease had been identified, and drugs targeting them were developed and proved to be extremely effective. But these drugs didn’t work for vitiligo—which told us that vitiligo involves different cytokines and a different part of the immune system,” he continues (see box on page 10). “And that’s what we needed to find out.”

This article tracks the novel and sometimes surprising immunologic portrait that Harris and his colleagues have been documenting (including the active immunologic role of keratinocytes), the therapeutic targets this has produced, imminent plans for human trials, and insights into the larger world of organ-specific autoimmune disease. Part of this sweeping progress includes the unexpected benefits of lucky encounters.

Direction: Vitiligo and Dermatology

After Harris entered the MD–PhD program at the University of Massachusetts and began his PhD research in a lab investigating juvenile diabetes, he realized that his fascination was with the underlying autoimmune pathology, not with studying or treating the disrupted endocrine function that results. Harris’s mentor encouraged his interest in autoimmune disease outside of the endocrine system and suggested that he pursue it via dermatology. Although Harris was excited to discover that many autoimmune diseases affect the skin, he was also strongly tempted by rheumatology. Then, back in medical school shortly after completing his PhD research, Harris ran into his doctoral mentor in a hallway late one night. “John—I have someone I want you to meet!” he said, and took Harris with him to the ICU.

“He introduced me to a 20-year-old woman with new-onset Type I diabetes, and asked me to do the physical exam,” Harris remembers. When she sat up so that he could listen to her lungs, he saw a sub-

(Continued on page 3)
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stantial patch of vitiligo on her back and asked when her skin disease had appeared. She told Harris that her diabetes and vitiligo—and two other autoimmune diseases—had all begun at the same time. He remembers his excitement as his future suddenly became obvious, “I could see her vitiligo. I could actually get my hands on her lesions! I could easily get skin samples to study the human disease and compare it to data from animal models! And vitiligo is linked to other immune diseases!” Dermatology was the ideal specialty for him. The autoimmune disease vitiligo would be an inspirational research and clinical focus, and Harris was pleased to learn that there were only a few labs worldwide studying it. Any research progress he made would have real impact.

Creating an Animal Model—The Essential First Step

Melanocytes synthesize melanin, providing color to skin, hair, and eyes while protecting against sun damage. Vitiligo involves a selective, progressive loss of melanocytes—and thus pigmentation—in the epidermis. When Harris made his commitment to study and ultimately treat vitiligo, CD8+ T cells were recognized as the agents of this melanocyte destruction, but there was no hint as to the essential cytokine pathway these T cells use to drive this disease—other than knowing that it is not TNF-α or IL-17, which are central to psoriasis. And patient skin had been found to contain higher than normal levels of the cytokine IFN-γ. IFN-γ is normally secreted by cells of both the innate and adaptive immune systems to trigger a cellular response to viral or microbial infection, but its role in the vitiligo disease process was a puzzle. The lack of an animal model meant there was no way to pursue these basic questions. Vitiligo primarily targets interfollicular melanocytes in human skin, but mice have melanocytes only in their hair follicles and existing vitiligo models involved only hair depigmentation. When Harris made his commitment to vitiligo, his first goal was to overcome this fundamental barrier.

He set his sights on engineering a mouse that produces epidermal depigmentation, the hallmark of human disease. It would have a prolific and permanent residential population of melanocytes in its skin, and its immune system would include cytotoxic cells specifically targeting these murine epidermal melanocytes. While Harris was still in medical school, he had actually begun to discover the components he needed. He needed to bring them together, then do the exacting work to create a more meaningful mouse model for vitiligo. He accomplished this during his combined research/residency program at the University of Pennsylvania and his post-residency fellowship year there. He also used his new model to begin exploring vitiligo itself, focusing on the action of IFN-γ in this autoimmune skin disease and then assessing its potential as a therapeutic target.

The Vitiligo Mouse Comes to Life

A transgenic mouse with black skin, reflecting the engineered presence of resident melanocytes in the epidermal basal layer and follicular epithelium, had already been created by B. Jack Longley, MD, a dermatopathologist at the University of Wisconsin, in his effort to study cutaneous mastocytosis and its hyperpigmented lesions. Longley had engineered this mouse with a mutant, overexpressed mast-cell growth factor called Kit ligand (KITL) protein. Other than the epidermal presence of melanocytes, all other cell populations were normal and representative of human skin. John T. Seykora, MD, PhD, on the dermatology faculty at UPenn, knew Longley and his work. He recommended Longley’s transgenic mouse to Harris as ideal for the vitiligo model he was conceiving, and introduced the two of them. Longley gave some of his mice to Harris to create his own population focusing on the action of IFN-γ in this autoimmune skin disease and then assessing its potential as a therapeutic target.

Harris’s first step in identifying the essential cytokine pathway that recruits and activates these T cells to produce vitiligo was to

protein, enriched in melanosomes, called PMEL. When these PMEL receptor CD8+ T cells were transferred to mice grafted with melanoma tissue, they shrank the human melanomas and—as a benign side effect that the researchers called vitiligo—also turned the mouse hair white. T cells with this same reactivity against PMEL had also been found in the blood of vitiligo patients. So in the context of melanoma they are therapeutic, but when they attack healthy melanocytes—as in vitiligo—they are pathologic.

These PMEL CD8+ T cells had been engineered to recognize both the mouse and human versions of PMEL, and Harris labeled them with green fluorescent protein so that their location and numbers could be tracked. He adoptively transferred them intravenously to his black-skinned mice, then expanded and activated these cytotoxic effector T cells by infecting the mice with a recombinant vaccinia virus that expresses human PMEL. Then Harris had to wait for a month or so to see if his approach was working or not, but epidermal depigmentation reliably appeared 4–5 weeks after the T cell transfer and activation. This pigment loss consistently involves the ears, rear footpads, and tail, and occasionally affects the nose and the trunk skin under the hair (see photos on cover). Stained sections of lesional skin from affected mice 5 weeks after induction of vitiligo revealed a patchy mononuclear infiltrate at the dermal-epidermal junction where melanocytes reside, as well as single-cell infiltration of the epidermis—highly resembling the findings in human disease.

IFN-γ and Vitiligo

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compare the immune proteins turned on in lesional vs nonlesional tissue, both in the mouse model and in human skin. “The most prominent one we saw in lesional skin from both was IFN-γ,” he says. “It was known to be secreted by CD8+ T cells. We also knew that it was required for successful melanoma immunotherapy. And there were no other prominent immunologic differences. So this was clearly the place to start.”

To determine if depigmentation requires IFN-γ, vitiligo was induced and then mice were treated with either a control antibody or one that neutralizes IFN-γ. In mice that began this treatment just 2 weeks after vitiligo induction, depigmentation was prevented. In those started long after induction when disease had stabilized, the antibody treatment reversed lesions that had already appeared. Tissue analysis showed that these anti-IFN-γ antibodies had dramatically reduced CD8+ T-cell accumulation in the skin in all instances, suggesting ongoing, active T-cell migration into the skin—a much more active portrait of depigmented skin than commonly thought—and pointing to IFN-γ as responsible for it. This made sense in terms of what was known about IFN-γ-dependent mechanisms that relate to T-cell homing to peripheral tissues—the local induction of chemokines, and the expression of adhesion molecules on endothelial cells.

Because the melanocyte niche in the basal layer of the epidermis is not vascularized, T cells that migrate into the skin—as in vitiligo—must navigate through the dermis to find their targets and mediate depigmentation. The specific signals that promote this melanocyte-specific T-cell migration into and through the skin during vitiligo were unknown. “Now that we had discovered that IFN-γ is so central to this disease process,” Harris says, “we wanted to know how it accomplishes this.”

Chemokines Enter the Picture: CXCL9, CXCL10, and CXCR3

Harris was still at UPenn, and the lab he was working in was studying the chemokines that IFN-γ induces. Chemokines are a family of small cytokines, with signaling dedicated to initiating and guiding the recruitment and migration of immune cells to sites of infection. (Continued on page 6)
Specialty Experts Chair Review of Research Award Proposals

DF Medical & Scientific Committee Chair: Lloyd S. Miller, MD, PhD—Pioneer in Combatting Staph Infections

Dr. Miller is an Associate Professor and Vice Chair for Research in the Department of Dermatology with joint appointments in the Departments of Medicine (Infectious Diseases), Orthopaedic Surgery, and Materials Science and Engineering at the Johns Hopkins University School of Medicine. He is internationally recognized for his trailblazing progress in understanding the body’s immune response and developing measures to prevent or treat infections caused by methicillin-resistant Staphylococcus aureus (MRSA).

Dr. Miller’s abiding passion for immunology had led him to dermatology. “The skin is an amazing immunologic organ that enables you to visualize the immune response in the patient and obtain tissue samples easily,” he says. When he began the Specialty Training and Advanced Research (STAR) program, the combined dermatology residency and post-doctoral research fellowship at UCLA, the most recent epidemic of MRSA infections—both hospital- and community-acquired—was peaking. The morbidity and mortality were extensive, and Dr. Miller saw “an unmet clinical need along with a major gap in understanding protective immunity.” He began to investigate immunity to S. aureus during his residency, eventually receiving a DF Dermatology Investigator Research Fellowship and subsequent NIH, industry, and foundation support.

Dr. Miller’s landmark discoveries have—among other benefits—uncovered immune mechanisms that helped guide vaccine and immunotherapies against S. aureus infections in humans, enriched capabilities for imaging infections, and led to the development of infection-resistant materials for prosthetic joints and other implants. His multiple appointments reflect this extensive spectrum of advances.

Dr. Miller received a DF Dermatology Investigator Research Fellowship in 2003 and 2004 to study the innate immune response to bacterial skin infections.

DF Clinical/Medical/Surgical/Dermatopathology Panel Chair: Anna L. Bruckner, MD, MSCS—Epidermolysis Bullosa Expert

Dr. Bruckner—Associate Professor of Dermatology and Pediatrics at the University of Colorado School of Medicine and Pediatric Dermatology Section Head at Children’s Hospital Colorado—is known internationally for her research and clinical expertise in epidermolysis bullosa (EB). She assumes Panel leadership after 4 years as a member. “I’ve been impressed with how rigorous and fair the evaluation process is,” Dr. Bruckner asserts. “It was a great honor to be asked to chair the Panel.”

Dr. Bruckner was set to become a pediatrician until her dermatology rotation at the end of medical school. “I was amazed on so many levels,” she recalls. “There were so many interesting conditions, and the people I was working with were truly one of a kind—smart, inquisitive, and great teachers.”

Dr. Bruckner completed residencies in pediatrics and dermatology, followed by a Fellowship in Pediatric Dermatology. She later earned a Masters in Clinical Science to gain formal training in clinical research methodology. Her outstanding expertise in EB was solidified with support from a DF Career Development Award, “and I cannot say enough about the importance of this award,” she notes. Today, she collaborates with basic science researchers working on genetic and protein replacement therapies, and also investigates emerging therapies through clinical trials.

Dr. Bruckner received a 1-year DF Research Grant in 2004 to study ichthyosis. In 2008 she received a Medical Dermatology Career Development Award to study epidermolysis bullosa.
or damage. Their names reflect their chemical structure, along with L to indicate ligand and R to indicate receptor. In the evolution of his vitiligo research, moving back and forth between his mouse model and patients, Harris found that the chemokines CXCL9 and CXCL10—the latter most especially—play significant roles in generating and maintaining vitiligo enabled by their common receptor, CXCR3.

Not only was CXCL10 highly expressed in patients’ skin and serum, but their autoreactive T cells expressed its receptor, CXCR3. These same observations were duplicated in the mouse model. Then Harris and his team repeated the vitiligo-creation steps with a critical difference. They engineered PMEL T cells lacking this chemokine receptor. The result was that disease-causing T cells did not accumulate in the skin, and depigmentation never occurred.

Then Harris carried out a series of experiments that eliminated the participation of either CXCL9 or CXCL10. In some, he knocked out the gene to prevent the chemokine’s synthesis; in others, he used an antibody to neutralize its actions. The results made it clear that CXCL9 helps to recruit T cells to the dermis, but it does not get them up to the melanocytes—so abrogating its presence did not reduce depigmentation. CXCL10 presents a very different story. It directs T-cell migration within the skin, bringing these autoreactive T cells from the dermis into the epidermis, where they find and destroy melanocytes. And abrogating its behavior dramatically reduced depigmentation.

Next, Harris wanted to see if neutralizing CXCL10 would also reverse disease once it was established. He took the 30% of mice with the most severe disease (ie, >50% depigmentation of their tails) and treated half of them with a placebo (an isotype control antibody), and half with a CXCL10-neutralizing antibody. Harris checked the mice daily after treatment began. Depigmented lesions in the placebo-treated mice showed no change as time progressed. But about 4 weeks after the neutralizing antibody treatment had begun in the experimental group, Harris suddenly saw the first signs of repigmentation. It was coming from the hair follicles on the tail (see box above).

“Vitiligo depends on this single chemokine,” Harris says. The central role of CXCL10 was now clear.

Harris remembers his elation and “incredible sense of discovery” when he spotted that very first evidence of returning pigmentation. “Part of it was the excitement from knowing that I had reasoned this out correctly, and my hypothesis was accurate. And the other part was realizing that this could actually be useful to patients who suffer with this disease!”

Harris sums up this group of observations. “We were able to show by several approaches that we could prevent vitiligo by blocking the process early, and also reverse it once depigmentation had already begun. These results also identified CXCL10 as a critical mediator of vitiligo pathogenesis in our mouse model of disease.”

These results also overturned the conventional conception of vitiligo lesions as merely an inactive state once depigmentation was complete. Instead, Harris had discovered, depigmentation has to be actively maintained. The ongoing recruitment of autoreactive CD8+ T cells to the epidermis—ensured by the chemokine CXCL10—is essential. Without this active maintenance, the melanocyte community will re-establish itself in lesional skin and restore pigmentation.

Combining these results with their initial success in blocking the involvement of IFN-γ strongly suggested early on that Harris had found the central cytokine pathway that drives this disease (see illustration on page 8).

Harris has a favorite analogy for explaining what chemokines do in producing vitiligo: “Imagine it’s summertime, and you’re walking up your driveway eating an ice cream cone that’s melting and leaving tiny drops spattering the ground behind you. A single ant wandering by happens on one of those drops, and within just a few minutes that same drop will be covered with 1,000 ants. The ant had emitted a chemical signal that drew the others—and this is a lot like what happens in vitiligo,” he adds. “The initial CD8+ T cell entering the epidermis finds a melanocyte and binds to the PMEL protein on its membrane, which causes it to secrete IFN-γ, which in turn activates these chemokines that are secreted locally at very high levels,” he continues. “Other CD8+ T cells pick up these intensely attractive chemokine signals, follow the scent, and flood in. They destroy the melanocytes in that area—and that is where the first spot of vitiligo forms.”

The Keratinocyte’s Unexpected Central Role

It was clear then that disease pathogenesis depended on IFN-γ and the chemokines it induced to promote T-cell recruitment to the epidermis where melanocytes reside. “But the skin is a complex organ,” Harris emphasizes. “It is much like the gut, another epithelial tissue that interfaces with the environment, contains a variety of resident cells, and is vulnerable to multiple inflammatory diseases. We knew it would be helpful to develop a more precisely defined sense of the vitiligo microenvironment and the distinct cellular contributions,” he adds. This would provide a mechanistic understanding of disease pathogenesis that might highlight and clarify therapeutic strategies. And sometimes this leads to interesting surprises.

Harris and his team conducted their search for greater clarity and detail using their vitiligo mouse model, in addition to a chemokine reporter mouse with chemokines fluorescence-labeled for tracking their expression, and patient tissue as well. They found that the initial inflammatory signals initiated by a small number of autoreactive T cells are then amplified by widespread chemokine production. “This transforms the epidermis into a chemokine-high niche in both the mouse model and human disease,” Harris notes.

The reporter mouse data characterized significant differences in the behavior and impact of CXCL9 and CXCL10. They bind to different regions of receptor-bearing cells, they mediate slightly different signals, their timing is different, and they reflect different aspects of disease activity. CXCL9 appears first, in sync with its role as a “recruit” signal. CXCL10 is a “fine-tune function” signal that appears somewhat later and reflects disease severity. This agreed with observations in human patients showing that both chemokines correlate with disease activity, but only CXCL10 reflects severity. This raises the possibility that targeting both chemokines may be necessary to treat active disease, but it may be possible to treat stable disease by blocking CXCL10 alone.

Harris wanted to home in on the source of this greatly increased chemokine presence. Keratinocytes were the logical candidate because they substantially outnumber other epidermal cell types in both mice (by 25:1) and humans (36:1). Immunohistochemistry on patient lesional skin confirmed this. Going back to the mouse,
Harris and his team engineered animals reflecting a series of eliminations, knocking out in turn the various possible sources for producing the IFN-γ signaling that initiates the explosion in chemokine production. Knocking out each of the immune cell populations in the epidermis had no impact on the appearance and progression of vitiligo lesions. But eliminating the keratinocytes' ability to respond to IFN-γ eliminated the chemokines and T-cell influx, and protected the animals from disease.

“Our mouse and human data showed us that keratinocytes are the major chemokine producers throughout the course of disease,” Harris explained. They actively participate and amplify the signal that brings in the flood of autoimmune T cells. The T cells themselves make just a very small amount of IFN-γ. This stimulates all of the keratinocytes in that area to begin making substantial amounts of CXCL9 and CXCL10, which they continue to produce steadily.

And this potent signal amplification by the keratinocytes turns out to be a key in contemplating therapeutic possibilities. “We found that inhibiting IFN-γ signaling only in keratinocytes is an effective treatment for vitiligo in these mice,” Harris points out. “This told us that if we can find a way to block IFN-γ signaling with a topical drug, which would treat the keratinocytes and only the keratinocytes, that could be a useful treatment.” And now this appears to be in progress, targeting the JAK-STAT (Janus kinase–signal transducer and activator of transcription) pathway. This pathway interacts with signals from cytokine receptors in a way that is essential for the cytokines' bio-

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logical activity (see illustrations at right and on page 14). The JAK inhibitors tofacitinib and ruxolitinib have been approved by the FDA for other diseases. An open-label clinical trial has reported efficacy for topical ruxolitinib in patients with vitiligo, in particular for facial involvement. Harris and his group are participating in two clinical trials in progress now, with more on the way.

Resident Memory T Cells and IL-15—A Potential Game Changer

This most recent study—and the one that Harris anticipates will have the most profound impact on treatment—was stimulated by the hallmark aspect of all existing treatments for vitiligo, both those currently used and those under investigation. No matter how complete repigmentation may be, once treatment is discontinued, the depigmented spots typically reappear right away—and in exactly the same locations. “This told us there has to be autoimmune memory in the skin,” Harris explains.

Studies appearing over the previous five years had described immune memory in the skin—also involving CD8+ T cells—against certain viruses. After the CD8+ T cells flood in and clear the virus, most of the T cells exit the skin. A very few sentinels remain behind as a precaution, so that if the virus ever returns a new immune response can be mounted immediately. These are called resident memory T cells (Trm). The involvement of CD8+ T cells suggested to Harris that autoimmune memory in vitiligo may well share this same pathway. “So we began looking for these memory T cells—and we found them, in our mouse model and in patient skin!” he says. Three other groups studying vitiligo had had the same suspicion at around the same time, and also documented the presence of Trm. It was clear that this memory phenomenon occurs in vitiligo, but no one had found a way to prevent the resident sentinels from forming, or to eliminate them once they appeared on the scene. Harris and his colleagues were determined to find a way.

Until then, studies of Trm had all been in the context of viral infections, with the goal of finding a way to have more of these vigilant cells, not less. “Our goal was finding a way to get rid of them,” Harris explains. “But how?” He and his team were stumped.

While they were trying to find some guidance, Harris had an incredibly lucky encounter at a Gordon Research Conference that he attended several years ago. He happened to meet Thomas Gebhardt, MD, an immunologist from the University of Melbourne in Australia. Not only did Gebhardt specialize in viral infectious diseases, but in particular, he was doing exciting work with PMEL. He had recently shown that IL-15 is required for their formation, as an IL-15 knockout mouse has only minimal numbers of them.

Harris, though, needed to know more. Is IL-15 required only for the formation of these specialized memory T cells, or for all their continued existence over time? He and his coworkers decided to find out if IL-15 is indeed a survival factor. And if the answer is yes, then IL-15 could be a treatment target. The goal of durable treatment might become a reality. “But we were stumped as to how to explore this,” Harris recalls. “A vitiligo mouse with IL-15 knocked out would only replicate Gebhardt’s work demonstrating that Trm will not form without it. It could not show us if IL-15 is also essential to survival once they are formed.”

Then Harris had another chance encounter—with J.Xun Tso, PhD, a scientist with decades of experience developing therapeutic antibodies. They had each been invited to speak at a meeting on alopecia areata because of their respective cutting-edge research on autoimmune diseases closely related to alopecia areata. Harris was studying vitiligo, and Tso was probing juvenile diabetes. By chance they ended up sitting next to each other in the audience during a panel session, having no idea who the other one was. “We got to talking,” Harris remembers. “Then at one point, Tso mentioned that he had developed an IL-15 antibody. And I said: ‘We have these resident memory T cells that we think might be dependent on IL-15, and we’re looking for a way to test this.’ Tso responded: ‘Oh . . . I’ll send you my antibody.’ He did,” Harris says. “And we tested it. And it worked—and the rest is history!”

Inhibiting IL-15—The Specifics

IL-15 is constitutively secreted by a large number of cell types, keratinocytes included. It was regarded early on simply as a T-cell growth factor, but is now recognized to play an important role in innate and adaptive immunity. This includes directing the killing of virus-infected cells. The biology of the IL-15 receptor is complex. Its structure can involve from one to three modules (named CD122, CD215, and CD132), with different combinations depending on the cell expressing it and the local setting. One of the single receptor-modules is CD215, the membrane-bound receptor for IL-15 that the keratinocyte expresses at the same time as IL-15. Memory T cells entering the epidermis in vitiligo express the exclusive combination of CD122 + CD132 (CD132 is also a receptor subunit for at least a half dozen other interleukins).

Producing IL-15 and its CD215 receptor at the same time enables the keratinocyte to capture and display this cytokine instantly preventing it from moving away into the dermis or bloodstream. This maintains the epidermis as a high-IL-15 zone that keeps memory T cells in the immediate area and enables them to interact with IL-15. Some of these memory T cells are the Trm responsible for rapidly re-establishing vitiligo lesions when treatment stops.

Tso’s IL-15 antibody targeted CD122. Harris and his team began intraperitoneal treatment 3x weekly at 12 weeks after initiation of vitiligo, a point representing long-standing, stable disease. They assessed both short-term (2 weeks of maintenance dosing) and long-term (8 weeks of maintenance dosing) treatment, and documented durable repigmentation in their vitiligo mouse with each regimen (see photos on page 10). Short-term blockade was accompanied by reduced effector function of PMEL Trm, measured by a substantial drop in IFN-γ production. Long-term blockade fully depleted all of the PMEL T cells from the skin, including the Trm. “Taken together, the data indicate that CD122 blockade may be used to treat vitiligo and that longer systemic administration results in depletion of autoreactive Trm and other memory T cell pools,” Harris states.

Then they added one further variation: “Because short-term systemic administration of the anti-CD122 antibody had durably reversed (Continued on page 10)
What a Difference DF Funding Can Make

John E. Harris, MD, PhD, is on the verge of radically transforming care for patients suffering with vitiligo, a common and disfiguring autoimmune disease with, as yet, no FDA-approved medical treatments. He has progressed rapidly in advancing knowledge of the autoimmune pathways that cause this disease and now is closing in on a treatment goal that has remained unmet—skin that remains normal after treatment is stopped. Dr. Harris has developed a highly targeted treatment that inhibits a novel pathway. He and his team have confirmed its capability in the mouse model he developed, and now they are preparing to move to clinical trials.

Dr. Harris began his research with a 1-year DF Research Grant (2008) for In Vivo Imaging of Cellular Events in a Mouse Model of Autoimmune Vitiligo, and completed this project with a 1-year DF Dermatologist Investigator Research Fellowship (2009). A 3-year DF Research Career Development Award (2010–13) supported Defining the Autoimmune Response in Vitiligo. In 2014, he received a 3-year DF Stiefel Scholar Award to investigate Skin-resident Memory T Cells in Vitiligo (made possible by the generous gift of Charles and Daneen Stiefel).

Current therapies—whether off-label treatments or more helpful targeted drugs (experimental or repurposed) in clinical trials—suffer from the same deeply frustrating drawback. The disfiguring depigmented lesions return just as soon as treatment stops. Dr. Harris eventually realized that lesional skin must contain some kind of autoimmune memory that immediately reactivates the melanocyte-destructive events when treatment is discontinued. He found the source (resident memory T cells [T_{RM}]), learned that the cytokine IL-15 is critical to maintaining them, and successfully pursued a way to inhibit IL-15 locally and eliminate them. This IL-15 inhibitor produces what seems like a miracle in the vitiligo mouse. Brief treatment not only consistently reverses this disease and restores pigment to affected skin—but the effects last long after treatment has been discontinued. Now human trials are on the horizon.

“This treatment currently holds the most promise for durable therapy, and would not have been possible without the DF,” Dr. Harris emphasizes. “The research bringing it to this point was funded primarily by my DF Stiefel Scholar Award, supplemented by private philanthropy,” he adds. “I did not have NIH funding for this study.”

Dr. Harris is grateful for the investment that the DF made in him at critical junctures, beginning with his first project. Dr. Harris developed an animal model—the vitiligo mouse—to enable meaningful research in his lab and others to progress. His Stiefel Scholar Award—supporting the study that he anticipates will have a profound impact on treatment—“came at a particularly important time, allowing me to continue moving forward despite limited and uncertain funding from the NIH.” Now he anticipates a safe and short-term treatment with long-lasting effects—an exciting new option for vitiligo patients.

“Providing funding for deserving research is key to continued significant progress in the ability of dermatologists to care for their patients,” Dr. Harris underlines. “And the Dermatology Foundation is one of the most important groups doing this. I'm a big believer in the Dermatology Foundation!”
T Cells and Their Inflammatory Cytokines—A Thumbnail Sketch

The job of T cells is to detect and protect us from threats, and each of the three response branches has a specific focus. Normally the system works well, but sometimes these protective responses hold the potential to go awry and target healthy self cells. The result is autoimmune disease. **Type 17 cytokine responses** are designed to fight extracellular organisms, threats like bacteria and yeasts. This pathway was eventually found to drive the pathology of psoriasis as well, and that disease is successfully treated now by biologics that inhibit its activity. **Type 2 cytokines**, which normally recognize and protect against multicellular parasites such as worms and flukes, were discovered to be active in early atopic dermatitis. Recent biologic drugs targeting this pathway have dramatically improved management of this chronic inflammatory skin disease. **Type 1-dependent cytokines**—the route involved in vitiligo—normally protect against intracellular threats, cells that have become potentially dangerous because they have been altered by malignant transformation or by the incorporation of a virus. The CD8+ T cell subgroup equipped to recognize melanocytes normally protects against melanoma. But in some people it responds to normal melanocytes as if they are the enemy. Current research will ultimately result in biologic drugs to reverse these changes and prevent their recurrence.

Disease, we decided to test a short course of local, intradermal treatment to determine if we could achieve similar clinical efficacy with less drug and less impact on circulating T cell populations," Harris explains. They began at 12 weeks after vitiligo induction with a loading dose for 2 weeks, then 2 weeks of maintenance. Then they stopped treatment—and watched over the next 10 weeks as significant repigmentation occurred in the experimental group of mice.

Harris concluded that "targeting IL-15 in vitiligo—unlike existing therapies—could provide a durable treatment option for patients, with longstanding effects after a limited treatment course." Crucial to this is blocking the interaction of the autoreactive T cell with the keratinocyte-presented IL-15—and this is exactly what the anti-CD122 antibody enabled.

**IFN-γ and IL-15: A Cooperative Relationship**

These two cytokine pathways have a temporal relationship, and are responsible for two different anti-melanocyte T cell populations. IFN-γ, working with CXCL9 and CXCL10 and the CXCR3 chemokine axis, brings the causal autoreactive T cells into the skin and then the epidermis. Then, after they encounter IL-15 presented on the keratinocytes that express it, these autoreactive CD8+ T cells upregulate IFN-γ production at the dermal-epidermal junction to bolster their function, and become dependent on IL-15 for their survival as they establish residence in the epidermis and destroy the melanocytes there. At some point Tumor necrosis factor, the Tumor necrosis factor signal for more T cells via IFN-γ, CXCL9, and CXCL10. "It's a self-perpetuating situation," Harris says. "They come in to hold the fort, and call in reinforcements when they're needed." And the keratinocyte produces both of these cytokines, somewhat like an orchestra conductor leading a complex piece of music and bringing in the different groups of instruments when needed.

**Looking at Treatments**

Current medical treatments for vitiligo—topical steroids, calcineurin inhibitors, and narrowband UVB (nbUVB) phototherapy—are all off-label. These non-targeted, moderately effective approaches all involve significant shortcomings. Narrowband ultraviolet B light is only provided in select facilities and requires time away from work or school multiple times a week. Topical steroids are impractical when large body surface areas are affected, and they carry the risk of systemic absorption with suppression of the adrenal axis, in addition to striae and skin atrophy. Topical calcineurin inhibitors appear to have fewer of these risks, but they are costly and less effective, and treat only focal disease. Although potent forms of systemic immunosuppression have been reported to halt disease progression and result in repigmentation, the risks are substantial and usually deemed unacceptable compared to the benefits. So finding an effective targeted therapy with a good safety profile would be a significant advance. Even better would be a treatment that is durable, and thus can be stopped for a substantial length of time once repigmentation is complete. And the ideal is treatment that will permanently eliminate the disease.

Beginning their search for better treatments for vitiligo patients, Harris and his team looked in several directions. Attempting to repurpose existing drugs is extremely appealing because safety data are already available and regulatory approval for a new use would be expedited. Developing a new drug in line with his breakthrough understanding of the pathways driving vitiligo involves far greater effort, but may hold more substantial promise of highly durable or permanent results.

**Repurposing Medications**

IFN-γ signaling turns out to require activation of STAT1 (signal transducer and activator of transcription 1) (see illustrations on page 8 and page 14), and recent in vitro studies of the cholesterol-lowering medication simvastatin had shown that it can also inhibit STAT1. Harris and his team first tried it in his mouse model and were pleased with the results. It prevented vitiligo when given right after induction, and reversed depigmentation after lesions were present. Although simvastatin did not affect serum CXCL10 levels, it did reduce the number of autoreactive CD8+ T cells infiltrating the skin. Adding simvastatin to cultures of these melanocyte-specific CD8+ T cells upregulates IL-15, which normally recognize and protect against multicellular parasites such as worms and flukes, were discovered to be active in early atopic dermatitis. Recent biologic drugs targeting this pathway have dramatically improved management of this chronic inflammatory skin disease. **Type 1-dependent cytokines**—the route involved in vitiligo—normally protect against intracellular threats, cells that have become potentially dangerous because they have been altered by malignant transformation or by the incorporation of a virus. The CD8+ T cell subgroup equipped to recognize melanocytes normally protects against melanoma. But in some people it responds to normal melanocytes as if they are the enemy. Current research will ultimately result in biologic drugs to reverse these changes and prevent their recurrence.

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**Durable treatment.** Treatment with the anti-CD122 antibody reverses disease in mice with established vitiligo, and to an equal degree whether given long-term (top photos) or short-term (bottom photos). (From JM Richmond et al. See Suggested Readings. Reprinted with permission from AAAS.)
CHART A COURSE TO SYMPTOMATIC RELIEF

The efficacy of Class 1 halobetasol with safety proven for up to 8 weeks of dosing

A NEW POTENCY CLASS OF STEROID LOTION

BRYHALI™ (halobetasol propionate) Lotion, 0.01% is a corticosteroid indicated for the topical treatment of plaque psoriasis in adults.

Important Safety Information

Warnings and Precautions
- BRYHALI Lotion has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis during treatment or upon cessation of treatment; periodic evaluation may be required.
- Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hyperglycemia, and glucosuria.
- Children may be more susceptible to systemic toxicity when treated with topical corticosteroids.
- Local adverse reactions may include atrophy, striae, telangiectasias, hypopigmentation, and allergic contact dermatitis. Some local adverse reactions may be irreversible.
- Use of topical corticosteroids may increase the risk of posterior subcapsular cataracts and glaucoma. If visual symptoms occur, consider referral to an ophthalmologist.
- Use an appropriate antimicrobial agent if a skin infection is present or occurs, and if prompt response is not seen, discontinue use until infection has been adequately treated.
- Discontinue BRYHALI Lotion if allergic contact dermatitis occurs.

Adverse Reactions
- The most common adverse reactions (≥1%) were upper respiratory tract infection, application site dermatitis, and hyperglycemia.

To report SUSPECTED ADVERSE REACTIONS, contact Customer Service at 1-800-321-4576 or FDA at 1-800-FDA-1088.

Please see Brief Summary of full Prescribing Information on following page.
BRYHALI™ (halobetasol propionate) Lotion, 0.01% is indicated for the topical treatment of plaque psoriasis in adults.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS

Hypothalamic-Pituitary-Adrenal (HPA) Axis Suppression
BRYHALI has been shown to suppress the hypothalamic-pituitary-adrenal (HPA) axis. Systemic effects of topical corticosteroids may include reversible HPA axis suppression with the potential for glucocorticoid insufficiency. This may occur during treatment or upon withdrawal of treatment with the topical corticosteroid.

The potential for hypothalamic-pituitary-adrenal (HPA) axis suppression with BRYHALI was evaluated in a study of 19 adult subjects with moderate to severe plaque psoriasis involving ≥20% of their body surface area (BSA). HPA axis suppression was reported for 1 (5.6%) subject at Week 4 and for 3 (15.8%) subjects at Week 8. All 3 subjects had normal HPA axis suppression test with discontinuation of treatment [see Clinical Pharmacology in full Prescribing Information].

Because of the potential for systemic absorption, use of topical corticosteroids, including BRYHALI, may require that patients be evaluated periodically for evidence of HPA axis suppression. Factors that predispose a patient using a topical corticosteroid to HPA axis suppression include the use of more potent corticosteroids, use over large surface areas, occlusive use, use on an altered skin barrier, concomitant use of multiple corticosteroid-containing products, liver failure, and young age. An adrenocorticotropic hormone (ACTH) stimulation test may be helpful in evaluating patients for HPA axis suppression.

If HPA axis suppression is documented, attempt to gradually withdraw the drug, reduce the frequency of application, or substitute a less potent steroid. Manifestations of adrenal insufficiency may require supplemental systemic corticosteroids. Recovery of HPA axis function is generally prompt and complete upon discontinuation of topical corticosteroids. Systemic effects of topical corticosteroids may also include Cushing’s syndrome, hyperglycemia, and glucosuria. Use of more than one corticosteroid-containing product at the same time may increase the total systemic exposure to corticosteroids. Pediatric patients may be more susceptible than adults to the effects of systemic toxicity from the use of topical corticosteroids due to their larger surface-to-body mass ratios [see Use in Specific Populations].

Concomitant Skin Infections
Use an appropriate antimicrobial agent if a skin infection is present or develops. If a favorable response does not occur promptly, discontinue use of BRYHALI until the infection has been adequately treated.

Allergic Contact Dermatitis
Allergic contact dermatitis with corticosteroids is usually diagnosed by observing failure to heal rather than noting a clinical exacerbation. Consider confirmation of a clinical diagnosis of allergic contact dermatitis by appropriate patch testing. Discontinue BRYHALI if allergic contact dermatitis occurs.

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 clinical practice. In randomized, double-blind, multicenter, vehicle-controlled clinical trials, 426 adults with plaque psoriasis were treated with BRYHALI and had post-baseline safety data. Subjects applied BRYHALI once daily for up to eight weeks. Table 1 presents adverse reactions that occurred in at least 1% of subjects treated with BRYHALI and more frequently than in vehicle-treated patients.

Table 1: Adverse Reactions Occurring in ≥1% of the Subjects Treated with BRYHALI through Week 8

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>BRYHALI (N=284)</th>
<th>Vehicle (N=142)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Application Site Dermatitis</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1%</td>
<td>0%</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

Pregnancy
Risk Summary
There are no available data on BRYHALI use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

In animal reproduction studies, increased malformations, including cleft palate and omphalocele, were observed after oral administration of halobetasol propionate during organogenesis to pregnant rats and rabbits. The available data do not support relevant comparisons of systemic halobetasol propionate exposures achieved in the animal studies to exposures observed in humans after topical use of BRYHALI.

The background risk of major birth defects and miscarriage in the clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data
Halobetasol propionate has been shown to cause malformations in rats and rabbits when orally administered during organogenesis at doses of 0.04 to 0.1 mg/kg/day in rats and 0.01 mg/kg/day in rabbits. Halobetasol propionate was embryotoxic in rabbits but not in rats. Cleft palate was observed in both rats and rabbits. Omphalocele was seen in rats but not in rabbits.

Lactation

Risk Summary
There are no data on the presence of halobetasol propionate or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production after treatment with BRYHALI.

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. It is not known whether topical administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in human milk.

The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BRYHALI and any potential adverse effects on the breastfed child from BRYHALI.

Clinical Considerations
Advise breastfeeding women not to apply BRYHALI directly to the nipple and areola to avoid direct infant exposure.

Pediatric Use
Safety and effectiveness of BRYHALI in pediatric patients under the age of 18 years have not been evaluated.

Because of higher skin surface area to body mass ratios, pediatric patients are at a greater risk than adults of HPA axis suppression and Cushing’s syndrome when they are treated with topical corticosteroids. They are therefore also at greater risk of adrenal insufficiency during or after withdrawal of treatment. Adverse reactions including striae have been reported with use of topical corticosteroids in infants and children [see Warnings and Precautions].

HPA axis suppression, Cushing’s syndrome, linear growth retardation, delayed weight gain, and intracranial hypertension have been reported in children receiving topical corticosteroids. Manifestations of adrenal suppression in children include low plasma cortisol levels and an absence of response to ACTH stimulation. Manifestations of intracranial hypertension include bulging fontanelles, headaches, and bilateral papilledema [see Warnings and Precautions].

Geriatric Use
Of 284 subjects exposed to BRYHALI in clinical trials, 61 subjects were 65 years or older. Clinical trials of BRYHALI did not include sufficient numbers of subjects age 65 years and older to determine whether they respond differently from younger subjects.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of halobetasol propionate.

Halobetasol propionate was not genotoxic in the Ames assay, in the sister chromatid exchange test in Chinese hamster somatic cells, in chromosome aberration studies of germinal and somatic cells of rodents, or in a mammalian spot test. Positive mutagenicity effects were observed in a mouse lymphoma gene mutation assay in vivo and in a Chinese hamster micronucleus test.

Studies in rats following oral administration of halobetasol propionate at dose levels up to 0.05 mg/kg/day indicated no impairment of fertility or general reproductive performance.

PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Patient Information).

Manufactured for:
Dow Pharmaceutical Sciences, a division of Valeant Pharmaceuticals North America LLC
Bridgewater, NJ 08807 USA

By:
Valeant Pharmaceuticals International, Inc.
Laval, Quebec H7L 4A8, Canada

U.S. Patent Numbers: 6,017,847 and 8,809,307

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Based on 9652102
November 2018

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cells diminished their proliferation and reduced IFN-\(\gamma\) production. A patient who had repigmented with simvastatin was described in a case report. But Harris’s follow-up with a 6-month double-blind, placebo-controlled phase II clinical trial was disappointing. He observed 15 men, ages 18–64, with lesions affecting from 3% to 50% of their body surface area (BSA). After other therapies had been discontinued for the necessary time period, the treatment group received 40 mg of simvastatin daily for the first month, then 80 mg daily for the remainder. “The treatment group actually experienced an average worsening of disease,” Harris reports. One patient in particular experienced an episode of inflammatory flare, although ultimately he partially repigmented. The study overall “does not support the use of oral simvastatin for treating vitiligo,” Harris says. This may actually reflect the dosing limitations when it comes to human use to avoid potential toxicity. Long-standing disease may also hinder responsiveness.

Harris collaborated with Brett King, MD, PhD, a dermatologist in the department at Yale University, to look at the therapeutic effect of the oral JAK inhibitor tofacitinib. The JAK-STAT pathway is critical to cytokine function in general, and success had been reported in using tofacitinib to treat severe alopecia areata, another autoimmune disease that often co-occurs with vitiligo and also involves CD8+ T cells and IFN-\(\gamma\). “This suggests that a helpful targeted therapy in one disease may also be effective in the other,” Harris explains. With a few case reports already pointing in this direction, King led the effort to examine a 10-patient retrospective series. Their review revealed that tofacitinib treatment had led to repigmentation only when paired with concomitant light exposure, either sunlight or nbUVB phototherapy. Although there was no apparent effect when tofacitinib was used as monotherapy, it achieved repigmentation even when paired with normally ineffective nbUVB doses. For some patients, even normal daily sun exposure was sufficient. This was informative. King concluded that repigmentation requires two different actions to occur simultaneously—suppression of inflammation in lesional skin plus stimulation of melanocytes to leave their stem cell niche in the hair follicle bulge to seed the epidermis (see box on page 6).
Tofacitinib is significantly more effective at suppressing the inflammation, and phototherapy has good efficacy at melanocyte stimulation. Harris would like to see prospective clinical trials.

**Research-Generated Therapy: CXCR3 Inhibition as Possible Treatment**

Harris also began to think about the possibility that inhibiting CXCL10’s receptor—CXCR3—might present an approach to vitiligo therapy (see illustration at right). Interestingly, there was already a pipeline of drugs that had been inspired quite some time ago when this IFN-γ pathway had first been discovered but before it had been linked to vitiligo. People suspected that it probably played an important role in inflammatory diseases, and the anti-CXCR3 drugs that emerged from development were tested in psoriasis, Crohn’s disease, inflammatory bowel disease, rheumatoid arthritis, and lupus. Disappointingly, they had provided little benefit. Eventual progress in understanding T-cell pathways and recognizing that none of those autoimmune diseases are dependent on IFN-γ signaling explained this string of failures. And now Harris had identified vitiligo as an IFN-γ-dependent disease.

He began by treating his mouse model from 2 to 7 weeks after vitiligo induction, comparing two alternatives. One was an antibody that simply neutralized CXCR3 function and thus blocked the migration of autoreactive CD8+ T cells into the skin. The other was an antibody that actually depleted the cells expressing the chemokine receptor. This turned out to be significantly more effective, because it actually removed the autoreactive cells rather than simply not allowing their entry. It also “outperformed other treatments we have previously explored in this model,” Harris said. He saw this as the most encouraging possibility at that point.

**In Memory of Dr. Stephen Katz—An Extraordinary Leader**

Stephen I. Katz, MD, PhD, passed away suddenly in the early morning of December 20. “Dermatology and the greater universe of medicine have lost one of our foremost leaders,” said Dr. Kim B. Yancey, president of the Dermatology Foundation. “Though our sense of loss is profound, it will be eclipsed by the joy, warmth, optimism, and wisdom that Steve brought to the lives of so many.”

Dr. Katz has held a prominent role in the advancement of dermatology through his outstanding tenures as Chief of the Dermatology Branch of the National Cancer Institute (1977–2001) and Director of NIAMS (since 1995). His work on cutaneous immunity was foundational. Often recognized as a remarkably gifted teacher, he has educated, trained, and inspired generations of dermatologists who, in turn, have had national and international impact. More than 20 of Dr. Katz’s trainees have gone on to become department chairs. His seminal impact on progress in the specialty is reflected in part by the eminent scientific institutions that elected him to membership and by the exceptional number of awards and accolades he has received over the years.

A former trainee, now a department chair, remarks that “Steve’s scientific, clinical, and educational strengths are complemented by a deep humanism, warmth, and sense of humor that made him not only a teacher, but a mentor, a role model—and a friend.”

The 2013 recipient of the DF Lifetime Career Educator Award, Dr. Katz humbly described the essence of his satisfaction with his career in dermatology. It has been “in teaching, and in developing a core of scientists who went on to develop their own independent leadership positions in the U.S. and around the world. That is tremendously satisfying—and gives me great joy.”

The Dermatology Foundation extends its heartfelt condolences to Dr. Katz’s family and to his friends across the globe. We are also deeply thankful for the profound impact he has had on the specialty as an outstanding scientist, influential educator, and exceptional leader.
form. But may take years for the lesions to return, and when they do, the patient can be retreated successfully. Harris is in the midst of planning for a clinical trial, and the best source for keeping up to date with opportunities to enroll in this or any other potential trials is his newsletter, Vitiligo Clinic and Research Center News. Sign up for it with the following link: https://www.umassmed.edu/vitiligo/about/subscribe/ "We welcome patients and dermatologists getting in touch," Harris says.

In Progress and On the Horizon  
Michael D. Rosenblum, MD, PhD, an immunodermatologist at the University of California, SF, is doing foundational research on the central preventive role of skin-resident regulatory T cells (Tregs) in cutaneous autoimmune disease (see Dermatology Focus, Winter 2017/18). It was known that eliminating Tregs increases the severity of vitiligo many times over, and Harris and Rosenblum began a collaborative project several years ago to find out why. Published research from other labs has also implicated an important role for Tregs in vitiligo, but the details have been contradictory. Harris and Rosenblum believe they can contribute to understanding their role, including data from several new studies in human patients that they are preparing for publication.

Harris and his group are participating in clinical trials on JAK inhibitors, although the lesions return just as soon as treatment is discontinued.

The more that Harris and his team learn about the factors and interactions that initiate and maintain vitiligo, the more complex the scenario becomes—and the more they realize what remains to be learned. His vitiligo mouse model remains integral to this progress. “We frequently start with hints from our mouse model,” Harris explains. “Then we look at human skin to make sure those hints are present, and make sense. We construct a hypothesis incorporating what we know, then we jump back to the mouse model to test it mechanistically and functionally by knocking out or inhibiting a critical component.” At this point, Harris et al. have hatched out two immune pathways in vitiligo, one involving IFN-γ with CXCL9 and CXCL10, the other with IL-15 and T₃₂₃.

“Our more immediate goal is identifying the most effective target for therapeutic intervention to achieve a durable reversion to normal skin—and I think our anti-IL-15 treatment will fill that need,” Harris points out. “My goal is to continue digging deeper and deeper,” he adds, “and continue improving treatment.” Harris and his team are using cutting-edge technologies to dig below the surface. “Our ultimate goal is a cure—completely eliminating all components of vitiligo—and that is going to require a still greater depth of understanding of this disease.”

Final Thoughts—Starting at the Beginning

Stressed melanocytes emit a signal that is misinterpreted by the autoreactive CD8+ T cells to mean that they have been damaged and must be eliminated (see illustration on page 14). This stress is produced by environmental factors in some cases, and is genetically based in others.

“Perhaps the most important details yet to be worked out,” Harris muses, “revolve around how melanocytes signal stress in vivo, how this stress signal is interpreted by the immune system, and how this leads to disruption of immune tolerance.” And in a broader framework, Harris suspects that research in vitiligo may be the future key to understanding the pathogenesis of organ-specific autoimmunity in general—especially in cases where the target organ is less accessible than the skin.

Suggested Readings


2019 DF Annual Meeting Events:
Mark Your Calendar

As you make your plans to travel to Washington, DC at the beginning of March, we hope you include the Dermatology Foundation’s events in your schedule. Join your many colleagues from across the country at the Annual Meeting of Membership to hear the latest news about the DF’s efforts to enable advancements in patient care, and to recognize this year’s honorary awardees and the recipients of the DF’s 2019 research awards.

Friday, March 1 – Sunday, March 3  
DF Exhibit Booth #2001
Walter E. Washington Convention Center

Saturday, March 2
DF Annual Meeting of Membership & Awards Presentations
Practitioner of the Year—Tina Alster, MD
Lifetime Educator Award—Jeffrey P. Callen, MD
Clark Finnerud Award—Jeffrey Sugarman, MD, PhD
Marquis Ballroom, Salon 9/10 of the Marriott Marquis Hotel
5:30 – 6:30 pm

Sunday, March 3
Annual Leadership Gala
7:30 – 9:00 pm
The National Museum of Women in the Arts
Pre-Gala Young Leaders Reception:
6:45 – 7:30 pm
Co-sponsored by:
Lilly USA, LLC
Galerma Laboratories, LP
Ortho Dermatologics
Celgene Corporation
(By invitation only—tickets required)


Introducing the Executive Committee’s Newest Members

The Dermatology Foundation is delighted to welcome the four most recent members to join the Executive Committee of the Board of Trustees. The Committee carries out the primary role in leading the DF, which includes directing fundraising efforts, overseeing the Research Awards Program, and defining the Foundation’s strategic direction. These EC members are long-term, devoted volunteers who have taken an active role in furthering the DF’s mission—to enable advancements in patient care. In their new roles, each has brought their acumen, perspective and dedication to the conscientious guidance of the Foundation.

Yvonne E. Chiu, MD
Medical College of Wisconsin and Children’s Hospital of Wisconsin

Renée J. Mathur, MD
Geisinger Wilkes Barre

Kishwer S. Nehal, MD
Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine

John T. Seykora, MD, PhD
Perelman School of Medicine, University of Pennsylvania