Jean L. Bolognia, MD

Introduction. Dr. Bolognia grouped the “barrage of new treatments for melanoma and other malignancies” that have emerged in the past 8 years into 2 categories. Kinase inhibitors are daily oral drugs that target specific mutations. In the case of melanoma, they initiate a rapid response but resistance eventually develops. Checkpoint-blocking monoclonal antibodies, also referred to as immune checkpoint inhibitors (ICI), are administered intravenously and manifest a slower initial response, but if an antitumor response occurs, it tends to be long-lasting. The first ICI approved was the anti-CTLA-4 antibody ipilimumab, followed by anti-PD-1 (eg, nivolumab, pembrolizumab) and anti-PD ligand-1 (eg, atezolizumab) antibodies. While initially approved for stage 4 melanoma, they and the kinase inhibitors are now an option for stage 3, and a wide range of malignancies—from non-small cell lung cancer to bladder cancer to metastatic kidney cancer to metastatic cutaneous squamous cell carcinoma and advanced basal cell carcinoma—are treated with ICIs.

Molecular pathways and related side effects. The CTLA-4 molecule is an immune-dampening tool used by regulatory T cells to prevent hyperinflammatory and autoimmune responses. When the membrane protein B7 on a dendritic antigen-presenting cell binds to CTLA-4 on a T cell, it creates an inhibitory signal. Blocking this... (Continued on page 3)
This coming February, the Dermatology Foundation’s acclaimed annual 3-day program that expands your clinical expertise like no other will return. Attendees consistently rate it the best of the best. The first half of each day begins with a relaxed breakfast clinical conversation, followed by the morning’s information-packed formal program. Exceptional faculty—leaders in their respective areas of dermatology and sought-after teachers—present talks filled with cutting-edge information. The eagerly awaited informal Therapeutics Forum provides a casual evening setting for a unique Q&A session with faculty. Take time to enjoy the lovely beachfront setting. Return home with a treasure trove of cutting-edge pearls that you can put to use immediately.

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interaction via anti-CTLA-4 antibodies leads to immune stimulation (i.e., inhibition of inhibition). **PD-1** (programmed cell death protein 1) is a receptor on T cells; its ligand is **PD-L1**, hence the “L” in the abbreviation. This checkpoint normally dampens the effector phase of T-cell-mediated immunity in peripheral tissue. Many cancers—melanoma included—hack into this system, using the ligand to silence tumor-recognizing T cells. Both anti-PD-1 and anti-PD-L1 antibodies block this ability. As single agents for the treatment of melanoma, nivolumab and pembrolizumab provide better efficacy and a better side effects profile than ipilimumab does. The combination of ipilimumab plus nivolumab enhances efficacy but unfortunately leads to a significant increase in side effects.

**Immune Checkpoint Inhibitors: Mechanisms**

- **CTLA-4**
  - T regulatory (T reg) cells are dampeners in the immune system to prevent overproduction of reactive immune cells and the risk of autoimmune disease
  - CTLA-4 is a protein necessary for the T reg cells to suppress overactive dendritic cells
  - **Inhibiting this protein leads to immune stimulation**

- **Checkpoint inhibitors**
  - PD-1: Programmed cell death protein 1, a T cell co-inhibitory receptor
  - PD-L1: Programmed cell death protein 1 ligand, expressed on antigen-presenting cells and many tumors
  - **Inhibiting the PD-1/PD-L1 interaction leads to immune stimulation**

**Immune-related adverse effects (irAEs).** Inhibiting these immune checkpoint allows an immune attack against the cancer, but the lack of precise targeting produces a spectrum of autoimmune-like inflammatory-related adverse effects referred to as irAEs. The skin is commonly affected, and dermatologists will be seeing an increasing number of patients with cutaneous irAEs. Because use in earlier stages involves patients with increasingly better prognoses, “it is important to be aware of the side effects of these drugs so that you can counsel patients on the risk/benefit ratio of treatment.”

**Cutaneous side effects.** The organizational framework Bologna finds most helpful involves dividing the more common side effects into four major groups: (1) **eruptions** (morbilliform, lichenoid, eczematous, psoriasiform); (2) **bullous diseases** (often bullous pemphigoid); (3) **SCARs** (severe cutaneous adverse reactions such as Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]); and (4) **leukoderma** (a good prognostic sign). She listed the symptoms and gradations within each group, adding: “you already know several of the autoimmune endocrinopathies these patients can develop, as they are also associated with vitiligo.” Bologna discussed the lack of terminology consensus for groups 1 and 4, with terms such as maculopapular appearing in dermatologic publications when the lesions are clearly lichenoid or psoriasiform. In addition, multiple terms—vitaligo, vitiligo-like, leukoderma, hypopigmentation, and depigmentation—are used to describe areas of pigment loss. (For a review of extracutaneous irAEs, see New England Journal of Medicine. 2018;378:158-68.)

**Treatment and dermatology’s critical role.** Bologna presented her modified, simplified annotated version (with deletions and highlighted additions) of the extensive and complex guidelines recently published in the Journal of Clinical Oncology, which reflect oncologists’ nearly exclusive reliance on corticosteroids. “Their therapeutic ladder starts with topical corticosteroids for grade 1 side effects, then moves to increasing doses of oral and then intravenous corticosteroids for more severe disease. It is very important to note that dermatologists can recommend nonsteroidal, less immunosuppressive treatments for these patients, and thus have a critical role to play.” For **lichenoid eruptions**, for example, acitretin or nbUVB can be prescribed; for **bullous pemphigoid** doxycycline plus nicotinamide or, if more severe, dupilumab can be used. In discussing treatment of the **SCARs** SJS and TEN, anti-TNF agents (eg, etanercept) represent a possible alternative therapy.

When a skin eruption to an antibiotic occurs, the major interventions are its discontinuation and choosing a substitute antibiotic. In the case of grade 2 or 3 cutaneous irAEs, however, the patient is given a drug holiday rather than having the medication discontinued. Dermatologists can help to determine when the ICI should be reinstated. (Continued on page 5)
Pediatric atopic dermatitis (AD)—the most prevalent pediatric inflammatory disorder—affects roughly 13% of children and adolescents in the U.S. This chronic, costly, high-morbidity skin disease often begins in infancy, and is characterized by prominent pruritus, eczematous lesions, excoriations, lichenification, crusting, oozing, and dry and painful skin. Many suffering with moderate to severe disease are undertreated or untreated. The past decade’s exceptional progress in recognizing and understanding the complex immunopathology of AD is just beginning to expand the therapeutic toolbox for moderate and severe disease, with substantial therapeutic promise in the pipeline. An invaluable addition to these emerging treatments would be the ability to stop severe disease even before it starts, and Dr. Tiffany C. Scharschmidt—the 2021 Sun Pharma Research Awardee—is committed to making this a reality.

She has identified the initiating event: a dysfunctional relationship with the skin microbiome that develops after birth in the setting of a defective skin barrier, a key risk factor for pediatric AD. Since then she has been probing what goes wrong, why, and the immunologic consequences.

Dr. Scharschmidt’s prior research determined that early-life interactions between the immune system and our healthy skin bacteria—our commensal microbiome—are essential in establishing healthy, noninflamed skin. Once she discovered that a competent skin barrier is essential to this outcome, she turned to AD because it involves an inherited barrier dysfunction that is present at birth, often due to defects in filaggrin. Using special filaggrin-deficient mice and tools to track specific T cells that develop in response to Staph epidermidis, Dr. Scharschmidt learned—unexpectedly—that an incompetent barrier disrupts our immune relationship with skin commensals, and produces an inflammatory instead of a “tolerogenic” response to Staph epidermidis. And this was her Aha! moment. “I realized that even before AD patients begin to manifest their inflammatory skin disease, their defective skin barrier has already set the stage.”

Dr. Scharschmidt’s Sun Pharma Research Award will enable her to gain the granular understanding needed to begin translating her discoveries to potential treatments. She will clarify the role of commensal-specific T cells that develop in filaggrin-deficient mice to see if they contribute to the pathology seen during AD flares. She will also perform complementary human studies to dissect the skin immune response in pediatric AD patients. Her ultimate objective is developing what she calls “smart” topical treatments for at-risk infants, targeting the skin microbial community and/or the cytokines they elicit to prevent these early events in the atopic march. “Looking beyond curing patients who already have severe AD, my hope is to prevent, or at least mitigate, severe AD in as many infants as we can.”

Dr. Scharschmidt recalls that she “has always loved to ask questions and figure out how things work.” During medical school at UCSF, she participated in a program enabling her to spend a year in an NIH lab. She chose to work with Julie A. Segre, PhD, a Senior Investigator who at that time was transitioning her genomics lab from the study of skin barrier development to examining the skin microbiome. Dr. Scharschmidt’s project spanned both of these areas, and she was immediately smitten—the role of the skin microbiome in both health and inflammatory skin diseases became her passion. Following that, her experiences in a UCSF clinic for complex skin diseases ignited her love of medical dermatology—due to its intersection with internal medicine, the skin’s accessibility for research, and its perfect fit with her visual strengths. Dr. Scharschmidt is now a dermatologist, microbiologist, and immunologist at UCSF who cares for patients with severe inflammatory skin diseases, and devotes the majority of her time to her research. “My laboratory investigates the

(Continued on the back cover)
Bolognia then discussed what she calls outlier cutaneous side effects, most notably panniculitis, sarcoidosis (the dermatologist can be the first one to identify this), and atypical squamous proliferations. The latter are often related to lichenoid inflammation, and the treatment regimen includes potent topical corticosteroids.

Q&A:

Janet A. Fairley, MD, Moderator

You noted that oncologists tend to rely on steroids for all of these diagnoses. Do they inhibit the efficacy of the checkpoint inhibitors?

Some studies have observed decreased antitumor effect with higher dose corticosteroids, especially when prescribed early on, while other studies have not reported an adverse effect. Therefore the topic remains controversial. That said, dermatologists can assist in minimizing the use of corticosteroids.

What are your thoughts on IL-12, IL-23, and IL-17 inhibitors for severe psoriasiform reactions?

If severe, yes. However, when earlier in the disease course, an oral retinoid at a low dose—beginning at 10 mg/day of acitretin—is an effective start.

What is the prognosis of these bullous pemphigoid eruptions? How long does it take for them to resolve when immunotherapy is discontinued?

Think of these eruptions as you would drug-induced lichen planus or cutaneous subacute cutaneous lupus, with a spectrum of disease that varies from easy-to-treat to moderate to severe. In some patients, “the horse is out of the barn” and the cutaneous irAE persists after immunotherapy has been discontinued. Even after completion of the course of immunotherapy new cutaneous irAEs—such as bullous pemphigoid—can develop. Perhaps some patients with bullous pemphigoid actually have a subclinical lichenoid reaction that has exposed BMZ antigens.

With a severe reaction that requires interrupting treatment, does it make sense to change immunotherapy agents?

Switching agents or not requires a complex team discussion of risk-benefit ratios.

Do you use IV Ig treatment for patients with a TEN-like reaction?

I think there is a movement toward the use of etanercept in an acutely ill patient because of fewer side effects.

Does leukoderma occur exclusively in melanoma patients treated with these checkpoint inhibitors, or is it equally common with other malignancies?

Because some of the T cells are reacting to peptides from the melanogenic enzymes and melanosomal matrix proteins, it is much less common outside of melanoma.

Chat 2: An Update on Atopic Dermatitis (aka Psoriasis 2006)

Jim R. Treat, MD

Introduction. In 2006, treatments for psoriasis consisted solely of topical steroids, light therapy, methotrexate, and cyclosporine, with some early biologics, but we were on the cusp of an explosion in effective medications. “That is exactly where AD is now,” Dr. Treat said. He reviewed the expanding treatment spectrum, summarized the understanding of AD’s pathophysiology that is guiding a raft of new and highly effective emerging therapeutics, and focused on a few of them.

Pathophysiology overview. In 2006, AD was still regarded as a hyperkeratotic dry skin condition involving an impaired skin barrier (sometimes with a filaggrin mutation), and dendritic cells recognizing external allergens and irritants that generated the itch. Itching impairs their focus and productivity. Scratching damages their skin, which risks infection, and blood on their shirt provokes negative reactions from schoolmates. They feel negatively about themselves socially and emotionally. Because the treatment goal is to clear people and reduce itch as much as possible to restore normal lives, “we want to avoid undertreating them. For years we lacked effective therapies, but now new and emerging treatments are expanding our options.”

Do not undertreat. Any discussion of AD must begin with the pervasively debilitating impact of moderate-severe disease on the child and family. These children itch unbearably and scratch all the time. Itching impairs their focus and productivity. Scratching damages their skin, which risks infection, and blood on their shirt provokes negative reactions from schoolmates. They feel negatively about themselves socially and emotionally. Because the treatment goal is to clear people and reduce itch as much as possible to restore normal lives, “we want to avoid undertreating them. For years we lacked effective therapies, but now new and emerging treatments are expanding our options.”

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targeted treatments work in some patients but not others). Basophils are prominent in flares. This new awareness presents a number of therapeutic targets.

### What Causes Atopic Dermatitis?

(circa 2006) (circa 2021)

AD Irvine, WH Irwin McLean. JID. 2006;126:1200–2 (reprinted with permission of Elsevier); T Litman. APMIS. 2019;127:386–424 (reprinted with permission from Wiley).

### Topical treatment options: 2021.

Preventive postnatal efforts using a daily emollient (petrolatum) to preserve the skin barrier in high-risk babies was modestly supported by early data, but a recent very large study found no effect. Treat advises this only when there is a strong family history of atopy.

We still include the classic treatment stepladder “that we have used to treat AD for years, but are now moving beyond it with other options.” For wet wrapping with a medium-potency topical steroid, “ensure an ample supply of medicine, instruct them to soak in the tub for 10–15 minutes, then apply topical steroid and wet gauze for 2–4 hours.” In a small trial, SCORAD decreased from 50 to 15. To avoid the downsides of long-term steroid use, Treat discussed pimecrolimus, tacrolimus, and the newer crisaborole and their “definite role in maintenance and preventing flaring, and in sensitive skin areas.” Crisaborole has recently been approved down to 3 months of age, “and it is exciting to have a nonsteroidal medication we can actually use in young children.” It may burn on application, “but is usually very well tolerated acrally as long as the application site is not very inflamed.”

### Systemic alternatives: 2021.

Remaining on prednisone results in severe flare when coming off, so Treat’s rare use is only as a bridge to another systemic medication. The classic options are methotrexate, azathioprine, and cyclosporine. Dupilumab—the new drug for patients unresponsive to topical medications—normalizes pruritus and EASI by knocking out the IL-4a receptor to decrease the effects of IL-4 and IL-13. Approved for children ≥6, it is in trials in younger children down to 6 months. “Dupilumab has been life-changing for many of the patients we place on it.” New data document its ability to restore and maintain a healthy skin microbiome, which normally loses diversity and overgrows *Staph aureus* during flares. Some adolescent and adult patients on dupilumab experience facial dermatitis, which typically responds to systemic antifungal treatment or topical calcineurin inhibitors.
**On the horizon.** Drugs are in trial that block most components of the primary immune pathway in AD. Treat profiled several in later trials that inhibit targets in the JAK/STAT pathway component. He hopes that a topical JAK inhibitor will be approved, and talked about both topical (ruxolitinib with the FDA decision due in September, and tofacitinib) and oral (abrocitinib and baricitinib) candidates. He also described the injectables tralokinumab (anti-IL-13) and nemolizumab (anti-IL-31).

**The bottom line.** “This new world is where psoriasis was 10–15 years ago. We’ve had topical steroids and calcineurin inhibitors for a long time. Fortunately, we’ve had dupilumab for the past few years. We’re about to have many more options targeting multiple points in this pathway, and hopefully we’ll see a new drug every year. We’ll be able to treat all of our patients more effectively and benefit their lives in a truly impactful way.”

**Beyond Medications? What Else is On The Horizon?**

- Proposed mechanism for topical probiotic therapy with Roseomonas mucosal
  - Decreases *S. aureus*
  - Decreases TLR5 so less binding to flagellin
  - Activates TNFR-2 epithelial repair

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**How do you feel about patch testing, and when it is appropriate?**

It potentially makes a profound difference as a steroid- or systemic drug-sparing agent. AD patients have a lot of broken, open skin and frequently become sensitized to compounds smeared on these areas. Whenever I consider prescribing a systemic medication, I consider patch testing first. If I find that something their skin is regularly exposed to has exacerbated their AD severity, this will save them from a lot of unneeded therapy.

**How do you choose between pimecrolimus vs tacrolimus vs crisaborole?**

First get people better with topical steroids, which are quick-acting, then move to maintenance. Each steroid-sparing topical has pros and cons. Crisaborole is approved down to age 3 months vs 2 years for tacrolimus/pimecrolimus, but it burns on application. (Mix with a moisturizer before applying to reduce burning.) The calcineurin inhibitors have thousands of patient-years of supporting data debunking their black box warnings. Choose one for the face and eyelids to avoid crisaborole’s initial burning sensation. For maintenance of body/arms/legs, I prefer a topical steroid mixed with moisturizer twice weekly. If a nonsteroidal option is needed, the patient/parent chooses.

**Is dupilumab your treatment of choice for systemic therapy?**

It is my first-line systemic therapy for AD because it really helps people get back to their lives.

**Do you see dupilumab-induced conjunctivitis often in kids?**

Not often, but when we do, we work with an ophthalmologist with appropriate expertise.

**Do you provide specific bathing recommendations?**

Patients whose scratching exacerbates their AD do better when they bathe and moisturize every evening—if they are consistent about moisturizing within a few minutes of leaving the tub. I tell parents that eczema is like a cake with insufficient icing. Daily bathing with soap wipes off the remaining icing, so parents have to put it back on immediately or the cake will fall apart. Waiting until the skin has dried is the worst-case scenario. If not fastidiously prompt to moisturize, then bathe/moisturize only several times a week.

**How do you deal with parents hesitant to use a petrolatum-based product?**

I give them other moisturizer ideas. Some data support coconut, sunflower, and safflower seed oil (but not olive oil) as anti-inflammatory. Some people alternate—thicker petroleum jelly overnight and thinner oils in the morning. Petrolatum-free dimethicone moisturizers are very good, and moisturizers with ceramides can help.

**You mentioned the benefits of wet wrapping. Have you used dry wrapping?**

Not much, because it eliminates the basic value of wet wrapping. Soaking in the bathtub for 15 minutes softens the stratum corneum, enabling it to absorb the ointment more effectively. Because the wet part of the wrap is hydrophobic, placing it over the ointment prevents it from soaking into the dressing and robbing the skin of benefit.
Chat 3: Challenges and Opportunities in Addressing Health Disparities in Skin Cancer in Skin of Color Patients

Adewole Adamson, MD, MPP

Introduction. “Skin cancer prevention in skin of color is challenging,” Dr. Adamson stated. The incidence of new skin cancers in people with skin of color is dramatically less than in lighter skin types, it is likely not sun-induced, it is frequently identified at a more advanced stage, and clinical outcomes are often worse. “Balancing these realities presents difficulties, and we need to be very mindful about how we approach prevention in this population.”

Defining skin of color. Skin of color identifies individuals with skin types that are darker than white skin and have distinctive skin and hair characteristics. “Their incredible diversity makes skin cancer messaging difficult.” Adamson pointed out that “race does not necessarily equal ethnicity,” and discussed the deficits that impair survey study results. The single categories of Latinx and Indian subcontinent, for example, each represent a vast light-to-dark spectrum. “Cancer registries provide no granular detail regarding skin type, and use the blunt categories of race and ethnicity even though they are not necessarily related.”

What is “Skin of Color”?• Identifies individuals of racial groups darker than white
• Patients with skin of color have distinctive and diverse cutaneous/hair characteristics and disorders, and skin practices
• Their diversity makes it hard for skin cancer messaging

Yet we know that Fitzpatrick Skin Type is inversely related to skin cancer risk, likely related to increased epidermal melanin concentration in darker skin, which serves as a natural SPF (up to SPF 15). Whites are on average 70 times more likely to develop skin cancer. The amount of UV needed to produce erythema in Blacks is up to 33 times greater than in whites, and darker skin sustains far less UV-induced DNA damage.

Fitzpatrick Skin Type is Related to Skin Cancer Risk

Skin of color and skin cancers. BCC: incidence varies dramatically by racial group, with a 1-to-1,000 to 1-to-100 difference between those identifying as other-than-non-Hispanic white vs non-Hispanic white, but “we do not know what commonly drives production of BCCs in skin of color.” SCC: incidence is almost 500 times as common in non-Hispanic whites as in African Americans (incidence of 3/100,000). But SCC in skin of color is often diagnosed at a later stage, displays a more aggressive biology, and has a higher metastatic risk than sun-induced SCCs in white patients. Melanoma: incidence rates in individuals with skin of color are also dramatically lower, and have increased only very modestly in contrast to the steeply increasing incidence among non-Hispanic whites. Detection is substantially later (a Black person is 2.5 times more likely to be diagnosed at Stage 4), significantly impacting survival. The effect of immunotherapy in reducing mortality in skin of color patients is less certain, given that many of their melanomas are acral lentiginous and may not respond as well to this treatment.

Prevention. Because skin cancers are so rare in people with skin of color, screening for early identification—i.e., secondary prevention—would likely be a poor use of limited health resources. In discussing primary prevention, Adamson reviewed data indicating that sun exposure is not a factor in skin cancers in people with skin of color, including the typical acral location for melanoma. He also emphasized the challenges posed by the paucity of relevant studies, and the difficulty of collecting sufficient data with such a low tumor incidence. One retrospective study had to go back 40 years, for example, to identify just 43 cases of SCC. Adamson discussed his systematic review of literature assessing UV exposure and the risk of cutaneous melanoma in the skin of color population, noting the low-to-moderate quality of evidence at best. “In the 13 studies meeting inclusion criteria, I found an association among Black men, and 1 among Hispanic men.” A randomized, controlled trial of sunscreen application found that daily photoprotection modestly reduced melanoma incidence, but the study did not include people with dark skin. Given the rarity of skin cancers in skin of color, that they occur predominantly in non-sun-exposed sites (especially SCC and melanoma), and that data supporting sunscreen’s preventive value is still lacking, it is highly uncertain that sunscreen can reduce their melanoma risk. Our efforts should go to educating people of color that melanoma can occur, most likely acral, and to timely, adequate care once it develops.

Tertiary prevention. “Is the delivery of melanoma care equitable? This is the question that consumes me.” Adamson’s focus is to improve quality of life by eliminating delays and later complications,
A significant proportion of skin cancers occur on non-sun-exposed areas of the body.

Sun protection is uncertain to reduce the burden of skin cancer in most skin of color patients.

Educate patients that skin cancer can occur in dark skin.

Need better research into predisposing factors.

The final takeaway for skin of color. (1) We need to increase patients’ awareness of their potential to develop skin cancer. (2) Our opportunity for meaningful intervention is in delivering equitable and timely evidence-based care, not in advocating for sunscreen use or photoprotection. (3) Research is needed to identify the causes of skin cancer in darker skin types.

What is Needed: Final Takeaways

- Increase awareness among patients with darker skin types
- Equitable, timely access to evidence-based care
- Better research on causes of skin cancer on darker skin types

What type of sunscreen do you recommend for dark-skinned patients?

For a sunscreen, a tinted product may avoid or minimize the whitish cast. For something more cosmetically elegant, I recommend a chemical sunscreen with ingredients such as oxybenzone.

When folks with skin of color get melanoma, they have worse outcomes. Are their melanomas biologically more aggressive, or is lack of access to optimal care the problem?

I think it’s some of each. The most common type of melanoma in folks with skin of color—acral lentigious melanoma—is associated with a worse outcome regardless of race, ethnicity, etc. In addition, numerous studies show that the care people of color—Black people in particular—get for melanoma involves delays in surgery and in beginning treatment. We can’t change their tumor, but we can make sure that once melanoma has been identified, their care is optimized.

A full-body skin exam in the skin of color population is currently recommended every 1–2 years. Do you agree?

Even for white populations—where skin cancer is far more common—there is controversy regarding regular screening for reducing hard outcomes like death. So in a population already at very low risk, it is highly unlikely to improve. Instead, we have to achieve timely diagnosis through educating the skin of color community, and timely care. Thus I do not agree with regular skin cancer screening for average-risk individuals with skin of color.

Where do you think research should be focused?

Find out why folks of color with melanoma experience delayed and inferior treatment, and create effective interventions. Study acral lentigious melanoma. We need to figure out the actual causes of skin cancer in people with skin of color. Immunotherapy drugs that have been transformative for advanced melanoma may not be as effective for acral lentigious subtypes, which may not share the same immunogenicity.

Chat 4: When Mohs Surgery Really Matters

Jeremy S. Bordeaux, MD, MPH

Introduction. “One of my passions is doing what I call value-added Mohs,” Dr. Bordeaux said—“Mohs that really makes a difference in our patients’ lives.” This represents roughly 2% of his patients. He began by narrating his experiences with 2 recent male patients, each with a challenging basal cell carcinoma that prolonged surgery until late at night. One involved a 15 cm tumor on the arm and repair of the resulting large hole. The other man’s tumor had eaten through his nose; Bordeaux detailed the effective excision and multi-step repair that restored a normal appearance and maintained the airways. Then he discussed six scenarios in which “Mohs really matters.”

Dermatofibrosarcoma protuberans (DFSP). This very rare, nonfatal skin cancer (with 1,200–1,500 annually compared to 100,000 annually for melanoma) has a mean age at diagnosis of 41. DFSPs are not sun-induced. The underlying genetic mutation drives excess collagen production that appears as red-violaceous plaques, “with the most significant subclinical extension of any tumor we treat.” Bordeaux described a woman referred to him after a tumor excised by an outside surgeon came back as DFSP. It had been the size of a penny and barely visible, “but once I cleared her with Mohs, we were down to the abdominal muscles.” A wide local excision (WLE) of 2–3 cm with breadloafing will not produce clear margins, regardless of the pathology report. Tumor recurrence rates with WLE are upwards of...
20% on the extremities and 50% on the head and neck, but only 1.3% with Mohs. The National Comprehensive Cancer Network’s latest recommendations for first-line therapy for DFSP include only Mohs or another form of complete margin control.

Eyelid tumors. One of Bordeaux’s pet peeves is the physician who pronounces an eyelid tumor too large or too close to the eye for Mohs—“because that is when Mohs really matters.” It can be critical to retaining the eye, and Bordeaux presented several illustrative patients. One was a male patient with an eyelid tumor so large it was obscuring his vision. Mohs surgery and Bordeaux’s reconstruction procedures enabled full function of his lid within 2 days. Another was a female patient who would have lost the majority of both eyelids and risked losing her eyeball. The Mohs outcome retained her eye, greatly facilitated reconstruction, and she healed nicely.

Microcystic adenocarcinoma (MAC). This extremely rare tumor involves a defect at least 4–6 times larger than what is visible before surgery, with perineural extension in 60%–80%. The recurrence rate with WLE is above 50%, but is minimal with Mohs. Because the initial biopsy often does not provide sufficient information for detecting MAC, the diagnosis is typically made during Mohs surgery. “This illustrates the need to be thoughtful about sampling to provide enough tissues for the dermatopathologist.”

DFSP: Significant Subclinical Extension

Lentigo maligna (LM). Recurrence rates with WLE range from 8% to 20%. With staged excision this is close to 3%, and less than 1% with Mohs surgery. “I did staged excision until I realized that Mohs is far more convenient for the patient, and my patients have really appreciated it.” Bordeaux provided several patient examples, including a woman with a .3 mm LM that had been excised several times within the previous year, and pronounced ectropion. After 5 stages of Mohs, he repaired her ectropion and fixed her cheek with a rotation flap. Her appearance is now normal, and her LM has not recurred.

Genital tumors. For these squames—and occasionally extra-mammary Paget’s disease—the typical aggressive and debilitating surgery runs a high risk of hemipenectomy (even penectomy) and vulvectomy. “These may not be my favorite tumors to treat, but realizing what could happen if I was not treating them with Mohs, I know that I’m making a really positive impact on these people’s lives.”

(Continued on page 13)
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Photosensitivity and Risk for Sunburn Minimize unprotected exposure to ultraviolet light, including sunlight, sunlamps and tanning beds, during the use of ARAZLO Lotion. Warn patients with high levels of sun exposure and those with inherent sensitivity to sun to exercise caution. Instruct patients to use sunscreen products and protective clothing over treated areas when sun exposure cannot be avoided.

ARAZLO Lotion should be administered with caution if the patient is taking drugs known to be photosensitizers (eg, thiazides, tetracyclines, fluoroquinolones, phenothiazines, sulfonamides) because of the increased possibility of augmented photosensitivity.

Weather extremes, such as wind or cold, may be more irritating to patients using ARAZLO Lotion.

Adverse Reactions The most common adverse reactions (≥1% of patients and greater than vehicle) were: application site pain, dryness, exfoliation, erythema, and pruritus.

To report SUSPECTED ADVERSE REACTIONS, contact Bausch Health US, LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see Brief Summary of full Prescribing Information on following page.

Local skin reactions. Treatment with ARAZLO is contraindicated in pregnancy. ARAZLO may cause fetal harm when administered to a pregnant patient (see Warnings and Precautions; Use in Specific Populations).

The maximum severity generally peaked at Week 2 of therapy and decreased thereafter. The frequency of the adverse reactions was similar in studies with ARAZLO once daily at 0.01%, 0.025%, 0.050%, and 0.125% for 12 weeks. The majority of subjects were White (74%) and female (66%). Approximately 22% were Hispanic/Latino.

Embryofetal Toxicity: Based on data from animal reproduction studies, retinoid pharmacology and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. Safety in pregnant patients has not been established. The potential risk to the fetus outweighs the potential benefit to the woman; therefore, ARAZLO should be discontinued as soon as pregnancy is recognized.

In animal reproduction studies, tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in the TK6 tk+ reverse mutation assay and did not induce DNA damage in Chinese hamster ovary cells. A long-term study with topical application of up to 0.1% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.025, 0.050, and 0.25 mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to that observed based on AUC comparison.

A long-term study with topical application of up to 0.3% of tazarotene in a gel formulation in mice terminated at 88 weeks showed that dose levels of 0.025, 0.050, 0.25 mg/kg/day (reduced to 0.125 mg/kg/day for males after 41 weeks due to severe dermatologic toxicity) showed that dose levels of 0.05, 0.125, 0.25, and 1 mg/kg/day (reduced to 0.5 mg/kg/day for males after 41 weeks due to severe dermatologic toxicity) showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to that observed based on AUC comparison.

A long-term study of tazarotene following oral administration of 0.025, 0.050, and 0.25-mg/kg/day to rats showed no indications of increased carcinogenic risks. Based on pharmacokinetic data from a shorter-term study in rats, the highest dose of 0.125 mg/kg/day was anticipated to give systemic exposure in the rat equivalent to that observed based on AUC comparison. Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-teratogenic in an in vivo mouse microsome test.

There are no data on ARAZLO use in pregnant patients to inform a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Based on data from animal reproduction studies, retinoid pharmacology, and the potential for systemic absorption, ARAZLO may cause fetal harm when administered to a pregnant patient and is contraindicated during pregnancy. The potential risk to the fetus outweighs the potential benefit to the mother; therefore, ARAZLO should be discontinued as soon as pregnancy is recognized.

In animal reproduction studies with pregnant rats, treated fetal body weights and reduced skeletal ossification were observed after topical administration of a tazarotene gel formulation during the period of organogenesis at dose levels equivalent to the maximum recommended human dose (MRHD) (based on AUC comparison). In animal reproduction studies with pregnant rabbits, single incidences of known retinoid malformations, including spina bifida, hydrocephaly, and heart anomalies were observed after topical administration of a tazarotene gel formulation at 15 times the MRHD (based on AUC comparison) (see Data).

In animal reproduction studies with pregnant rats and rabbits, malformations, fetal toxicity, developmental delays, and/or behavior changes were observed after oral administration of tazarotene prior to or during pregnancy. At doses 10 or 20 times, respectively, the MRHD (based on AUC comparison). In pregnant rabbits, decreased litter size, decreased numbers of litters, decreased fetal body weights, and increased malformations were observed after oral administration of tazarotene prior to mating through early gestation at doses 6 times the MRHD (based on AUC comparison) (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of major birth defects, loss, and other adverse outcomes. In the U.S. population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Because of heightened burning susceptibility, minimize unprotected exposure to ultraviolet light including sunlight and sunlamps during the use of ARAZLO. Warn patients who normally experience high levels of sun exposure to use a sunscreen product and one with a sun protection factor of at least 15 with the narrowest wavelength spectrum (e.g., titanium dioxide, zinc oxide, avobenzone, padimate O, octinoxate, oxybenzone) because of the increased possibility of photosensitization.

Tazarotene was non-mutagenic in the Ames assay and did not produce structural chromosomal aberrations in human lymphocytes. Tazarotene was non-mutagenic in the CHO/HGPRT mammalian cell forward gene mutation assay and was non-teratogenic in an in vivo mouse microsome test.

No impairment of fertility or fertility was observed in male rats treated for 70 days prior to mating with oral doses of tazarotene up to 1 mg/kg/day which produced a systemic exposure 4 times the MRHD (based on AUC comparison). No impairment of mating performance or fertility was observed in male rats treated for 70 days prior to mating with oral doses of tazarotene up to 1 mg/kg/day which produced a systemic exposure 4 times the MRHD (based on AUC comparison). No impairment of mating performance or fertility was observed in female rats treated for 50 days prior to mating continuing through gestation day 7 with oral doses of tazarotene up to 2 mg/kg/day. However, there was a significant decrease in the number of estrous stages and an increase in developmental defects at that dose which produced a systemic exposure 6 times the MRHD (based on AUC comparison).
Scalp tumors. Large scalp tumors that are thought to be invading bone are normally treated with WLE. Bordeaux illustrated the difference that Mohs makes with a patient who came to him with positive margins after WLE, and had been told he needed resectioning that would include bone and involve mesh. Bordeaux did Mohs, and found the tumor growing into the periosteum but not invading the bone. He described the excision, repair, and grafting, plus radiation for the perineural invasion. The patient is doing well.

Conclusion. “When I am taking care of one of these patients, I may be at work until 8 or 9 in the evening, but I am making a difference in their lives—healthwise, socially, and emotionally. I am living my purpose.”

Q&A: Jack S. Resneck, Jr., MD, Moderator

What is your approach to margins using Mohs on DFSP?

Because DFSP can have extensive tentacles going wide and deep, giving our patients a higher cure rate takes precedence over preserving tissue to enable a less complicated or more aesthetically pleasing reconstruction. I want to clear it, so the first layer is at least 1 cm (unless there are tissue-preserving concerns) and goes down to fascia to provide a good look all the way around and all the way under. Once I have clear margins, I stop. I am fully confident in the outstanding skill of my histotech and lab in producing high-quality slides and my ability to read them.

For particularly large DFSP tumors, do you recommend radiation therapy after Mohs?

No further therapy is needed once you have confident negative margins. Any truly unresectable DFSP tumor is discussed by the Tumor Board to determine the appropriate systemic treatment—imatinib or another agent.

(Continued on page 14)
After you clear LMs with Mohs, do you take an extra margin for permanent sections?

As with DFSP, because my histotech and lab make exceptional slides and my ability to read them is on par with my dermatopathologist, I trust what I have done and do not take extra margins. Current research supports this.

Can you do Mohs for melanoma in patients who need a sentinel lymph node biopsy (SLNB)?

This is very important, because the frequent response is “no.” But at my institution we successfully do them both. SLNB is done first (by our head and neck surgeon, for example). We do Mohs ~1 week later—after the dye has disappeared and the swelling is down. And when I’m confronting a melanoma that risks not being fully sampled, I debulk the middle, cut vertical sections through that, and if the tumor gets upstaged to require an SLNB, I delay reconstruction. I simply clear that periphery, bandage the patient, and arrange for their SLNB.

What is your complication rate for the extremely large tumors you illustrated?

For most of my practice, my complication rate is close to 0.5%. For these large closures (~2% of my practice) it is 2–3%. Similar cases in the general head and neck surgical literature typically report a ~10% complication rate. Add to that the costs incurred by operating room use plus a several-day hospital stay.

If you could ask all of your referring general dermatologists to do one thing differently, what would it be?

Remember how important it is that Mohs be done on eyelid cases. For general dermatologists who are uncomfortable doing a biopsy near the globe, have your Mohs surgeon do it, not the ophthalmologist, to avoid the oculoplastic surgeon and no access to Mohs.

Apply Now for 2022 DF Research Support
October 15 Deadline

For 55 years, the sole purpose of the Dermatology Foundation has been to further the specialty and patient care. We address this mission each year by investing in the innovative research of emerging investigators who hold the clear potential to achieve scientific breakthroughs that lead to new treatments and cures. Today’s support of essential progress has evolved far from the annual handful of small awards provided in our early years. We are extremely proud of the broad range of significant advances in patient care our research support has enabled to date.

We are now accepting applications for 2022 research funding in 13 award categories. The specialty’s newest investigators are encouraged to apply for the support that will further the trajectory of their research and academic careers—for the ultimate benefit of patients everywhere.

Career Development Awards (CDAs):
3 years, $55,000/year
- Public Health CDA
- Clinical CDA in Dermatologic Surgery
- Physician Scientist CDA
- Science of Human Appearance CDA
- Medical Dermatology CDA
- Women’s Health CDA
- Research CDA
- Dermatopathology Research CDA
- Pediatric Dermatology CDA

Fellowships: 1 year, $30,000
- Dermatologist Investigator Research Fellowship

Grants: 1 year, $20,000
- Patient Directed Investigation Grant
- Basic Science Research Grant
- Women’s Health Research Grant

Earlier this year, we were delighted to award $2.7 million to 59 highly promising individuals, with research spanning the breadth of the specialty. Our investment represents 29 academic institutions and 29 areas of investigation. At the heart of this all is the proof that every step forward in understanding a skin disease or new approach to treatment holds the powerful potential to transform lives.

Applications for 2022 are eagerly awaited. The deadline is October 15, 2021 for CDA, Fellowship, and Grant applications. Information on the Diversity Research Supplement Award will be available later this fall. Everything you need to know is at dermatologyfoundation.org.
**2021 SEASIDE CHATS—ABOUT OUR FACULTY**

**Adewole Adamson, MD, MPP***  
Assistant Professor  
Division of Dermatology  
University of Texas at Austin Dell Medical School  
Dr. Adamson's primary clinical interest is in caring for patients at high risk for cutaneous melanoma, and he directs the Melanoma and Pigmented Lesion Clinic and the Dermatology Clinic at UT Health Austin. His research focuses on understanding patterns of health care utilization, including overuse and underuse in dermatology. Within this, he is interested in how effectively and efficiently the health care system delivers care to patients with skin cancer. He is passionate about health care disparities and how to improve them, focusing on dermatology patients and particularly those with melanoma. People with skin of color are a focus within each of his research areas of concern.

**Jean Bolognia, MD***  
Professor  
Department of Dermatology  
Yale School of Medicine  
Dr. Bolognia has served as President of the Medical Dermatology Society, the Women's Dermatologic Society, and the American Dermatological Association, as well as Vice-President of the Society of Investigative Dermatology, the American Board of Dermatology, and the International Society of Dermatology. She has been previously elected to the Board of Directors of the American Academy of Dermatology and the International League of Dermatological Societies. Dr. Bolognia is senior editor of the comprehensive textbook Dermatology and of Dermatology Essentials. Her many honors include the Medical Dermatology Society's Lifetime Achievement Award and the American Academy of Dermatology's Gold Medal. She is an honorary member of dermatology societies across the globe.

**Jeremy Bordeaux, MD, MPH***  
Professor  
Department of Dermatology  
Case Western Reserve University  
At University Hospitals Cleveland Medical Center, Dr. Bordeaux is Director of Mohs Micrographic and Dermatologic Surgery, Director of the Melanoma Program and of the Multidisciplinary Melanoma Tumor Board, and Director of the Micrographic Surgery and Dermatologic Oncology Fellowship. His clinical and research interests include prevention and treatment of melanoma, the epidemiology and prevention of skin cancers, and advanced cutaneous reconstruction. Dr. Bordeaux has won numerous awards, including the annual Theodore Tromovitch Award given to a Mohs surgeon for outstanding research. The dermatology residents at Case Western Reserve University have chosen him Mentor of the Year, Research Mentor of the Year, and Teacher of the Year.

**Jim Treat, MD**  
Professor  
Departments of Clinical Pediatrics and Dermatology  
Perelman School of Medicine at the University of Pennsylvania  
Dr. Treat’s primary clinical appointment is at the Children’s Hospital of Philadelphia, where he is the Pediatric Dermatology Education and Fellowship director. He directs the dermatology course for the Perelman School of Medicine and has won 19 teaching awards, including the 2016 Provost Award for Excellence in Teaching (University of Pennsylvania) and the 2013 Master Clinician Award (Children’s Hospital of Philadelphia). Dr. Treat was elected to the Academy of Master Clinicians at the University of Pennsylvania in 2020. He has given hundreds of invited lectures nationally and internationally, and is a contributing author to Andrews’ Diseases of the Skin.

**PROGRAM CO-CHAIRS**

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<tr>
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*Past DF Research Award Recipient

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2021 Seaside Chats Faculty Disclosures: Adewole Adamson, ME, MPP: Member, AAD Skin of Color and Skin Cancer Work Group; Jean Bolognia, MD: none; Jeremy Bordeaux, MD, MPH: none; Jim Treat, MD: Pfizer, Palvella Inc.

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Spring/Summer 2021  
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cellular and molecular mechanisms that mediate interactions between bacteria and the developing immune system in the skin, with the long-term goal of developing new therapeutic approaches.”

Dr. Scharschmidt’s midcareer Sun Pharma Research Award is her third from the DF. “The impact of my DF awards has been profound. The early-career awards were critical for building momentum, protecting my time, and creating my own niche. The Sun Pharma Research Award provides a unique combination of focus and freedom for addressing these clinically translational aspects of my research. I could not have expanded my research in this direction without it.”

The Foundation thanks Sun Pharma for their generous gift of $1 million to fund three midcareer research awards for outstanding investigators driving progress in treating challenging inflammatory skin diseases.

Dr. Scharschmidt plays central roles in the Benioff Center for Microbiome Medicine, the I-Micro Program, and the ImmunoX Program at UCSF. Her previous research support from the Dermatology Foundation includes a Dermatologist Investigator Research Fellowship (2012) and a Physician Scientist Career Development Award (2013).