Therapies for Melanoma:
What Every Dermatologist Needs to Know
Jean L. Bolognia, MD

Introduction. The 7 drugs approved by the FDA within the past 6 years for treating advanced melanoma, plus the 5 more approvals expected within the coming year, create a sizeable pool of new information to absorb. To facilitate understanding these drugs, Dr. Bolognia provided a simple organizational framework based on the 2 categories—kinase inhibitors and immunostimulators—that define their respective actions. She integrated helpful information including how the different classes of drugs work, respective efficacy and side effects, and important drug combinations.

Category 1: Kinase Inhibitors. These small-molecule drugs target specific kinases, and the latter have the ability to phosphorylate other proteins (and sometimes themselves). The level of protein phosphorylation can significantly alter activity. Under normal conditions, the MAP kinase signaling pathway—which consists of RAS and a series of kinases (BRAF, MEK, and ERK)—plays an important role in regulating cellular proliferation. However, somatic activating mutations in the genes encoding these proteins can lead to uncontrolled cellular proliferation. Notable is the BRAF mutation V600E, which is present in 40%–60% of melanomas. Kinase inhibitor drugs are oral, and taken daily for the long term rather than cycled every 3–4 weeks as with chemotherapy.

The BRAF Mutation. The appropriate melanoma patient for a kinase inhibitor has substantial tumor burden along with a tumor containing certain BRAF mutations, in particular V600E, less often V600K or V600D. V600E indicates substitution of glutamic acid (E) for valine (V) at position 600 in the BRAF protein. The current BRAF-inhibiting drugs are selective, ie, they bind BRAF proteins with these specific amino acid substitutions. Their names—dabrafenib and vemurafenib—provide clues to their purpose. Raf points to its BRAF
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When a receptor or cellular protein has kinase activity, the \textit{nib} ending is shorthand for \textit{inhibitor}. Tumor response among patients with the relevant mutation is rapid and high, but “their Achilles heel when used alone is the development of resistance.” Enhanced activity of MEK, a kinase downstream in the MAP kinase pathway, is one of the major causes of this resistance. Dual therapy—adding a MEK inhibitor, either cobimetinib or trametinib, to the selective BRAF inhibitor—significantly improves progression-free survival.

**Cutaneous Side Effects.** Bologna summarized the more common cutaneous reactions to these drugs and how best to manage them. She covered folliculocentric exanthems, photosensitivity, squamous papillomas, widespread keratoses, plantar hyperkeratoses, erythema nodosum, changes in melanocytic nevi, squamous cell carcinomas (SCCs), and keratoacanthomas (KAs). “When the exanthem is grade 1 or 2, the BRAF inhibitor can be continued and perhaps the dose reduced, but grade 3 reactions often require both a drug holiday and dose reduction.” Surprisingly, dual therapy actually reduces the occurrence and severity of multiple side effects, including papillomas, plantar hyperkeratoses, SCCs, and KAs.

**Category 2: Immunostimulators (checkpoint inhibitors).**

The immunostimulators are monoclonal antibodies (MAbs) that inhibit an inhibitory signal that has been constraining the endogenous immune response to the tumor. As a result, the antitumor immune response is activated. With no mutational requirement, these drugs—initially administered intravenously every 2–4 weeks—can be given to anyone with advanced disease. Given as a single agent, a smaller percentage of patients respond compared to BRAF/MEK dual therapy and the response takes longer to become manifest, but the responses that do occur are usually long lasting.

Ipilimumab was the first to be FDA approved. It is directed against CTLA-4 on T regulatory cells, which normally induces immune suppression after binding B7 on dendritic cells. In addition to autoimmune endocrine side effects, patients can develop dermatitis, exanthems, lichenoid reactions, leukoderma, toxic epidermal necrolysis, sarcoidosis, and bullous pemphigoid.

Next to be approved were nivolumab and pembrolizumab, which target the programmed cell death-1 (PD-1) protein on T cells. When PD-1 binds to its ligand, PD-L1, on tumor cells, this can lead to a reduced immune response. By targeting and inhibiting this interaction, an immune attack on the tumor can occur. The immune-related adverse events are similar to those of ipilimumab, but usually of a lower grade. In addition, as single agents both of these MAbs have a higher response rate than ipilimumab alone. The combination of an anti-PD-1 MAb plus an anti–CTLA-4 MAb leads to greater response rates, but at the cost of significantly augmented side effects. Trials are ongoing to examine anti-PD-L1 MAbs such as atezolizumab, avelumab, and durvalumab.
MINI-SYMPOSIUM: SKIN CANCER

Beating Melanoma: A New Assay That Predicts Response to Immunotherapy

Michael D. Rosenblum, MD, PhD

Introduction. Before Dr. Rosenblum discussed this research by his team at the highly collaborative Cutaneous Immunology Center, he described the innovative multiparameter flow cytometry technology that enables them to isolate and functionally study freshly harvested human skin cells from different cutaneous environments in health and disease states. They want to understand the range and complexities of immune behavior in these variously located cells, and explore how it affects cell functions. Hoping to characterize the immune microenvironment in metastatic melanoma, Rosenblum et al. applied multiparameter flow cytometry to freshly isolated metastatic melanoma samples from 40 patients about to begin PD-1 checkpoint inhibitor therapy. From this, they also hoped to find biomarkers that can predict who will respond to this therapy.

The Melanoma Microenvironment. As the patient treatment response data began coming in, the only immune marker that correlated with responding to nivolumab or pembrolizumab therapy was the presence of tumor-infiltrating T cells (TILs) expressing CTLA-4—which is targeted by ipilimumab and is irrelevant to the anti-PD-1 drugs. Then a more careful review found that the TILs with high CTLA-4 expression also had the highest expression of PD-1. Thus the CTLA-4 was actually a surrogate marker for the highest PD-1 expressers. The rest of the patient-response data made it clear that the presence and concentration of this double-positive T-cell subset correlates almost perfectly with patient response. Every patient whose tumor contained >30% of these double-positive TILs responded to anti-PD-1 treatment. None of those with <20% responded. And those falling between these two points were variable. Rosenblum discussed the molecular elements that come into play.

Implications. This discovery has been put to work clinically at Rosenblum’s institution. Patients with metastatic melanoma are now molecularly profiled at the start, and those with <30% of the critical cells are automatically given combination therapy (ipilimumab with nivolumab or pembrolizumab). Knowing that monotherapy would have no effect on these patients, the intense side effects from this combination therapy are considered worth it.
New DF President Looks to the Future

Earlier this year, the Foundation’s Board of Trustees enthusiastically welcomed Kim B. Yancey, MD, to his new role as president. Dr. Yancey is Chair of the Department of Dermatology at UT Southwestern Medical Center. Before that he chaired the Department of Dermatology at the Medical College of Wisconsin. This followed his tenure as a Senior Investigator at the NIH in the Dermatology Branch.

Dr. Yancey, an Annenberg Circle Sustaining member, has been a steadfast supporter of the Foundation for over 30 years. He is a dedicated volunteer who has held various roles in the annual Leaders Society and Annenberg Circle campaigns. He was also a former member and chair of the Medical and Scientific Committee which evaluates research funding applications each year. In recent years, Dr. Yancey was the Executive Committee liaison responsible for overseeing the DF’s Research Awards Program and ensuring it continues to meet the needs of the specialty.

Dr. Yancey has assumed the DF presidency at a time when the funding challenges for new and mid-career investigators have never been greater. He shares his thoughts on the essential role of the Dermatology Foundation and his aims for its future.

When did you learn about the DF?
“It was during my residency. I recognized that the DF supports young people in a manner that allows them to seek support from the NIH and other funding agencies from a position of strength. DF funding enabled trainees to develop preliminary data, experience, and publications that justified investment from other granting agencies. DF support empowered people in dermatology in a manner that other specialties lacked.”

What impact do you believe the DF has had on the specialty?
“The Foundation has shaped all aspects of dermatology. For over five decades, it has forged the specialty by developing and retaining young investigators and educators. These leaders have moved our field forward in virtually every dimension.

“Since its start, the DF has awarded approximately $70 million in funding through career development awards, fellowships, grants, and most recently, mid-career scholar awards. The Foundation is the largest supporter of our specialty apart from the NIH. The return on this investment is considerable. A recent survey of CDA recipients indicates that approximately 80% of these individuals have appointments in academics, and more than 80% of this group has subsequently received extramural support. We know that for every DF dollar awarded, more than $10 in NIH grants have been garnered to date.”

How do you envision the DF’s future impact?
“The DF will continue to focus solidly on supporting the future of dermatology. The degree of annual investment and its effect will be determined by how much funding the DF can develop and sustain.

“The future certainly holds a variety of challenges for virtually everyone in medicine and biomedical research. That’s why the self-investment in dermatology that the DF affords is so important. If you imagine yourself as the CEO of a biomedical enterprise, you know that some portion of your budget has to be devoted to research and development. The Foundation enables all members of our community to invest in our future.”

What are your goals for the DF?
“I have one simple goal—that every dermatologist and others in our greater community will become a member of the Dermatology Foundation. We can accomplish so much more if we do it together. The DF’s work helps us all further the future of dermatology as well as the treatments and therapies we provide our patients.”

What would you like to say to dermatologists who are not DF members?
“The specialty of dermatology and the patients that I have seen throughout my career have enriched my life in so many ways. For me, the best way to acknowledge this tremendous gift is to support the continued advancement of the specialty through the DF.

“For those who have not yet joined, I ask that you consider the importance of maintaining a strong, progressive specialty—for the benefit of every dermatologist and our patients. I hope you will all join me in supporting the DF.”
Nonsurgical Treatments for Skin Cancer

Anthony M. Rossi, MD

Introduction. Although surgery is the standard of care for melanoma and nonmelanoma skin cancers, nonsurgical approaches can be extremely beneficial: (1) when multiple surgeries risk excessive morbidity, (2) with field therapy or field cancerization, (3) in high-risk patients, and (4) for highly cosmetically sensitive patients. Dr. Rossi discussed several of the many nonsurgical options appropriate for basal cell carcinoma (BCC), SCC, and melanoma, including his own data.

For BCC. Know the tumor. One published study found 56% of BCCs sampled had mixed histologic subtypes, with half having both aggressive and low-risk types. Aggressive subtypes are less amenable to nonsurgical treatment options. “If considering nonsurgical treatment options and the initial biopsy samples only a small part of a larger lesion, re-biopsy to make sure you are not missing a more aggressive subtype.” Rossi discussed imiquimod (FDA approved for actinic keratoses [AKs] and superficial BCC) and photodynamic therapy (PDT) in detail, including his own implementation and guidance. He uses imiquimod off-label for nodular BCC, Bowen’s disease, and lentigo maligna (LM). Because PDT requires the appropriate light source/wavelength for meeting the different penetration requirements of thinner vs thicker lesions, know if you are dealing with superficial or nodular BCC. Rossi also described his encouraging experimental results with the fractionated CO2 laser guided by reflectance confocal microscopy both to ablate BCC and enhance PDT.

For SCC. For patients with actinic damage and scalp field cancerization, MAL (methyl aminolevulinate) PDT was shown to be superior to PDT with placebo vs cryotherapy vs liquid nitrogen vs 5-FU; after 2 treatments (1 month between them), at 12 months 80% show complete clearance. Of growing interest is the apparent preventive value of a cyclical PDT regimen with organ transplant patients. One study presented showed 64% of treated patients free of AKs and superficial SCCs after 12 months of multiple PDT rounds, compared to 26% without treatment. Rossi often uses intralesional methotrexate injections for keratoacanthoma SCC, and has published the imperative need to sample the entire lesion before commencing treatment to avoid missing a more aggressive segment underneath.

For Melanoma in Situ, LM. Rossi discussed his use of imiquimod, reiterating the need to ensure an adequate biopsy sample to avoid missing an invasive melanoma. For appropriate patients, Rossi aims for treatment at least 5 times weekly for 12 weeks (with break if needed). Confocal imaging is ideal for mapping the application area, then for informative follow-up.

Rare Skin Cancers: DFSP, Merkel Cell Carcinoma, Sebaceous Carcinoma

Jeremy S. Bordeaux, MD, MPH

Introduction. Dr. Bordeaux has begun studying the epidemiology of these rare cancers. Much of his data come from the SEER registries. He also provided critical treatment observations.

DFSP (Dermatofibrosarcoma Protuberans). There are 4.1 cases/1 million people, with an unchanging annual incidence in the U.S. of ~1,200. Female patients are at significantly greater risk for developing a second primary DFSP tumor (although this cancer’s rarity makes the absolute risk minimal), have a 2.58% greater risk for melanoma (not a negligible risk to begin with), and an increased risk for breast cancer. (A study of hormonal relationships is in progress.) Thus, monitoring visits with DFSP patients should include a body-wide search for DFSP tumors and melanoma. Inform the primary care physician of the breast cancer risk. DFSP incidence diminishes with age, but blacks are twice as likely as white age-mates to develop it. Deaths are more likely among blacks, men, and those with a head or upper limb tumor. The unpredictable, tentacled growth pattern of these tumors makes Mohs significantly more effective than excision.

Merkel Cell Carcinoma (MCC). This cancer is more frequent among older people and among men. There are 6 cases/1 million people, with ~2,000 annually in the U.S. The gradually increasing incidence is greater among women than men, but their survival rate is better at any stage. A sentinel node biopsy is critical for every patient. It will be positive in 30%–40% of patients (twice the rate in melanoma), and a positive node drops survival rate from ~90% to ~50%. Bordeaux outlined his approach to surgery based on tumor location and size, and sentinel node results.
Sebaceous Carcinoma. There are only 3 cases/1 million people, with 1,000 cases annually. Incidence is increasing slightly, more so in men, who are also twice as likely to develop this cancer. Older mortality data are flawed, and underestimate the reality. Make sure to work up new patients for Muir-Torre syndrome.

Epidemiology of DFSP
- This is the largest population-based study of DFSP, with a cohort of almost 7,000 cases.
- DFSP is a rare disease with an overall estimated incidence rate of 0.41 per 100,000 person-years.
- Incidence of DFSP has not changed over the last decade, in contrast to the rapid increase in incidence of melanoma and most non-melanoma skin cancers observed in the last few decades.
- This is the first report showing statistically higher incidence among women than men.
- Incidence among blacks is almost twice that of whites.
- Trunk is the most common anatomic location of this tumor except in men >80, for whom head is the most common location.
- DFSP remains a disease of low mortality.
- Worse survival is associated with increased age, male sex, black race, and anatomic location of the limbs and head.

Update: Epidemiology of MCC
- Males are more likely than females to be diagnosed with MCC.
- Risk of MCC increases with age.
- MCC is more commonly diagnosed as local or regional disease than advanced distal disease.
- The incidence of MCC is increasing, but the rate of increase is significantly less than in previous reports.
- The incidence of MCC in females is increasing at a faster rate than in males.
- The rates of increase in incidence of more advanced disease (regional and distal) are higher than that of local disease.
- Females survive longer than males at all stages of disease.

Sebaceous Carcinoma (SC)
- Incidence has increased significantly, primarily due to an increase among men.
- Incidence among whites was almost 3 times the rate among nonwhites.
- Male sex, black race, and extraocular location were associated with significantly higher all-cause mortality.
- However, overall case-specific mortality for SC decreased significantly.

MINI-SYMPOSIUM: MONITORING FOR MALIGNANCY

Approach to the Patient With Numerous Melanocytic Nevi
Jean L. Bolognia, MD

Introduction. Dr. Bolognia provided a practical approach to patients with a hundred or more melanocytic nevi and multiple atypical nevi. Many patients have similar-appearing nevi, and recognition of a person’s signature nevus can then allow detection of suspicion-warranting ugly ducklings. This approach requires a more “low power” examination of the patient. There are also types of atypical nevi—such as the “fried egg” nevus—that can elicit significant attention and concern on the part of patients, parents, and nondermatologists, often because of their size. “However, big does not necessarily mean bad, and these nevi often have an overall symmetry despite having more than one color.”

Signature Melanocytic Nevi
- Solid brown
- Large “fried egg”
- Small dark brown-black ± thin brown rim (lentiginous nevi)
- Eclipse—tan with brown rim*
- Cockade (cockarde)
- Pink eclipse—pink with brown rim
- Solid pink (often skin phototype 1)
- Perifollicular hypopigmentation
- Halo
- Nonpigmented (white)

Fried Egg Nevus. The name reflects its topography, with the flatter peripheral component reminiscent of the white portion of an egg. The elevated “yolk” can be located centrally or eccentrically. As the nevus ages, the flatter portion often fades away while the “yolk” becomes a flabby intradermal nevus. If there are superimposed suspicious findings, either clinically or by dermoscopy, and a biopsy is indicated, saucerization is an option.
Eclipse Nevus. Its characteristic brown rim (surrounding a tan center) can have an irregular starburst outline as well as be discontinuous. Although the latter gives rise to asymmetry, these nevi are benign. They are common on the scalp, especially in children in whom they represent a phenotypic marker or omen for “moliness.” The less common pink eclipse nevi are also found on the scalp. If a parent cannot be dissuaded from an excision of an eclipse nevus on the scalp, a specific dermatopathologist should be recommended to avoid possible over-reading of a special-site nevus.

Other Signature Nevi. Target nevi (aka Cockarde) look sufficiently like eclipse nevi (if you delete the brown center) that Bolognia regards them as “cousins.” It is not uncommon for them both to occur on the same patient or within the same family. In perifollicular hypopigmentation, a reduction in pigment surrounding the follicles, is a common feature.
Dermatologist and immunologist Michael D. Rosenblum, MD, PhD, assistant professor in the Department of Dermatology at the University of California, San Francisco, has just published convention-shattering research illuminating the autoimmune pathophysiology of alopecia areata (AA). It redefines the conventional concept of regulatory T cells (Tregs) and redraws the map of critical factors determining the production of new hair. Dr. Rosenblum’s research was supported by the DF’s 3-year Stiefel Scholar Award that he received in 2015. It was 1 of 3 such awards—generously funded by Charles and Daneen Stiefel—for outstanding investigators exploring autoimmune and/or connective tissue diseases.

Dr. Rosenblum’s overarching goal is to understand precisely how the skin and immune system interface, and ultimately develop targeted treatments to rebalance the immune system in patients suffering from autoimmunity and cancer. His immediate target is AA, one of the most common human autoimmune skin diseases. This became central for him as his earlier exploration of Tregs—and their ability to suppress inflammation—progressed. He was the first to establish the prolific and full-time residence of Tregs in healthy, uninflamed skin, where they cluster around hair follicles (HFs), which contain the stem cells (HFSCs) that differentiate into new hairs when telogen transitions to anagen. Dr. Rosenblum eliminated Treg cells in mice, hoping to discern evidence of their function in skin. He shaved their skin so he could observe any changes—and he saw, with astonishment, that this shaved hair never grew back.

Dr. Rosenblum came to discover that Treg function in the skin is unrelated to the immunosuppressive action that had been considered its single function. He was also struck by genome-wide analyses of AA patients highlighting genes also involved in cutaneous Treg behavior. Then with the support of his Stiefel Scholar Award, Dr. Rosenblum discovered that Tregs in skin actually control the HFSCs’ ability to differentiate and form a new hair. No Tregs—no hair. This startling discovery carries the potential for unraveling and treating a variety of human diseases of HFs in addition to AA. Because HFSCs are also involved in wound healing, Dr. Rosenblum is planning to study Tregs in this context as well.

Dr. Rosenblum is deeply grateful to the Dermatology Foundation for his ability to carry out this transformative research. “A large portion of what I have been able to achieve would never have been possible without the DF’s support,” he emphasizes.

“Establishing yourself as an independent investigator is one of the hardest things to do as a physician-scientist,” he explains. “My DF research fellowship and career development award enabled me to have a fighting chance. Then the Stiefel Scholar Award enabled me to take our research to this next level. I am honored to be a recipient of this exceptional award.”


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**The Power of Collaboration**

Dr. Rosenblum notes that four of his coauthors received early career research support from the DF: Drs. Cotsarelis, Liao, Ricardo-Gonzalez, and Scharschmidt. “Basic science investigators in dermatology are a relatively small group and it is very important for us to work together. We can achieve more collectively than we can individually—and funding and networking opportunities enabled by the DF greatly facilitate these collaborations.”
Noninvasive Imaging in Dermatology  
Anthony M. Rossi, MD

Introduction. Integrating emerging technologies to continue expanding our ability to visualize reality noninvasively improves our diagnostic and management capabilities. Dr. Rossi concluded his list of the more recent optical modalities with reflectance confocal microscopy (RCM), “the most mainstream now of this group” and one that he has incorporated into his work. It is noninvasive, gives cellular resolution, preserves the natural architecture of the skin, and allows for assessing the same tissue over time.

RCM. It is similar in concept to ultrasound, but uses optical reflectivity instead of ultrasound waves. Light from a laser source illuminating the target spot on the skin is reflected back onto a detector. Structures containing keratin or melanin appear bright under RCM. Rossi prefers the newer and highly versatile handheld VivaScope 3000 to earlier devices. It provides a 1-mm field of view with cellular resolution at a 200 μm depth (to the papillary dermis). Especially valuable is the ability to create and visualize various 3D structures by assembling real time individual images in various types of stacks, mosaics, videos, etc. Images can be reviewed in real time or later. Rossi explained how he uses RCM for diagnosis, identifying optimal biopsy sites, presurgical mapping, intraoperative decision-making, directing both surgical and nonsurgical treatments, and monitoring afterward.

Lentigo Maligna. Rossi focused on the substantial value of RCM for assessing and treating LM, diagnostically and therapeutically challenging tumors. For a large melanoma on the head, it is normally extremely difficult to determine how large the resection will be via surgery, or how wide a nonsurgical treatment area should encompass. Rossi showed a study of patients in whom dermoscopy–indicated margins were 60% smaller than indicated by RCM. Where standard margins are normally applied, RCM may document the need for a margin that is significantly larger or smaller. He provided illustrative examples from his recent study that emphasized this versatile device’s value in all phases of diagnosing, planning, treating, and monitoring, always beginning by creating a noninvasive image map and delineating the margins.

Diversity in Dermatology  
Bruce U. Wintroub, MD

Introduction. Dr. Wintroub began by sharing the experience that had opened his eyes after 45 years in dermatology and more than 30 years as a dermatology chair. He was interim dean of UCSF’s School of Medicine in December 2014 when he learned that their students were lying down along a main thoroughfare holding signs: White Coats for Black Lives. And they had organized simultaneous demonstrations at 82 other medical schools countrywide. “It was a moment in the history of our institution we will always remember, and a personal moment for me that made me begin to connect the dots about diversity.” A mutually respectful meeting followed. Wintroub listened—and began to learn.

First Steps. Although more than 50% of dermatologists are women now, racial and ethnic inequalities are severe. These racial and ethnic groups are formally termed underrepresented in medicine (UIM). For example, although 13.2% of Americans are African-American, they are only 4.8% of physicians and even less—just 3.5%—of dermatologists. For Latinos, these figures are 17.1%, 6.5%, and 4.8%. Yet diversity among the medical workforce has been shown to improve the patient care we offer. And a more diverse academic workforce will improve our research and our ability to meet the unique needs of these groups. “A diverse workforce is a better workforce.”

A Call to Action. Wintroub discussed the imperative need for multipronged action—by institutions, departments, professional organizations, and individual dermatologists—to alter perceptions on both sides of the divide, to improve percentages of blacks and Latinos graduating college, entering medical school, and matching for residencies.* The most concerning challenge is the huge gap between college and medical school. “We need to increase the number of medical students to reflect their percentage of the population.” Wintroub noted various early changes being discussed and implemented. “The journey begins with the first steps.”

Why Does Diversity Matter?

- Diversity among the medical workforce has been shown to improve patient care
- Race-concordant visits are longer and have higher positive ratings than race-discordant visits
- Minority physicians are:
  - More likely to care for patients of their own race or ethnic group
  - Practice in underserved areas
  - Care for poorly insured or uninsured patients
  - Care for patients with poor health status who use emergency rooms for healthcare
- Increasing UIM representation in the dermatology workforce may improve disparities in access to care and therapy
- A more diverse workforce may help address the growing discrepancy in geographic distribution of dermatologists
- A more diverse academic workforce may improve research focused on the unique needs of UIM populations

What Can We Do?

**Departments:**

- Make diversity an explicit goal of residency selection
- Change the residency interview format
- Shift emphasis away from test scores and publication numbers
- Prioritize competencies in addition to medical knowledge
- Recruit and retain more UIM academic physicians to serve as mentors
- **Spread the word**

**Dermatologists:**

- Be a role model for patients from underrepresented populations.
- Ask your UIM patients: “Why not be a doctor—and how about being a dermatologist?”

New Threats to Having a Choice of Dermatopathologist

**Philip E. LeBoit, MD**

**Introduction.** Dr. LeBoit—an academic dermatopathologist at a university-based dermatopathology lab that competes in the outpatient market with corporate labs—has witnessed profound change in the field he entered close to 40 years ago.

**The Rise of Dermatopathology.** LeBoit outlined dermatopathology’s unique origins, then described the field he had entered in 1985. The eastern U.S. and western U.S. had different systems, but neither one created barriers to choice. Given the increasingly restrictive forces in healthcare, the fact that dermatopathology originated quite differently from the rest of pathology makes it “very important now that dermatopathology has a huge say in how its practice evolves.”

**The Fall of Dermatopathology.** LeBoit detailed the changes as the forces governing the survival of dermatopathology labs—and thus free choice—shifted from clinical need and patient outcome to largely economic and financial concerns. In the early 1990s, the Clintons’ attempts to improve the healthcare system in the U.S. led to the ascendance of primary care and HMOs. This panicked small laboratories, leading to consolidation. The Electronic Medical Record (EMR) era opened the door to sub rosa quid pro quo situations. Many dermatologists receiving a donated EMR system from a large lab felt compelled to say thank you by switching to their dermatopathology service. Now, these large labs offer discounted fees to help meet meaningful use requirements. Many insurance companies have reduced the number of covered dermatopathologists. Various pressures are creating large-scale consolidation of private dermatology practices, many of which now insource dermatopathology. Insurance carriers are consolidating as well, and tend to choose large labs offering one-stop shopping. This eliminates most dermatopathology labs.

**Why Choice Is Important.** “No one has a monopoly on the truth, and dermatologists should have a big say in finding a dermatopathologist whose answers mesh with what they believe is in the best interests of their patients.” LeBoit enumerated the ways in which corporate dermatopathology is often the antithesis of this goal. “We have to convince insurance companies that things like cost and turnaround time and communication are not geographically fixed to a lab that is in-state.”

Emerging Barriers to Referral Choice

- Consolidation among dermatology practices
- Consolidation among insurance carriers
- Laboratory corporations offering large menus of services to insurers
- Restricted panels
- All of the above are driven by financial concerns, not patient outcome

Summary

- Dermatopathology is almost as old as dermatology, and has been integral to its development
- Although dermatopathology may no longer be a major vehicle for scientific discovery, it remains integral to dermatology—yet it may become unrecognizable except as an industry, or a vehicle for unethical behavior
- Defensive dermatopathology—ie, everything is atypical and needs re-excision—drives cost up
- Until everything is scientifically settled, dermatologists and their patients are best served by finding a dermatopathologist whose practice style/communication/ideology fit theirs

The Times, They are a Changin’

**Moise L. Levy, MD**

**Introduction.** Dr. Levy amplified this title, adding “…Or are they?” Then he focused on the enduring dynamic of being an effective physician, and his perspective that changes in technology, in the healthcare environment, etc. do not alter what he gives his patients and their families or the satisfaction he receives. He greets changes as opportunities for enhancing this.

**The Basic Lessons.** The heart of being a physician is the relationship with patients, and for a pediatric dermatologist, their families...
as well. He emphasized “the ultimate honor of how openly and freely patients open up to us.” Levy described early experiences that taught him to listen, whether a parent is sharing information and observations or a resident is sharing observations of a challenging patient. Increased communication “with our patients/families will help make earlier and better care decisions.” The ability to accept uncertainty avoids over-testing/biopsying and maintains honesty with patients/families. Working collaboratively as a team is critical, and remember that “the patient and family are also partners and collaborators—the essential collaboration that we started with when we came into medicine.” Changes occurring in the healthcare world “represent opportunity.” Levy stressed the mutual importance of mentoring and noted various options.

Looking Ahead. We need to use clinical and economic outcomes to re-evaluate the care we give our patients to know we are giving them our best. Encourage cross-disciplinary relationships; we gain so much from them. Stay focused on your desire to help people when confronting the challenges presented by EMR, by the need to solve racial inequality, by reimbursement issues, etc. Never forget that “the secret of the care of the patient is in caring for the patient” (FW Peabody, 1927).

What Are We To Do?

• Thoughts on where we have been
  – excellence from our teachers and colleagues
  – much has been gained from experiences with patients/families

• Thoughts on where we are going
  – we remain interested in doing the best for our patients/families
  – new scientific/technical resources—not threats, but assets
  – focus on what is right for the patient—engage our patients/families; integral part of interdisciplinary care model

• Come early….Stay late
• Continue to mentor—all will be better!
  – the patient is the focus of our attention

Now and Going Forward

• The patient/family as a partner/collaborator
• The patient is the boss!
• Newer medical curricula with patient stories as guides
• Better collaboration with other disciplines
• Better utilization of EHR (???), other technologies
• Genomics to help guide care
• Changes in medicine represent opportunities

Neurologic Complications of Biologics

• Progressive Multifocal Leukoencephalopathy (PML)
• Demyelinating disorders
  – Multiple sclerosis
  – Optic neuritis
  – Transverse myelitis
  – Acute inflammatory demyelinating polyradiculoneuropathy (AIDP): aka Guillain-Barré
  – Chronic inflammatory demyelinating polyneuropathy (CIDP)

Neurologic Side Effects of Dermatology Drugs—That We May Be Missing

Kenneth Fox, MD

Introduction. Dr. Fox, a neurologist in the community-based setting at Kaiser Permanente San Francisco, spoke of the neurologic and neuromuscular complications he encounters from several drugs used commonly in dermatology—the more recently incorporated biologic TNF-β blockers (eg, efalizumab, rituximab), and the more familiar IVlg and steroids. By the time Fox normally sees these patients, their symptoms have progressed. Increased awareness in the dermatology community will enable recognition of these potential side effects when they first emerge and addressing them early, limiting morbidity and mortality. For each disease, Fox described the clinical presentation, pathophysiology, appropriate clinical and diagnostic evaluation, and treatment.

TNF-α blockers. They are responsible for demyelinating disorders of varying location and nature. PML (progressive multifocal leukoencephalopathy) originates with a JC virus infection that reaches the brain, unleashing a sequence of effects producing neural dysfunction and upregulating the immune system. Optic neuritis typically presents as painless vision loss in one or both eyes. Transverse myelitis manifests clinically as spinal cord symptoms: weakness, sensory loss in the limbs, some bowel and bladder dysfunction. Multiple sclerosis presents with multifocal neurologic symptoms and/or lesions throughout the brain. The peripheral nervous system can also be affected, either as AIDP (acute inflammatory demyelinating polyradiculoneuropathy, known as Guillain-Barré), a rapidly progressive and potentially fatal ascending weakness, or the more indolently progressive or chronic CIDP (chronic inflammatory demyelinating polyneuropathy).

Older Drugs. One of the most common side effects with IVlg treatment is headache, especially in patients with a pre-existing primary headache disorder. Severe side effects include acute renal failure (especially in diabetics), stroke, thrombosis, Stevens-Johnson syndrome, serum sickness, encephalic meningitis, and anaphylaxis (especially in IgA-deficient patients, who require IgA-depleted formulations). The common theme is reduced blood flow from the hyper-viscosity caused by the large load of huge immunoglobulin proteins that entered the bloodstream. Fox’s preventive pretreatment regimen involves diphenhydramine or benadryl (and prednisone if headaches are an issue), with generous hydration. Steroid myopathy is a danger for patients on ≥40 mg for >4-6 weeks. If loss of strength is detected, discontinue steroids (or at least decrease below 40 mg/day and/or alternate days), and increase protein intake. Cardinal for chronic steroid use is regular exercise using American Heart Association guidance.

What’s New in Melanoma?

Jeremy S. Bordeaux, MD, MPH

Dermatologist Density and Healthcare Outcome. When studies showed that physician density influences healthcare outcomes, it was considered a function only of primary care physicians, not specialists. Because this ignores “the importance and value of what dermatologists bring as a specialty,” Dr. Bordeaux decided to

(Continued on page 15)
**ONYCHOMYCOSIS**
Your patient’s dirty secret?

**TIME TO CLEAN IT UP**
★ AT THE SITE OF INFECTION ★

**JUBLIA**
(efinaconazole)
Topical Solution 10%

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

**IMPORTANT SAFETY INFORMATION**
- JUBLIA is for topical use only and is not for oral, ophthalmic, or intravaginal use.
- Patients should be instructed to contact their health care professional if a reaction suggesting sensitivity or severe irritation occurs.


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

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

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

To report SUSPECTED ADVERSE REACTIONS contact Valeant Pharmaceuticals North America LLC at 1-800-321-4576 or FDA at 1-800-FDA-1088 or visit www.fda.gov/medwatch.

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


JUBLIA is a trademark of Valeant Pharmaceuticals International, Inc. or its affiliates.
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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

JUBLIA® (efinaconazole) topical solution, 10%

For topical use
Initial U.S. Approval: 2014

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

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

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

CONTRAINDICATIONS
None.

ADVERSE REACTIONS

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

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

Table 1: Adverse Reactions Reported by at Least 1% of Subjects Treated for up to 48 Weeks

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>JUBLIA N = 1227</th>
<th>Vehicle N = 413</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingrown toenail</td>
<td>28 (2.3%)</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Application site dermatitis</td>
<td>27 (2.2%)</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Application site vesicles</td>
<td>20 (1.6%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Application site pain</td>
<td>13 (1.1%)</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS

In vitro studies have shown that JUBLIA, at therapeutic concentrations, neither inhibits nor induces cytochrome P450 (CYP450) enzymes.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category C

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

Systemic embryofetal development studies were conducted in rats and rabbits. Subcutaneous doses of 2, 10 and 50 mg/kg/day of efinaconazole were administered during the period of organogenesis (gestational days 6-16) to pregnant female rats. In the presence of maternal toxicity, embryofetal toxicity (increased embryofetal deaths, decreased number of live fetuses, and placental effects) was noted at 50 mg/kg/day (559 times the Maximum Recommended Human Dose (MRHD) based on Area Under the Curve (AUC) comparisons). No embryofetal toxicity was noted at 10 mg/kg/day (112 times the MRHD based on AUC comparisons). No malformations were observed at 50 mg/kg/day (599 times the MRHD based on AUC comparisons).

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

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

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

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

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

NONCLINICAL TOXICOLOGY

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

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

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

PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (Patient Information).
Within a given county, a greater dermatologist density is associated with reduced melanoma mortality compared to counties lacking a dermatologist. Efforts to recruit dermatologists to counties currently lacking providers will likely result in a population-level decrease in mortality.

Increasing Compliance With Skin Self-examinations (SSEs)

- Patients exhibit distinctive learning styles:
  - Visual
  - Aural
  - Reading/writing
  - Kinesthetic
  - Multimodal combination
- We increased the performance of SSEs with a multimodal approach:
  - Computer-Assisted Learning SkinSafe education
  - Hands-on skin self-exam tutorial
  - Telecommunication reminders
- Future research targets the efficacy of personalized behavior modification techniques that are specific to SSEs and sun-protective actions and based on a patient’s learning style and preference.

What’s New in Photoprotection

Henry W. Lim, MD

Introduction. Photoprotection comprises the multiple elements that help to protect skin from the side effects of sunlight and thus enable people to enjoy the many benefits of outdoor activities. Seek shade, wear protective clothing/hats/sunglasses—and use sunscreen. Dr. Lim discussed recent developments in the complex world of sunscreens.

Products. There are currently 750 sunscreen products (organic and mineral) in the U.S., some with SPF greater than 100. All UV filters are considered OTC drugs and thus under FDA regulation. Compared to Europe, the filters available in the U.S. are more limited; currently, 8 filters are in an FDA docket waiting for approval. The UVA filter oxybenzone—the 2014 Allergen of the Year and rarely used in Europe now—is in 70% of the non mineral sunscreens here. And although there are no known safety risks in humans, concerns have been raised that it kills adult coral reefs. Lim noted the unsupported controversy about retinyl palmitate, and discussed nanoparticles and the lack of concerning evidence for current sunscreen use on healthy skin. Antioxidants are not UV filters, but protect against UV-induced DNA damage. Sunscreens are significantly more protective when they include stabilized, biologically active antioxidants.

Beyond UV. A startling discovery showed that UV-induced DNA damage in melanocytes—cyclobutane dimers (CPDs)—continues after the completion of light exposure. This is mediated by reactive oxygen species and melanin, especially pheomelanin. Lim described the effect of visible light on skin and its possible role in conditions aggravated by sun exposure, eg, postinflammatory hyperpigmentation (PIH), melasma. Antioxidants may be beneficial. Erythropoietic protoporphyria (EPP) and solar urticaria benefit from the α-MSH analogue afamelanotide’s ability to increase melanin, and thus tolerance to visible light. It is under FDA review for EPP.

Nontopical Agents. Lim listed potential agents, noting them as promising adjuncts, not replacements, for topical products. He spoke about extracts from the tropical fern Polypodium leucotomos (available OTC in the U.S.), which has antioxidant and anti-inflammatory benefits. This may have a role in protection against visible light.

Antioxidants & Sunscreens

- Sunscreen + antioxidants >> sunscreen alone in:
  - Suppressing UV-induced pigmentation, depletion of Langerhans cells, induction of MMP9
  - Suppressing infrared-A induction of MMP1

Possible Clinical Implications: Visible Light Protection

- Visible light may have a role in conditions aggravated by sun exposure—such as PIH and melasma—especially in dark-skinned individuals
- Currently available organic (chemical) UV filters are not sufficient to protect the skin from these effects
- Antioxidants may be beneficial

Antioxidants & UV
• Antioxidants:
  – Resveratrol
  – Vitamin E, vitamin C
  – Tea extract ([-]epigallocatechi-3-gallate)
  – Retinyl palmitate
• Low SPF, but protect against UV-induced DNA damage, immune suppression, and depletion of Langerhans cells
• Need to be sure they are stable and biologically active

Nontopical Photoprotection
• Polypodium leucotomos extract: tropical fern
• Oral nicotinamide: the amide of vitamin B3
• Afamelanotide: α-melanocyte stimulating hormone analogue
• Promising as adjunctive photoprotective measures
• Not to replace current regimen of photoprotection

Inpatient Dermatology: New Observations, New Recommendations
Lindy P. Fox, MD

Introduction. Dr. Fox, a hospitalist, shared some of her group’s informative observations from the past 5–10 years, and the resulting recommendations.

Calciphylaxis. Fox described a 65-year-old female patient—with rheumatoid arthritis, diabetes, and atrial fibrillation—who first alerted her to the scenario of nonuremic calciphylaxis in the setting of warfarin exposure. Shortly after her subtherapeutic dose of warfarin was increased she developed calciphylaxis-like lesions, distally rather than in the more fatty areas expected for warfarin-associated skin disease. Histology pointed to calciphylaxis. Similar patients followed—all warfarin-exposed (average treatment duration of 3 years), mostly women, with an average age of 60. Unlike classic uremic calciphylaxis, prognosis is very good.

Cutaneous Reaction to Cytarabine. The patient—a 65-year-old female patient—with rheumatoid arthritis, diabetes, and atrial fibrillation—who first alerted her to the scenario of nonuremic calciphylaxis in the setting of warfarin exposure. Shortly after her subtherapeutic dose of warfarin was increased she developed calciphylaxis-like lesions, distally rather than in the more fatty areas expected for warfarin-associated skin disease. Histology pointed to calciphylaxis. Similar patients followed—all warfarin-exposed (average treatment duration of 3 years), mostly women, with an average age of 60. Unlike classic uremic calciphylaxis, prognosis is very good.

Cytarabine Papular Purpuric Eruption
• Looks awful!
• Most often appears after med discontinued, so must think about it to make diagnosis
• Clinically and histopathologically benign

Recommendations
• Reassurance
• OK to re-expose to cytarabine

Acute Inflammatory Edema
• Turn the patient over
• Don’t biopsy

Recommendations
• Reassurance

Herpes Zoster
• Patients with herpes zoster are viremic
• Virus may aerosolize from the skin or respiratory tract
• Inpatient dermatologists treat all disseminated zoster and zoster in immunocompromised hosts with IV acyclovir

Recommendations
• Cover lesions with hydrocolloid dressing
• Contact and airborne precautions for all hospitalized patients
• Consider IV acyclovir in disseminated disease and immunocompromised patients

(Continued on page 18)
The Dermatology Foundation is grateful to the following corporations for their generous contributions last year. Their support furthers the DF’s mission to develop and retain tomorrow’s leaders in the specialty, enabling advancements in patient care.

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Herpes Zoster. Fox noted likely scenarios involving both immunocompetent and immunocompromised patients, localized and disseminated disease, outpatient and inpatient settings. She highlighted areas of inadequate or newly transforming knowledge, stressing the comprehensive need for broad infection control measures. Immunocompetent patients with localized disease are actually viremic, as varicella zoster virus DNA is found in their vesicle fluid and saliva. From the saliva, it can be aerosolized everywhere. Fox detailed needed precautions, including the use of hydrocolloid dressings rather than gauze.

The Use of Botulinum Toxin for Nondermatologic Issues

Kenneth Fox, MD

Introduction. The initial clinical applications of botulinum toxin (Botox) were neurologic, first to treat strabismus in pediatric patients, then expanding to blepharospasm—which enabled recognition of its cosmetic value. Although for some time the spotlight has been on its cosmetic applications, Botox also benefits innumerable patients with neurologic disorders. This is an active component of Dr. Fox’s practice. Botox has multiple advantages. Its local action and relatively long-term effect reduce or eliminate reliance on daily oral (and sedating) agents, it is usually reversible, side effects are generally minimal (especially at lower doses), and any remote effects are subclinical. Fox profiled some of the important application categories.

Botox and Neurologic Disease. Fox sees one or more patients a week with hyperkinetic movement disorders. He discussed hemifacial spasm (from an aberrant nerve reinervation, often following Bell’s palsy) and blepharospasm, including the resistance to Botox that some patients may develop. Dystonias can be focal—due to overuse, eg, writer’s or musician’s cramp—or affect multiple segments. More generalized dystonias are challenging. Fox commonly treats spasticity, adding Botox (coupled with other antispasmodics) when first-line treatments are inadequate. Hypersecretory disorders include hyperhidrosis (generally treated by a dermatologist) and sialorrhea, the heavy drooling that can occur in later stages of Parkinson’s and Alzheimer’s diseases. Botox is a helpful adjunct in treating chronic pain. “Patients with tightness complaints tend to respond exquisitely.” Fox also discussed Botox in treating headache (FDA approved), which he uses to help break a headache cycle, especially with bruxism.

Conclusions. Botox can be a dramatic life-changer for those patients who need it. Of the numerous and interesting neurologic conditions for which Botox can be helpful, it is applied mainly to hyperkinetic and hypertonic movement disorders. Doses tend to be much higher than those in cosmetic procedures, and the resultant high cost of treatments demands especially careful and thoughtful use.

Application Categories
- Hyperkinetic movement disorders
- Dystonias
- Spasticity
- Hypersecretory syndromes
- Pain/Headache

The Benefits
- Local injections* with highly targeted approach
- Reversible therapeutic effects and side effects
- Reduces or eliminates requirement for toxic oral medications
- Safe in trained hands
- Does it really have just local effects?
  - Neuromuscular junction transmission defects have been recorded in torticollis
  - Effects are uniformly subclinical

Summary
- Numerous applications for botulinum toxin in neurology
- Mainly applied to hyperkinetic or “hypertonic” movement disorders
- Becoming widely used as an adjunct for chronic pain conditions
- Doses tend to be much higher than those used for cosmetic goals

Consider Planned Giving and Include the DF in Your Will

The Dermatology Foundation’s successful support of significant research, and promising teachers and investigators has helped to dramatically further the understanding and treatment of skin diseases and disorders. The DF remains equally important for future progress. Planned giving—arranged in the present as a charitable bequest in your will—allows DF supporters to continue supporting advancements in all areas of the specialty.

Only monetary donations can be accepted. Explore your options with your attorney or financial advisor, and be sure to identify the Foundation, a 501(c)3 organization, as the gift recipient in your will or other instrument. Sandra Benz, Executive Director, will be pleased to discuss any questions that arise (847.328.2256).
2017 CLINICAL SYMPOSIA FACULTY Proceedings—Part II

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MD: none. Anthony M. Rossi: Allergan, Mavig, Canfield, Galderma,
DF Awardees Find Keys to Baldness and Gray Hair

Important research has shed light on two significant questions in hair biology, elucidated by investigators in the Department of Dermatology at UT Southwestern. The team is led by associate professor Lu Q. Le, MD, PhD, working closely with Chung-Ping Liao, PhD, an assistant instructor.

They identified the elusive progenitor cells that directly gives rise to the new hair shaft—and they have nailed down the unique protein within these progenitor cells that enables melanocytes to pigment the newly forming hair. Their discoveries were published in the April 15 edition of Genes & Development and captured attention in the scientific and popular media across the country.

Dr. Le had originally planned to explore what causes the neural tumors in neurofibromatosis type 1, which develop from Schwann cells—specialized neural cells identified by the presence of the transcription factor Krox20. He suspected a role for the protein called SCF (stem cell factor), so he eliminated it in all Krox20-expressing cells in experimental mice. He knew this would delete SCF in Schwann cells, and looked for effects on tumor development. To the team’s astonishment, the hair on these mice turned completely gray.

SCF clearly exists in the hair follicle. Dr. Le knew that Krox20 had already been found there, and he and Dr. Liao were intrigued by this possible partnership in hair. The team learned that mice who lose Krox20-producing cells in the hair follicles become bald, and thus that the Krox20-containing follicular cells are the long-sought hair shaft progenitor cells. They also discovered that these cells initiate SCF synthesis, and that SCF’s sole function in hair is responsibility for hair pigment. Now Dr. Le’s team plans to explore Krox20–SCF changes with aging, and assess Krox20 in hair development and in male pattern baldness. They also anticipate exploring therapeutic possibilities.

Liao C-P, Booker RC, Morrison SJ, Le LQ. “Identification of hair shaft progenitors that create a niche for hair pigmentation.” GenDev2017;31:744–56. (See DF website for link to complete article.)

Lu Q. Le, MD, PhD
Chung-Ping Liao, PhD

Dr. Le received a 2008 DF Career Development Award (CDA). Dr. Liao is a current CDA recipient.