Merkel Cell Carcinoma: Bringing a Rogue Skin Cancer Under Control

Paul Nghiem, MD, PhD—Head of Dermatology and George F. Odland Endowed Chair at the University of Washington—became a passionate and committed explorer somewhat over 10 years ago when he took his first game-changing steps into the uncharted territory of Merkel cell carcinoma (MCC), the rare and highly lethal skin cancer (see box on page 8) he had come to specialize in managing. A little-known skin cancer at that time, its ~46% mortality at 5 years—nearly three times that of melanoma—makes it a truly feared skin cancer. Yet MCC was so off the radar back then that almost no major centers had a true interest in caring for this unique clinical entity. There was little agreement on how to treat early disease, and the toolbox for effective treatment of advanced disease was empty.

Nghiem’s transformative series of “firsts” in MCC began with the most basic—developing a clear clinical profile to facilitate recognizing MCC and help reduce these pronounced, often fatal, delays before diagnosis. He and his team continued to improve clinical management, refined our understanding of the carcinogenic mechanism of the Merkel cell polyomavirus (MCPyV) following its landmark discovery by Chang and Moore in 2008, and developed useful diagnostic, prognostic, and now therapeutic tools. Nghiem and collaborators have confirmed and mapped the prominent immunologic epitopes of this skin cancer, and are currently assessing the efficacy of novel immunotherapy agents in MCC patients. During this time Nghiem has amassed a repository of more than 1,150 patients with clinical longitudinal data plus blood and tissue specimens. He has also established a large and active MCC organization that includes physicians, scientists, and patients and their families. MCC is no longer an obscure and overlooked skin cancer.

Ironically, Nghiem’s initial research focus bore no resemblance to his current predominant interest in MCC. He had

Focus on Research

Hair Follicle Stem Cells Au Naturel—Their Secrets Uncovered With Real-Time Videos

Valentina Greco, PhD
Associate Professor of Dermatology, Cell Biology, and Genetics, Yale Stem Cell Center, Yale Cancer Center; Yale School of Medicine

Greco is dramatically transforming what we know about hair follicle stem cells and the regeneration process through her innovative adaptation of intravital imaging for studying them (see box on page 11). This astonishing noninvasive microscopy technique marries 3D video capability with microscopic resolution to probe a fraction of a millimeter below the skin surface of live animals and observe the ongoing actions of individual cells in real time. Until this quiet revolution, scientists have relied on in vitro images—static snapshots that seriously risk missing critical steps in the regeneration process, substantially slowing the pace of research and eventual clinical advances.

Intravital microscopy enables identifying real-time cellular behaviors and their consequences, and the molecular signals that drive them. In essence, intravital imaging peeks through a microscopic keyhole to

Typical MCC lesions. Two characteristic primary lesions, including sun-exposed location and nontender, nonpruritic nature. Top: the left upper eyelid of an 85-year-old man, with typical red-purple color; initially misdiagnosed as a chalazion. Bottom: the left small finger of a 70-year-old man. (Reprinted with permission from AS Moshiri et al. See Suggested Readings.)

(Continued on page 2)

(Continued on page 11)
been a hard-core cell biologist, and his unanticipated intersection with MCC was not initially welcome. A few years in, though, he realized he had actually found his perfect match in a highly aggressive skin cancer that is strongly linked to the immune system. And his hands-on experience investigating cellular behavior in the lab turned out to be invaluable preparation for his research into MCC. It expanded his perspective, enriching the questions he has been able to ask and the ways in which he has sought to answer them.

**How It All Began**

Nghiem was a Stanford medical student doing a dermatology rotation at Harvard when he met Harley Haynes, MD, a powerful force as a dermatologist and teacher. “Harley got me interested in dermatology, or otherwise I’d have been an oncologist,” Nghiem recalls. Then his dermatology residency brought him back to Boston (the Harvard/MGH program) in 1995, where he encountered an elderly male patient of Dr. Haynes with an odd bump on his lip. Nghiem did the biopsy, it turned out to be MCC, and he managed the patient together with Haynes. They were both frustrated by the absence of information on how to deal with this tumor.

Several years later, Haynes was asked to write a chapter on MCC for the American Cancer Society’s upcoming book on skin cancer. As he passed the assignment over to Nghiem, Haynes said: “You’ve seen one case, so you’re an expert in MCC—you’ll be able to do it.” Nghiem was not thrilled. He knew nothing about MCC, and the extended effort needed to educate himself would interfere with his UV-cell cycle biology projects. He was convinced “it would be a complete waste of time,” but felt unable to say no to his mentor.

And that acquiescence changed his life. Because once Nghiem finally began his preparatory reading for this chapter, he was astonished to discover “a really interesting skin cancer! It’s much more aggressive than any of the other skin cancers. It’s much more tightly linked to the immune system than either melanoma or basal cell cancer. And we don’t know anything about it.” He enjoyed writing the chapter.

By the time the book appeared in 2001, Nghiem was an attending dermatologist at the Dana Farber Cancer Institute. “Patients began coming to us from all over the New England area and beyond. Suddenly I was seeing MCC often,” he says, “and I became acutely aware that—in addition to this cancer being extremely interesting and mysterious—there was a huge need for someone to pay attention to it.”

Initially, the challenge for Nghiem was in learning how best to care for these patients clinically. He never anticipated the engrossing research questions and important progress that lay ahead. So he continued his research in the cell cycle zone while he and Haynes gradually developed some effective management approaches for local and regional disease. For MCC patients with metastatic disease, the situation remained hopeless.
AEIOU—Clinical Characteristics at Diagnosis

Nghiem’s first published step aimed at earlier diagnosis. He was very concerned that the healthcare community’s widespread unfamiliarity with this rare skin cancer meant that localized disease was often unrecognized. Thus a great many MCC patients were not correctly diagnosed until their disease had metastasized—an often deadly delay in diagnosis. Disease-specific survival for local disease was >90% at 3 years. It fell to 52% once nodal involvement was clinically detectable, and about 10% for those with distant metastatic disease at diagnosis. The medical community needed a guide to recognition, but “there was no available systematic analysis that defined MCC’s characteristic clinical features,” Nghiem says. So he took his first exploratory step into the uncharted territory of MCC—and organized a study “to identify key clinical features to assist the clinician in recognizing when a biopsy may be warranted, and identify this aggressive skin cancer at an earlier and potentially more curable point.”

In 2007, three medical centers in Boston and two in Seattle provided data on 195 patients. The patient profile that emerged was overwhelmingly white (98%), above age 50 (90%), and with a slight preponderance of men. Profound immunosuppression characterized roughly 10% of this patient group, far higher than in the general population. It reflected HIV, chronic lymphocytic leukemia (CLL), and solid organ transplantation. Most lesions appeared on sun-exposed skin, usually the head and neck. And among the 106 patients for whom a presumed clinical diagnosis was reported, almost 99% of them had been incorrect—including the 56% that were reported, almost 99% of them had been

The First Consensus Staging System—And Don’t Ignore the Nodes

Conflicting and inadequate staging systems appearing over past years, along with the lack of solid prognostic data, also complicated management of these patients. Nghiem led a large team from around the country and tackled this via a total of 5,823 prospectively enrolled MCC cases from the National Cancer Data Base that were followed up for a median of 5.3 years. They assessed the prognostic significance of tumor size, the reliability of clinical vs pathologic nodal evaluation, and the extent of disease at presentation to produce the first consensus staging/prognostic system for this cancer.

The pivotal point to emerge from this analysis was the compelling importance of biopsy for nodes that appear clinically negative. Previous studies had already found that approximately 1 in 3 patients with clinically node-negative local disease actually have microscopic spread to the nodes. Nghiem confirmed this, then documented the consequences of relying solely on a clinical node assessment in patients with clinically local-only disease. For patients with pathologically proven negative nodes, the 5-year survival outcome was 76%. This fell to 59% for those who underwent only clinical nodal evaluation. (See graphs and tables below.) So biopsy-based node evaluation has prognostic import, as well as treatment implications for the therapeutic management of involved nodes and node beds.

For cases presenting with local disease, stage I involves smaller tumor size—c2 cm—and the best survival at 5 years. Stage II involves tumors >2 cm, and the new substage

(Continued on page 7)
Dr. Warwick Morison has spent many years as a master clinician, teacher, speaker, and author in the field of photomedicine and photobiology. A close colleague praises Dr. Morison’s “productive balance between his busy private practice and actively teaching his fellow clinicians, residents, and attendings. His dedication to excellence in all areas has been constant.”

Dr. Morison first encountered his subspecialty in 1975 at Harvard Medical School and Massachusetts General Hospital. He had come to Boston from the U.K. in search of a research fellowship in dermatology, opting for a new environment after medical school and initial dermatology training in his native Australia and then London. Unexpectedly, Dr. Morison was asked to run the PUVA program at Massachusetts General Hospital, the wellspring of innovation in photomedicine, and simultaneously aided in setting up his own photoimmunology research lab for his fellowship. He found modern photobiology and photomedicine extremely intriguing. “And it is enormously satisfying, because the vast majority of people you treat get better.”

After teaching at Harvard for six years, Dr. Morison accepted a senior research position at an NCI immunobiology lab and joined the dermatology faculty at nearby Johns Hopkins University (he is now Professor) to teach photomedicine. A decade later he opened his private practice in Baltimore—still the only one in Maryland specializing in photomedicine. “Phototherapy works in roughly 35 to 40 different diseases now, and in many cases can be the most successful treatment,” he points out. “It gives me real satisfaction to use my experience and skills to solve my patients’ skin problems.”

Dr. Morison also investigates UV light treatment in various skin disorders and is currently focusing on morphea, scleroderma, and graft-vs-host disease. For many years he has also been a sought-after speaker and visiting professor, an important contributor in professional and patient-advocacy organizations, and has published prolifically. Dr. Morison’s textbook, Phototherapy and Photochemotherapy of Skin Disease, set the standard for his field. He also served as Editor-in-Chief of the Photomedicine Society’s journal for nine years.

Dr. Morison continues to enjoy working with the residents at Johns Hopkins, and on a volunteer basis at the University of Maryland. When asked about the time he invests in instructing residents, he says: “I enjoy teaching them because they enjoy being taught. That is why I have been doing this for over 30 years.”
“Dr. Maria Chanco Turner brings a remarkably broad vision to the concept of education,” a colleague points out. “For decades, she has taken a personal interest in the clinical education and professional success of fledgling dermatologists during their tours of duty at the NIH and beyond. She gradually developed a national following of Turner-educated devotees who now represent a ‘Who’s Who in Academic Dermatology’.”

Dr. Turner’s training to be an effective teacher and mentor began in the Philippines. Her mother was a physician who provided health care to the indigent, and her father specialized in tropical diseases. Their strong focus on academics, research, and charitable involvement became her values as well. After completing her medical education and partial residency in internal medicine in Manila, Dr. Turner was accepted into Yale’s dermatology residency program. “The specialty fascinated me because you can see the disease right in front of you.”

Dr. Turner moved to Washington, DC, right after her residency and taught in Howard University’s dermatology department for two years. In 1966, while caring for her young children, she became a part-time staff dermatologist at an HMO—the only part-time position she could find at a time when few women were in dermatology. George Washington University Medical School was right across the street, and soon Dr. Turner began to mentor residents and medical students. With her children in high school, she accepted a full-time faculty position there. A decade later, former mentor Dr. Steven Katz at the NIH offered her the position of Chief of the Dermatology Branch’s Consultation Service.

Dr. Turner’s responsibilities at the NIH included the education and supervision of clinical fellows and arranging the biweekly grand rounds that became a hugely popular resource for dialogue and learning. She was also very involved in clinical trials and in multidisciplinary research studies. She greatly enjoyed the interdisciplinary clinical collaboration: “I consulted on patients with infectious diseases, cancers, genetic syndromes, and the with fellows taking care of them—and I was really teaching by preceptorship, not lecturing.” A former NIH dermatology fellow credits Dr. Turner with “giving me my clinical skills. She taught me to look at things with a completely different eye than any other attending ever had.” Dr. Turner’s impact and reputation as an exceptional educator spread quickly. She became a visiting professor at dermatology training programs across the country, and a mentor to third-year dermatology residents through a diverse number of specialty organizations.

Dr. Turner has been Senior Clinician Emerita at the NIH since 2009, and continues to regard her former fellows as family. She also continues to volunteer at the Spanish Catholic Center’s clinic, dispensing care for indigents in the Washington, DC area.

In a colleague’s words, “Maria represents the very best with respect to education in our field.” Dr. Turner shares that she has built her career on a simple philosophy. “It is not just about the specialty of dermatology,” she explains. “It’s also about how you live your life and how you relate to others. All of that is part of the equation.”
AC Sustaining Members Make Substantial Commitment

The Dermatology Foundation Board of Trustees deeply appreciates the exceptional support provided by its 2015 AC Sustaining members. Each has gone beyond their $25,000 AC contribution to invest an additional $5,000 a year in dermatology’s future. The DF’s 135 Sustaining members are recognized below according to their cumulative AC giving threshold.

### $125,000

<table>
<thead>
<tr>
<th>Name</th>
<th>Name</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murad Alam, MD*</td>
<td>Peter G. Ehrnstrom, MD*</td>
<td>Bruce U. Wintroub, MD*</td>
</tr>
<tr>
<td>Andrew K. Bean, MD*</td>
<td>James O. Ertle, MD*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robert B. Ash, MD</td>
<td>Waine C. Johnson, MD</td>
<td>Désirée Ratner, MD*</td>
</tr>
<tr>
<td>Rodney S.W. Basler, MD**</td>
<td>Robert E. Jordon, MD</td>
<td>Phoebe Rich, MD*</td>
</tr>
<tr>
<td>Eugene A. Bauer, MD*</td>
<td>Gerald C. Krueger, MD</td>
<td>Carl B. Rountree, MD</td>
</tr>
<tr>
<td>Ronald R. Brancaccio, MD*</td>
<td>Mark Lebwohl, MD*</td>
<td>Neil S. Sadick, MD</td>
</tr>
<tr>
<td>Clay J. Cockerell, MD*</td>
<td>Stuart R. Lessin, MD*</td>
<td>William S. Sawchuk, MD*</td>
</tr>
<tr>
<td>Kevin D. Cooper, MD*</td>
<td>Eugene Mandrea, MD*</td>
<td>William A. Steele, MD*</td>
</tr>
<tr>
<td>Michael J. Ebertz, MD*</td>
<td>Elizabeth I. McBurney, MD*</td>
<td>Michael D. Tharp, MD*</td>
</tr>
<tr>
<td>Richard L. Edelson, MD*</td>
<td>Gregory G. Messenger, MD</td>
<td>Jonathan S. Weiss, MD*</td>
</tr>
<tr>
<td>Janet A. Fairley, MD*</td>
<td>Warwick L. Morison, MD</td>
<td>Kim B. Yancey, MD*</td>
</tr>
<tr>
<td>Lisa A. Garner, MD*</td>
<td>Howard Murad, MD**</td>
<td></td>
</tr>
<tr>
<td>James J. Herrmann, MD*</td>
<td>Thomas G. Olsen, MD</td>
<td></td>
</tr>
<tr>
<td>Julie A. Hodge, MD, MPH*</td>
<td>Nicholas V. Perricone, MD*</td>
<td></td>
</tr>
</tbody>
</table>

### $75,000

<table>
<thead>
<tr>
<th>Name</th>
<th>Name</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas W. Andrews, MD</td>
<td>Charles L. Heaton, MD</td>
<td>Luette S. Semmes, MD*</td>
</tr>
<tr>
<td>Stuart M. Brown, MD∞</td>
<td>Jean M. Holland, MD</td>
<td>Mark P. Seraly, MD*</td>
</tr>
<tr>
<td>Jeffrey P. Callen, MD</td>
<td>Mark J. Holzberg, MD</td>
<td>Christopher R. Shea, MD</td>
</tr>
<tr>
<td>Valerie D. Callender, MD</td>
<td>Tim Ioannides, MD</td>
<td>Michael T. Siegel, MD</td>
</tr>
<tr>
<td>Marc R. Carruth, MD*</td>
<td>Robert S. Kirsner, MD, PhD*</td>
<td>David N. Silvers, MD</td>
</tr>
<tr>
<td>Jennifer C. Cather, MD*</td>
<td>Joseph C. Kvedar, MD*</td>
<td>Stephen C. Somach, MD</td>
</tr>
<tr>
<td>S. Wright Caughman, MD</td>
<td>Philip LeBolt, MD</td>
<td>Thomas Stasko, MD</td>
</tr>
<tr>
<td>Mark G. Cleveland, MD, PhD*</td>
<td>James D. Maberry, MD</td>
<td>Robert A. Swerlick, MD</td>
</tr>
<tr>
<td>Lisa M. Cohen, MD</td>
<td>Donald J. Miech, MD</td>
<td>Maurice A. Thew, MD</td>
</tr>
<tr>
<td>Gerald E. Cooley, MD*</td>
<td>D. Scott Miller, MD</td>
<td>James L. Troy, MD</td>
</tr>
<tr>
<td>Lynn A. Cornelius, MD</td>
<td>Stanley J. Miller, MD</td>
<td>David Wacker, MD</td>
</tr>
<tr>
<td>Gregory J. Cox, MD</td>
<td>George J. Murakawa, MD, PhD</td>
<td>Donald S. Waldorf, MD**</td>
</tr>
<tr>
<td>Peggy S. Crawford, MD</td>
<td>Douglas N. Naversen, MD*</td>
<td>Heidi A. Waldorf, MD*</td>
</tr>
<tr>
<td>Judith E. Crowell, MD*</td>
<td>Kishwer S. Nehal, MD*</td>
<td>Kent D. Walker, MD</td>
</tr>
<tr>
<td>Karynne O. Duncan, MD*</td>
<td>Seth J. Orlow, MD, PhD</td>
<td>Susan H. Weinkle, MD</td>
</tr>
<tr>
<td>W. Christopher Duncan, MD</td>
<td>Marta J. Petersen, MD*</td>
<td>Kathleen M. Welsh, MD</td>
</tr>
<tr>
<td>Patrick R. Feehan, MD</td>
<td>Kathleen A. Remlinger, MD*</td>
<td>George B. Winton, MD</td>
</tr>
<tr>
<td>Marian C. Finan, MD</td>
<td>Jennifer M. Ridge, MD*</td>
<td>Ruth A. Yates, MD</td>
</tr>
<tr>
<td>Alvin E. Friedman-Kien, MD</td>
<td>Franziska Ringpfeil, MD*</td>
<td>Melanie L. Zahner, MD</td>
</tr>
<tr>
<td>Maria C. Garzon, MD</td>
<td>Rudolf R. Roth, MD*</td>
<td>John J. Zone, MD</td>
</tr>
<tr>
<td>Mitchel P. Goldman, MD*</td>
<td>James T. Sandwich, MD*</td>
<td>John A. Zalla, MD</td>
</tr>
<tr>
<td>C. William Hanke, MD</td>
<td>Harry W. Saperstein, MD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marina A. Ball, MD</td>
<td>Tiffani K. Hamilton, MD</td>
<td>Jack S. Resneck, Sr., MD</td>
</tr>
<tr>
<td>Terry L. Barrett, MD</td>
<td>Mark Herron, MD</td>
<td>Laura E. Skelchick, MD</td>
</tr>
<tr>
<td>Timothy G. Berger, MD</td>
<td>Carol L. Huang, MD</td>
<td>Vera Y. Soong, MD</td>
</tr>
<tr>
<td>Anneli R. Bowen, MD</td>
<td>Sewon Kang, MD</td>
<td>Marcia G. Tonnesen, MD</td>
</tr>
<tr>
<td>Glen M. Bowen, MD</td>
<td>Gail A. Kleman, MD</td>
<td>Julian J. Trevino, MD</td>
</tr>
<tr>
<td>Richard A. Clark, MD</td>
<td>E. Michael Kramer, MD</td>
<td>Allison T. Vidimos, MD</td>
</tr>
<tr>
<td>David J. Clemons, MD</td>
<td>Renée J. Mathur, MD</td>
<td>David T. Woodley, MD</td>
</tr>
<tr>
<td>Steven R. Cohen, MD, MPH</td>
<td>Neeraja C. Mattay, MD</td>
<td>Scott L. Zahner, MD</td>
</tr>
<tr>
<td>William F. Cosulich, MD</td>
<td>Ali Molin, MD</td>
<td>James A. Zalla, MD</td>
</tr>
<tr>
<td>Kathy A. Fields, MD</td>
<td>Angela Yen Moore, MD</td>
<td>*Annenberg Circle Founder</td>
</tr>
<tr>
<td>Ronald E. Grimwood, MD</td>
<td>Marliza I. Perez, MD</td>
<td>*Multi-year pledge</td>
</tr>
<tr>
<td></td>
<td>Donald I. Posner, MD</td>
<td>*Deceased</td>
</tr>
</tbody>
</table>

### $50,000

<table>
<thead>
<tr>
<th>Name</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### $30,000

<table>
<thead>
<tr>
<th>Name</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*AC Sustaining members make substantial commitment.*

**From the Public**

Mitchell S. Wortzman, PhD
IIC includes a deeply invasive primary tumor. For patients presenting with distant metastatic disease, nodal and primary tumor status are not relevant for staging. Because approximately one-third of MCC patients who undergo only clinical evaluation of their nodes are understaged—as they in fact have occult microscopic nodal involvement—the most significant feature of Nghiem’s staging system is inclusion of the method for determining negative node.

This staging system was a definite step forward, but one with limitations because “tumor dimension is of limited prognostic value,” Nghiem said. “It provided only a 15% relative survival difference at 5 years between patients with small local and large local disease.” This means that patients in the best prognostic category for MCC—stage Ia, local tumor ≤2 cm with pathologically proven nodal status—still have a disease-associated mortality of 21% at 5 years. Compare this with stage Ia melanoma patients, whose 5-year cancer-associated mortality is just 4.7%.

Improving the prognostic accuracy of this staging system had to wait for established biomarkers.

### An Immunologic Cancer: The Turning Point—And the First Biomarker

“The single biggest turning point in our research was an experiment that I thought wasn’t going to work,” Nghiem shares. But the unexpectedly happy outcome revealed the direction for understanding this cancer, and thus for pursuing treatment. And it enabled Nghiem to identify a biomarker that functions as an independent predictor of survival.

The study was old-fashioned by today’s perspective—a simple Affymetrix mRNA microarray to chart a transcriptome-wide assessment of gene expression levels in the tumors from 35 patients. Patients included those with excellent clinical outcomes and those with rapidly progressive disease. When Nghiem and his team analyzed the combination of biological pathways that were turned on and turned off in the tumors from each group, they thought they might identify a single tumor suppressor or oncogene that contributes to the tumor’s aggressiveness. But instead, they found themselves looking at definitive genetic signatures strongly associated with patient prognosis. Especially prominent were the amplified immune response processes associated uniquely with tumors from patients with excellent outcomes. This genetic fingerprint centered on genes linked with cytotoxic CD8+ T cells that had formed against the cancer and actually penetrated the tumor. A critical component of this genetic signature was the genes expressed in a Th1 immune response, including the critical presence of IFN-γ. A Th1 response is most effective against pathogens that have infiltrated the host cells. (Th2 responses, on the other hand, are most effective against extracellular threats.) This pattern predicted that CD8 T cells were likely infiltrating tumors with good outcomes.

In a larger confirming study, every single patient with robust infiltration of CD8 T cells had survived their cancer. And among patients with only a weak intratumoral immune response, survival was just 60%. (See graphs above.) And thus the presence of an active intratumoral immune response became a very suggestive MCC prognostic biomarker.

Nghiem explains that with this particular genetic signature, “nature is telling us that survival is not about which pathway was mutated in becoming cancerous. It is about the patient’s effective immune response to this cancer.” After discovering the existence and fundamental message of this genetic signature, Nghiem told his team that “all of our poker chips are going in the immune direction. We never once looked back in any significant way about the dominant importance of the immune system in this cancer—and that conviction has been fully borne out.”

A corollary involves the stage-independent prognostic impact of systemic immunosuppression. Systemic immunosuppression—whether from disease or medication—prevents any viable immune response to this cancer. So it is not only a risk factor for developing MCC, but turns out to profoundly affect survival. Nghiem’s team found that this group’s MCC-specific survival at 3 years was only 40%, compared to 74% for comparable patients with no known systemic immune suppression. He emphasizes the need to follow the skin of immunosuppressed patients extremely closely, and biopsy with a low threshold of suspicion.

As a side note, Nghiem was delighted to find himself suddenly in the thick of cancer immunology. “This had always been the most interesting area to me,” he says. He had decided not to pursue it for his postdoc in the latter 1990s in part because a renowned cancer immunologist he had talked with at that time cautioned him that the field was still "merely empirical," and instead advised him to choose an area that was "real science." But by the time of Nghiem’s fundamental discovery not even 15 years later, the intervening progress in technology and knowledge had brought cancer immunology into the scientific realm.

### Tackling the Virus—Early and Late Genes, Cancer-specific Antibodies, and a Disease Marker

MCPyV, the polyomavirus identified in 2008 whose DNA had been found in ~80% of MCC tumors and was thought to contribute to genesis of this disease, had also been detected in more than half of the general population. It turned out to be an infection acquired during childhood, and people who have been infected carry serum antibodies to the viral capsid—its protein shell. Nghiem wanted to identify the immune responses to this virus. That would help him and his team get to know the virus, and hopefully gain a better understanding of the clinical responses to this cancer.
Nghiem and his lab team found their answer in the virus’s early genes—also called tumor-associated antigens, or TaGs—which become active when the virus first penetrates host cells. They initiate the cellular machinery for self-perpetuation by inducing resting cells to enter the actively dividing S phase. Then viral DNA is replicated along with the cell. Once this process is in motion, the early genes initiate transcription of the late viral genes, which simply encode the structural proteins comprising the viral capsid.

The early genes—with large (LT-Ag) and small (ST-Ag) components—turned out to be specific to the tumors. LT-Ag is the oncoprotein that promotes cell division. It is truncated in MCC tumors, because the right-hand side of the protein must be lost or it would lead to cell destruction.

Nghiem et al used multiplex serology and a case-control design (with 205 cases and 530 population controls) to inspect between-group differences in frequency, titer, and specificity of anti-MCPyV antibodies. Not only did antibodies to an epitope in the truncated LT-Ag segment appear almost exclusively in MCC cases, but antibody titer was indicative of tumor burden. Titters fell rapidly in patients whose cancer did not recur, but rose rapidly in those with progressive disease. And in patients who went on to develop metastases, the rise in LT-Ag titer preceded clinical detection of their disease spread.

It was clear that these antibodies “do not effectively protect against disease progression,” Nghiem pointed out. Instead, they reflect it. Nghiem’s belief that “tracking this antibody titer holds promise as an MCC disease marker” was borne out with the clinically useful serology test that became available in 2014 (www.merkelcell.org/sero).

Cellular Immunity—MCPyV-specific T Cells

Then Nghiem moved from humoral to cellular immune behavior. The fact that immunosuppressed patients are significantly more susceptible to developing and dying from MCC highlights how critical cellular immunity is in preventing and controlling this disease. There were no reports yet of T cells reactive specifically to this virus, so Nghiem decided to start the ball rolling.

He and his team created a tool for locating T cells that specifically target MCPyV. They constructed a tetramer—a tiny synthetic molecule composed of several peptides taken from the virus’s LT-Ag together with a corresponding Major Histocompatibility Complex (MHC) protein—that functioned as a molecular magnet for attracting and isolating virus-reactive CD8 and CD4 T cells. They worked with blood from both MCC patients and MCC-free control subjects. They found virus-specific T cells in the blood from over 60% of MCC patients, and in 0% of their control subjects. Nghiem et al found that these virus-specific T cells had penetrated the tumor (ie, they were among the tumor-infiltrating lymphocytes, or TILs). And virus-targeted CD8 T cell levels were far higher in tumor than in blood.

Nghiem was struck now by his recognition that MCC tumors develop and persist despite their highly prominent population of T cells specifically recognizing the virus’s replication-promoting oncoproteins. This had to imply the presence of effective immune evasion mechanisms mounted by these tumors to prevent these T cells from acting.

Two Immune Checkpoint Inhibitors Put T Cells on Hold

Now Nghiem wanted to understand why the tumors controlled the T cells instead of the other way around. So he led a search for molecular pathways that block these virus-specific CD8 T cells from responding. The ultimate goal would be therapies designed specifically to overcome the evasive pathways involved.

This study—carried out with a small group of MCC and control individuals to track the frequency and functional state of their virus-specific CD8 T cells over time—benefited from an extensive library of longitudinally collected, clinically annotated blood specimens. Nghiem and his team isolated, identified, and characterized T cells from tumors and blood. And they also searched T cells and tumors for the different cell-surface markers known to be expressed in the key T-cell-inhibiting pathways.

Again, not a single control subject had detectable blood levels of MCPyV-specific CD8 T cells. But significant levels were found in 64% of patients with virus-positive tumors. As before, results showed these virus-specific T cells waxing and waning in synchrony with tumor burden. They increased when disease progressed, and decreased with effective treatment.

The second phase of this investigation detected two prominent immune-inhibiting pathways, both immune checkpoint in-

MCC: A Thumbnail Sketch

This very rare, highly aggressive neuroendocrine tumor was first described in 1972. In 2008, Patrick Moore and Yuan Chang found a novel human polyomavirus integrated into the genome of the majority of MCCs. (Chang and Moore had also been the first to identify the virus responsible for Kaposi’s sarcoma 14 years earlier.) The U.S. saw ~2,000 newly diagnosed cases in 2015.

Nghiem explains that the rarity of this cancer is due to the multiple genetic events that must occur with the polyoma virus, a highly unlikely series of rapid mutations that he calls “the perfect storm.” The immune evasion mechanisms brought into play underlie its aggressive character. MCC has by far a higher recurrence rate and death rate than melanoma, and it behaves differently as well. The narrow-margin excision typically adequate even for melanoma is often not applicable to MCC because this cancer will jump discontinuously for up to 5 cm. Thus local control requires much greater care. Risk factors include age >50, UV light exposure, and immune suppression. The reported incidence has more than tripled over the past 20 years, in part because of cytokeratin-20 staining introduced in 1994, in part because of a more at-risk population (greater UV exposure, increasing survival at older ages, and increasing prevalence of immune suppression).

A mouse model for MCC has finally been developed, which should substantially expand the questions that can be explored.
hibitors. The receptors enabling tumors to co-opt these pathways were expressed far more prolifically on MCC-associated T cells in tumor and blood than on T cells targeting any other human viruses to which the patients had been exposed during their lifetime. And these inhibitory markers often appeared together on the same T cells.

The best known and most studied of these pathways—with blocking agents already in clinical trials—was PD-1 (programmed death 1). The PD-1 receptor, expressed primarily on the surface of activated CD8+ effector T cells, is the linchpin for a peripheral pathway designed to moderate local inflammation. But it can backfire when a malignant tumor is the T cell target, because many tumors have the capacity to upregulate their production of a protein that interacts with PD-1 to shut down these attacking T cells. This ligand for the receptor on the T cell is termed PD-L1.

Nghiem et al learned from a group of 35 MCC tumors they studied that PD-1 expression on MCPyV-specific T cells is maintained at high levels throughout the disease course. In addition, the presence of its ligand PD-L1 in the tumor microenvironment correlates positively with the number of CD8 lymphocytes infiltrating the tumor (see the graph and slides at right). So the higher the number of intra-tumoral CD8 T cells, the higher the expression of PD-L1 by tumor cells to keep them inactive. And if the ligand and receptor could be prevented from coupling, that would translate to a larger, more effective T-cell pool for attacking the tumor.

Blocking the T-cell–expressed receptor or binding the tumor-expressed ligand would prevent them from coupling, and remove the brakes on the immune response. Two treatments in clinical trials at the time—the humanized monoclonal antibodies nivolumab and pembrolizumab, designed to block the PD-1 receptor on T cells—were creating immense excitement for their unprecedented success in treating advanced melanoma and several other challenging cancers. They were protecting or potentiating an existing immune response—and this is exactly what Nghiem wanted to accomplish in MCC.

The immune checkpoint receptor Tim-3 (T-cell immunoglobulin and mucin domain-containing molecule-3) has taken much longer to begin gaining recognition and study. Tim-3 exhibits several unique features that make it an intriguing candidate for the next wave of therapies targeting immune checkpoints in cancer, and it is considered likely to be the next hot ticket in cancer immunotherapy. An important advantage to Tim-3 is its highly selective expression, which should translate to substantially reduced toxicity. It is found only on T cells that have already differentiated toward an IFN-γ–producing Th1 phenotype, primarily on intratumoral T cells. And because it is not redundant but works differently than PD-1 does, in theory they should create a highly effective clinical partnership. Tim-3 receptor blocking agents are currently performing well in preclinical studies. And the efficacy of the Tim-3/PD-1 co-blockade observed in preclinical models of cancer has been termed remarkable.

### Blocking Immune Checkpoint Inhibitors in the Culture Dish

Because PD-1 and Tim-3 were already targets of agents in clinical development, Nghiem was able to test them in vitro in a 7-day stimulation assay. His team combined MCPyV-specific CD8 T cells with potent tumor peptides, then added blocking antibodies to some of these cultures to see if any of them could restore an active immune response. At the end of 7 days, Nghiem and his team observed significantly augmented production of IFN-γ by the T cells when blocking antibodies were part of the mix. Because IFN-γ is an essential component of an active Th1 immune response, it was clear evidence that these checkpoint inhibitors were effective in restoring the T cells’ ability to do their job against MCC tumors in vitro.

### Blocking the PD-1 Pathway in Clinical Trials

Nghiem is focusing therapeutically on the PD-1 pathway for now because blocking agents are available for clinical trials. Nivolumab and pembrolizumab—anti-PD-1 agents—have already received several FDA approvals for cancer therapy, beginning with advanced melanoma. Avelumab is an experimental anti-PD-L1 antibody.

An open-label, single-arm phase II trial of pembrolizumab involves 26 treatment-naïve patients with advanced unresectable MCC who are not immunosuppressed and do not have autoimmune disease. The drug is given by infusion every 3 weeks. When interim results were reported at a meeting this past September, 71% of the 14 patients scanned for signs of disease at that point had shown an objective response to this therapy. “Responses were rapid, and appear more

---

**MCC Tumors: Correlation Between CD8+ T Cells and PD-L1 mRNA expression**

![Image](https://via.placeholder.com/150)

**CD8+ infiltration and PD-L1 expression in MCC tumors. Immunohistochemical analysis in two representative tumors illustrates the correlation between CD8+ T cell infiltration (left top, bottom) and PD-L1 expression by tumor cells (right top, bottom). (Reprinted with permission from OK Afanasiev et al. Clin Cancer Res. 2013;19:p.5358.)**
durable than we see with chemotherapy,” Nghiem reports. “With chemotherapy, at 90 days half of our patients have progressed and gone off treatment. But many of the patients in this trial have demonstrated profound shrinkage of tumor that has not rebounded.” Therapeutic responses were even experienced by the 2 patients required to discontinue after 1 to 2 doses because of grade 4 adverse effects. An expansion cohort of patients already treated with chemotherapy is being planned.

Nghiem is now also involved in an international multicenter phase II open-label study with an experimental drug, treating 88 patients who have progressed after at least one chemotherapy regimen. This past November, the FDA granted breakthrough status to this experimental drug for treating MCC.

As a stark counterpoint to these trials, Nghiem is about to publish the results of his analysis of the efficacy of chemotherapy in treating metastatic disease. The data were culled from the detailed records of 62 patients. Responses occurred in 53% of patients, but were typically of limited durability and produced toxicity that impaired quality of life. Median progression-free survival was 3 months, and median overall survival from the start of first-line chemotherapy was 9.5 months.

And More.....

Nghiem pursues a full research agenda in addition to his clinical activities. Ongoing multidisciplinary investigations span molecular, cellular, and human in vivo studies, and his Seattle team now follows over 1,150 patients with MCC for outcomes and clinical trials.

Nghiem has also begun exploring the roughly 20% subgroup of MCC cases not associated with the polyomavirus. It had already been determined that these tumors contain a great many more mutations than virus-positive tumors do. Nghiem recently found this subtype to be significantly more aggressive, with an increased risk of disease progression and death that requires more aggressive follow-up for these patients. Yet it is currently not standard to analyze tumors for viral presence. Nghiem believes this will change in the next few years, as it is easy to determine if the virus is present or not, and the result often has management and follow-up implications.

Nghiem also continues to update his Merkel Cell Carcinoma website: www.merkelcell.org. It provides essential information to patients and their physicians and provides links to a great range of resources that includes support groups. And the group also serves to recruit patients for research.

Nghiem and his collaborators have brought MCC and the unfolding story of potential treatment avenues into awareness, and into the modern age.

Suggested Readings


Focus on Research

Hair Follicle Stem Cells Au Naturel—Their Secrets Uncovered With Real-Time Videos

(Continued from cover)

observe fluorescence- and dye-marked epithelial and mesenchymal cells, for example, as they go about their daily lives. Elements of the hair follicle niche (see illustrations at right and on page 12) can be manipulated and the consequences followed as they occur, exploring increasingly complex questions about how cells interact with each other and with their immediate environment, and how specific microenvironments or combinations of factors control cell fate.

A Developmental Biologist Discovers Stem Cells and the Skin

Greco had not expected to study the skin, or to achieve the first direct, real-time visualization of epithelial stem cell divisions in uninjured living animals. She had studied cancer cell biology in Palermo, Italy, where she grew up, then was accepted to do doctoral work in developmental biology at a highly respected lab in Germany devoted to parsing the factors that underlie the development and patterning of the fly wing. Greco perfected her microscopy there. “And as developmental biologists, we were very aware of stem cells,” she says. The recognition of tissue-specific regenerative stem cells had begun to emerge, and they fascinated her. She wanted to learn about them in depth.

Greco’s post-doc affiliation—which pursued her new passion for stem-cell biology—brought her to the U.S. to Elaine Fuchs’ lab at The Rockefeller University. Fuchs’ lab is devoted to understanding mammalian skin. And a major focus there is trying to puzzle out how the multipotent stem cells of mammalian skin give rise to the epidermis and hair follicles.

Greco came to realize that the skin is the ideal stand-in for studying stem cells in other tissues. “The hair follicle stands up as a paradigm for stem cell biology, as several of its diverse cellular components—such as mesenchymal and epithelial cell types, as well as signaling pathways involved—are conserved in many other tissues,” Greco explains. In addition, the hair follicle has unique advantages over other tissues—its ease of accessibility and its continuous pattern of regeneration as it cycles through active growth (anagen), regression (catagen), and rest (telogen) (see illustration on page 12). The extensive molecular and morphological characterization already achieved by standard techniques allowed for the ready identification of the hair follicle’s stem cells, undifferentiated layers, and differentiated layers based on the shape and position of the compartments they reside in (see illustrations above and on page 12).

Bringing Intravital Imaging to the Skin

When Greco first moved to Yale and set up her lab, “we wanted to find out if the hair

Intravital Imaging: How It Works

The 2-photon intravital microscopy system that Greco and her group developed includes a sapphire laser that generates a beam to the scanner, and a variety of mirrors, filters, and other components that direct and manipulate the laser beam and record the eventual images. The system can view about 150 micrometers—one-tenth of a mm—below the surface, which is sufficient for observing the hair follicle (HF) in mouse skin. The ear is an ideal observation site because the HFs there are parallel to the skin surface. These HFs cycle very similarly to those elsewhere on the body, but their horizontal orientation—rather than vertical—means that the entire HF, top to bottom, is easily captured. Epidermal cells are marked with green fluorescence, and Greco figured out that a simple epithelial nuclear marker is the best for tracking individual cells within the HF. Greco puts the mouse to sleep with isoflurane—a halogenated ether used for inhalational anesthesia in humans—delivered via nasal cone. The sleeping animal is placed comfortably on a heated plate to keep body temperature constant. The ear is gently shaved, placed on top of a support, then the specialized microscope lens is placed on top of it.

When a mouse first becomes a subject, a careful map of the selected observation site is prepared so that the identical spot on that ear, and thus the carefully marked cells under the skin, can be easily observed over a repeated sequence of follicle regeneration cycles. The map begins with an identifiable vein pattern on the skin, augmented with a tiny tattoo, to mark the gross region. The follicles below the skin surface are often organized in distinct and stable clusters of 3 to 5 follicles, enabling a precise map for locating the cells to be observed. A cell of interest is labeled genetically and permanently with a color that makes it stand out from the rest, and all of its progeny carry this mark as well.

A larger field of view can be created by acquiring adjacent fields of view and stitching them together, like creating a mosaic with tiles.
Regeneration. The hair follicle undergoes a downwards extension that incorporates the germ—the progeny—within it. Cell divisions are greater in the germ, and oriented along the axis of follicle growth. (Reprinted with permission from P Rompolas et al. Nature. 2012;487:p.499.)

germ and bulge stem cells are functionally different, if their functions are influenced by the niche, and if they are—then how does it happen?" Her first approach was to create several mouse lines that she manipulated genetically so that she could restrict the expression of a reporter gene or eliminate alleles in her two mouse populations. But this approach failed.

At the same time, Greco had decided to try a collaboration with Yale colleague Ann Haberman, whose multiple activities included an intravital imaging facility. This was her first encounter with real-time live imaging, and she was unprepared for the impact. “Until you have used this, until you have seen this with your own eyes, you cannot possibly understand the power of this specific technology,” she states.

“We played around with a two-photon microscope and with different fluorescence-tagged cell lines until I found a way to observe live cell division events in the hair follicle for the first time,” Greco recalls. It took a year from the day she first walked into her own lab to reach the point “where we knew we were ready to start setting up the system for live imaging. The game was on,” she says.

Greco and her lab team began by creating a real-time 3D document of normal anagen and telogen behavior. Over the next several years they manipulated various elements of the hair follicle stem cell niche to generate answers to important questions. In this first—and so far only—use of intravital imaging for capturing the dynamic realities of mammalian hair follicle stem cells, Greco has documented their unexpectedly complex and intricately determined behavior, the profound influence of their microenvironment, and some surprising activities carried out by their epithelial cell neighbors. She and her team have consistently turned orthodox views on their ear.

**Watching Stem Cells and Their Progeny**

This groundbreaking initial study served two purposes. It provided important new information about factors involved in regulating hair regeneration, but it also validated the ability of intravital microscopy as a uniquely effective tool available for gaining a true understanding of hair stem cells and the factors that drive the regenerative process.

“We used a transgenic mouse line that marks all of the epithelial nuclei in the skin by expressing a fusion protein that includes green fluorescent protein. Its strong nuclear signal can resolve individual cells.” The horizontal orientation of the hair follicles they observed enabled them to visualize the entire follicle and identify the location of stem cells and their progeny based on their distinct morphological features.

During regeneration, the lower part of the hair follicle undergoes a major architectural reorganization. The mesenchyme transitions from being extruded from the epithelium to being encompassed by it (see illustration above). “This led us to propose that changes in tissue architecture may rely on other cellular processes in addition to cell divisions.”

Greco et al. continuously visualized stem cells and their progeny throughout the sequence of events that achieve physical regeneration, and also assessed how the mesenchyme influences their behavior. Because they were able to observe cellular mechanisms of growth regulation directly, they could investigate functional requirements of hair-follicle components with precision during the process of physiological regeneration. They found stem cells to be quiescent during the initial stages of hair regeneration and the progeny to be more actively dividing, which was all consistent with earlier data. But Greco and her team found this activity to be spatially organized within follicles. The functional contribution of hair germ cells is mostly to give rise to differentiated cells. The stem cells located in the bottom part of the bulge will become new hair germ cells in the next cycle. “We also learned that both germ and bulge stem cells are dispensable. If they are removed by laser ablation, nearby epithelial cells come in and make sure the job gets done.”

In an earlier study, Greco had found that signals released by the mesenchyme activate the progeny at the beginning of the hair regeneration cycle. So now they ablated the mesenchyme to see what would happen. And by ablating the mesenchyme and tracking hair follicles over an extended time, they were able to show the pivotal role of the mesenchyme for stem cell activation and hair regeneration. When the mesenchymal niche was removed, regeneration stalled. These results “placed more emphasis on the stem cell niche than on the stem cells themselves,” Greco observed.

Greco points out the extended relevance of what she has begun to learn about how hair follicle stem cells function. “Given that components of the stem cell microenvironment are conserved across different tissues, our findings will probably be informative for other tissues as well,” she explains. And more broadly, understanding the process of physiological regeneration.**

**Dr. Greco received a DF Research CDA in 2012 for Live Imaging of Hair Follicle Stem Cells During Normal Regeneration and Cancer.**

(Continued on page 15)
JUBLIA®
(efinaconazole)
Topical Solution 10%

ONYCHOMYCOSIS*
STEALING THE SHOW?

FIGHT IT
AT THE SITE OF INFECTION*

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

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

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

IMPORTANT SAFETY INFORMATION
• JUBLIA is for topical use only and is not for oral, ophthalmic, or intravaginal use.
• Patients should be instructed to contact their health care professional if a reaction suggesting sensitivity or severe irritation occurs.
• The most common adverse reactions (incidence >1%) were (vs vehicle): ingrown toenail (2.3% vs 0.7%), application-site dermatitis (2.2% vs 0.2%), application-site vesicles (1.6% vs 0%), and application-site pain (1.1% vs 0.2%).
• JUBLIA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus, and should be used with caution in nursing women. The safety and effectiveness in pediatric patients have not been established.

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


BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

JUBLIA® (efinaconazole) topical solution, 10%

For topical use
Initial U.S. Approval: 2014

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

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

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

CONTRAINDICATIONS
None.

ADVERSE REACTIONS

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of 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 compared to rates observed in practice.

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

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

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 prenatal 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).

VALEANT Pharmaceuticals North America LLC
Manufactured for: Valeant Pharmaceuticals North America LLC, Bridgewater, NJ 08807 USA
Manufactured by: Kaken Pharmaceutical Co. Ltd, Shizuoka, Japan
Product of Japan
U.S. Patents 8,039,494; 7,214,506
Based on 9391902 DM/JUB/15/0076 Issued: 02/2015
how stem cell and progeny behavior are regulated in physiological conditions may be critically relevant for advancing our use of stem cells in regenerative medicine, and for uncovering the cellular mechanisms that go awry in cancer and other diseases.

**Location, Location, Location—Spatial Organization Within the Niche Influences Stem Cell Fate**

The fact that stem cell niches in mammalian tissues are often heterogeneous and compartmentalized was clear. Still undetermined was whether distinct niche locations affect the fate of their resident stem cells. The hair follicle is a highly compartmentalized niche. Stem cells reside in the bulge, and a pool of progenitors—called the hair germ—is clustered in a different niche location directly below it (see illustration on page 12). It was not clear whether any given stem cell has the potential to generate every lineage, or whether its precise niche location imposes its fate. To explore this question, Greco and her group developed a way to mark single stem cells to identify their initial position within their niche to enable them to revisit and track the same lineages over a sequence of weeks to months. They also used laser-induced cell ablation to test whether hair follicle stem cells are required for hair regeneration, and also to address how injury-induced cell mobility between different niches affects their fate.

What they learned as they watched the activities of the stem cells they had marked is that location matters. Being a stem cell does not automatically translate to producing new cells. Most of those within the bulge do not participate in the subsequent hair cycle. They either remain quietly in the bulge or disappear. Only a small fraction of bulge cells produced lineages, and these new cells were confined to the relatively undifferentiated outer layer called the outer root sheath (ORS). In addition, this small reproductive fraction tended to reside in the lower half of the bulge compartment, closer to the germ. Cells located in the hair germ itself, however, consistently contributed to hair follicle growth by generating differentiated lineages. (See graphs above.)

Greco’s group tracked these various bulge lineages over two consecutive hair cycles to determine their longterm fate. Those in the upper bulge compartment that had not disappeared after the first cycle quietly remained there. But those lower-bulge stem cell progeny in the ORS that had survived the regression phase of the next hair cycle were the big surprise. They had relocated, following a pathway that had never been suspected. They had entered the hair germ, and become part of the stem cell population generating differentiated cells (see photo and graph below).

Greco and her group were also able to demonstrate the resilience of the bulge and germ, and the fact that neither one is indispensable. After using a laser to ablate all of the stem cells in either the bulge or germ at the onset of hair growth—ie, the first occurrence of telogen—the damaged niche consistently recovered its lost cell population, regained its anatomical features, and proceeded with hair regeneration. And when one niche had been damaged beyond its ability to function, the remaining niche temporally took over its functions. The key to this resilience rested on a functional interaction between the epithelium and the mesenchymal dermal papilla.

Probing more deeply into the cellular mechanisms of niche recovery, “we performed time-lapse recordings shortly after bulge laser ablation,” Greco says. In the days following this ablation, they observed a significant influx of labelled epithelial cells into the niche. There was no such influx into niches that had not been damaged. And this new population rapidly took on the characteristics of the stem cells that had been ablated. “We found that these ‘new’ niche cells not only contributed to re-establishing the lost bulge compartment, they also participated in subsequent hair growth.”

Identifying the factors that govern niche microenvironments “is paramount for understanding the mechanism of stem cell fate determination, and thus our ability to manipulate stem cells for therapeutic purposes,” Greco notes.

**Adding β-catenin**

The Wnt/β-catenin signaling pathway is significantly involved in stem cell regulation during fetal development, and in the maintenance of adult stem cells of various lineages. But how this pathway induces specific subgroups of cells to organize growth during tissue regeneration had remained a mystery. Because this pathway plays a role in the genesis of a number of cancers, Greco hoped that intravital microscopy would shed some light. She and her team used a technique that allowed them to genetically activate β-catenin specifically within the hair follicle stem cells and their progeny and achieve constitutive activation of Wnt signaling. Once they had introduced this permanent “on” switch for β-catenin and Wnt, they found themselves observing an attribute of β-catenin that had not been suspected. The β-catenin-mutant cells co-opted wild-type stem cells, which then formed new ectopic axes of hair growth. And there was more. These behaviorally altered wild-type cells begin to proliferate as the mutant cells do, contributing still further to the expansion of mutant hair growths. Their final observation told the lab team that this β-catenin-driven growth occurs without any need for involvement of the physiological mesenchymal niche. It had taken on a life of its own, independent of the regulatory influences that normally govern hair follicle regeneration.

Greco’s experiments with the mutant β-catenin cells suggest a model in which the mutant β-catenin cells influence wild-type cells to proliferate and contribute to the formation of new growths, achieving this via Wnt ligand secretion. In addition, Greco’s data provided visual evidence that Wnt/β-catenin signaling acts through a non-cell autonomous mechanism to support this collective cellular growth. Non-cell autonomous behavior occurs when genotypically mutant cells cause other cells—regardless of their genotype—to exhibit the mutant phenotype. (In cell autonomous behavior, the mutant phenotype is exhibited only by the mutant cells. Wild-type cells continue behaving normally.)

Greco reflects on her goal. “I want to get at the cellular and signaling mechanisms of tumor growth. Our insights into skin tissue regeneration prompted us to explore how critical signaling pathways control dynamic stem cell behavior and
“Thank You” Leaders Society Volunteers

The DF Board of Trustees expresses heartfelt gratitude to each and every campaign volunteer. These dermatologists volunteered substantial time and effort in the 2015 Leaders Society campaign to benefit the specialty’s future.

ALASKA
Chair
Peter G. Ehrnstrom, MD

ARIZONA
Chair
Lindsay Ackerman, MD

CALIFORNIA–Bay Area
Chair
Eric S. Fomer, MD
Vice Chairs
Anna K. Haemel, MD
Anubhav N. Mathur, MD, PhD
Susana M. Ortiz-Urda, MD, PhD
Michael D. Rosenblum, MD, PhD
Tiffany C. Scharschmidt, MD

CALIFORNIA–Los Angeles
Chair
Jashin Wu, MD
Vice Chairs
Jeffrey J. Crowley, MD
Paul S. Yamauchi, MD, PhD

COLORADO
Chair
Robert P. Dellavalle, MD, PhD
Vice Chair
Peggy B. Liao, MD

CONNECTICUT
Chair
Oscar R. Colegio, MD, PhD
Vice Chair
Sarika Ramachandran, MD

DISTRICT OF COLUMBIA–Beltway
Chair
William S. Sawchuk, MD
Vice Chair
Robert A. Silverman, MD

GEORGIA
Chair
Travis Blalock, MD
Vice Chair
Brian P. Pollack, MD, PhD

IDAHO
Chair
Ryan S. Owslay, MD

INDIANA
Chair
Norma H. Schmitz, MD
Vice Chair
Annette M. Dinneen, MD

IOWA
Chair
Kent D. Walker, MD
Vice Chair
John H. Wollner, MD

KANSAS
Chair
Colleen M. Reisz, MD

LOUISIANA
Chair
Sarah C. Jackson, MD
Vice Chairs
Steven C. Heard, MD
Stephen Klinger, MD
Frankie G. Rholdon, MD
Amie Shannon, MD

MAINE
Chair
Glen D. Goldman, MD
Vice Chair
Joseph C. Pierson, MD

MARYLAND–Baltimore Area
Chair
Saif U. Syed, MD
Vice Chairs
Jane T. Chew, MD
Jennifer Z. Cooper, MD
Diane S. Ford, MD

MASSACHUSETTS
Chair
John E. Harris, MD, PhD
Vice Chair
Teresa M. DeGiacomo, MD

MICHIGAN
Chair
David R. Byrd, MD
Vice Chairs
Peter J. Aronson, MD
Catherine A. Nordby, MD

MINNESOTA
Chair
Michael J. Ebertz, MD
Vice Chairs
Kristen P. Hook, MD
Sarah Schram, MD

MISSISSIPPI
Chair
Angela B. Wingfield, MD

MISSOURI
Chair
Scott W. Fosko, MD
Vice Chair
Nicole Burkemper, MD

MONTANA
Chair
Ryan S. Owslay, MD

NEVADA
Chair
Misty D. Caudell, MD

NEW HAMPSHIRE
Chair
James G. Dinulos, MD

NEW JERSEY–North
Chair
Adrian L. Connolly, MD

NEW JERSEY–South
Chair
Warren R. Heymann, MD

NEW YORK–Downstate
Chair
Kishwer S. Nehal, MD
Vice Chairs
Francis W. Iacobellis, MD
Sherri K. Kaplan, MD
Erica H. Lee, MD
Anthony M. Rossi, MD
Jennifer A. Stein, MD
Michael B. Whittow, MD, PhD

NEW YORK–Upstate
Chair
Jeffrey R. LaDuca, MD, PhD

NORTH CAROLINA
Chair
Craig N. Burkhardt, MD
Vice Chairs
Donna A. Culpin, MD, PhD
William W. Huang, MD, MPH

NORTH DAKOTA
Chair
Ryan S. Owslay, MD

OHIO–Northern
Chair
Jonathan Bass, MD
Vice Chairs
Jaye E. Benjamin, MD
Eliot N. Mostow, MD, MPH
Carol C. Slover, MD
Stephen C. Somach, MD

OHIO–Southern
Chair
Julian J. Trevino, MD

OREGON
Chair
Douglas N. Naversen, MD

PENNSYLVANIA–Eastern
Chair
Carrie Ann R. Cusack, MD
Vice Chair
Christina L. Chung, MD

PENNSYLVANIA–Western
Chair
Renée J. Mathur, MD
Vice Chair
Paul J. Ruschak, MD

RHODE ISLAND
Chair
Leslie Robinson-Bostom, MD
Vice Chair
H. William Higgins, II, MD, MBE

SOUTH DAKOTA
Chair
Ryan S. Owslay, MD

TENNESSEE
Vice Chair
Vineet Mishra, MD

TEXAS–Dallas
Chair
Rebecca L. Euerer, MD
Vice Chair
Seemal Desai, MD

TEXAS–Eastern
Vice Chair
Vineet Mishra, MD

TEXAS–Houston
Vice Chair
Vineet Mishra, MD

TEXAS–San Antonio/Austin
Chair
Allison J. Stocker, MD
Vice Chairs
John Browning, MD
Thomas L. Davis, MD
Catherine L. Kowalewski, DO
Vineet Mishra, MD

TEXAS–West
Vice Chair
Vineet Mishra, MD

VERMONT
Chair
Glenn D. Goldman, MD
Vice Chair
Joseph C. Pierson, MD

WEST VIRGINIA
Chair
Stuart R. Lessin, MD

WISCONSIN
Chair
Sam T. Hwang, MD, PhD
Vice Chair
Barbara Dahl Wilson, MD

WYOMING
Chair
Ryan S. Owslay, MD

DERMATOLOGIC SURGERY CAMPAIGN
Chair
Elizabeth I. McBurney, MD
Vice Chairs
Elise P. Barnett, MD
Ramona Behshad, MD
Mariah C. Brown, MD
M. Laurin Council, MD
Eva A. Hurst, MD

DERMATOPATHOLOGY CAMPAIGN
Chair
John T. Seykora, MD, PhD
Vice Chairs
Maxwell A. Fung, MD
Leslie Robinson-Bostom, MD

* Enrolled three or more new LS members
decisions. So my lab combined genetic approaches with live imaging to investigate the role of this evolutionarily conserved pathway during tissue growth.” Their real-time observations of single cells uncovered a novel mechanism of action for β-catenin within the hair follicle stem cell environment that evades the niche’s homeostatic influences. Mutant β-catenin recruits wild-type epithelial cells that induce de novo hair growths that ultimately result in tumors. Greco points out that “this work changes our understanding of how cells that carry these mutations can interact with neighboring cells, and then how tumor initiation and progression may be fueled.”

**Tissue Homeostasis: The Unknown Part of the Equation**

Tissue homeostasis reflects a balance between cell production and elimination, ie, growth and regression. The research focus has always been on understanding the factors that initiate and maintain hair follicle regeneration. Yet tissue homeostasis—which is necessary for healthy tissue—requires ways to keep the pool of stem cells healthy and not too large. Information on how this needed winnowing takes place has been missing. “In contrast to tissue growth,” Greco notes, “the cells and molecular signals required for tissue regression were still unknown.” It was assumed that tissue regression in the hair follicle is mediated through programmed cell death, but unclear which cells are removed, and why. Do cells die because they have become fatally depleted—ie, intrinsic cellular exhaustion, or are they actively eliminated by unidentified extrinsic factors. Greco wanted to identify the cellular behaviors and molecular mechanisms of regression that counterbalance growth to maintain tissue homeostasis.

Using intravital imaging with time-lapse recordings of epithelial nuclei that were made visible by the incorporation of green fluorescent protein, Greco was in for a series of surprises. One was that cell death did not occur uniformly. Cells in the suprabasal layer do not die during regression, but simply are eliminated through upward terminal differentiation.

Cell death comes only to cells in the basal epithelial layer, and how this happens was the next surprise. Conventional thinking has assumed that cells become exhausted and self-destruct, and then phagocytic immune cells migrate in to remove the debris. But cell death did not reflect the inability to continue functioning. Instead, it involves what Greco calls “spatial gradient apoptosis.” Basal layer stem cells are marked for death simply because of where in that layer they reside. They are not dysfunctional, because inhibiting regression results in an excess of basal epithelial stem cells with good regenerative abilities.

And the decision-making mechanism is extrinsic. Through cellular and genetic ablation, Greco and her co-workers show that epithelial cell death is induced through transforming growth factor-β (TGF-β) activation and mesenchymal crosstalk. So the mesenchyme has central regulatory impact on both sides of the equation—growth and regression.

Completely unexpected was the reality that Greco discovered about the post-apoptosis clean-up. “We definitely captured cell death in the basal epithelial layer,” Greco says, “but we never saw the cellular debris leave the area.” It remained in the basal layer, and she and her team watched it disperse around neighboring basal epithelial cells within the surrounding epithelium. And then—these neighboring cells ate them. They were internalized and cleared away by their neighbors (see photos above) in a completely self-contained process within the regressing basal epithelium. This was a rare example of epithelial cells functioning as phagocytes.

**Conclusions**

Greco is pursuing her understanding of the complexities of niche signals and behavior, and she continues to develop refinements to the technology she works with that expand the degree of detail she is able to see, and to manipulate. Greco has also begun to apply her technology to studying tumor biology in the context of keratoacanthoma. This skin tumor can spontaneously regress, and can also give rise to squamous cell tumors. “We feel that our knowledge of hair follicle growth and regression might help us understand how this tumor regression can occur,” Greco says.

Greco also invites everyone who would like to see intravitral imaging at work to visit her website: www.grecolab.org. It contains many links to their videos of stem cells in action.

**Suggested Readings**


137 New Leaders Society Members in 2015

The Foundation welcomes its newest Leaders Society members. Their annual contribution of $1,500 reflects their commitment to the specialty and their confidence in the DF’s ability to identify and effectively support the development of tomorrow’s leaders.

**ALABAMA**
Eric W. Baum, MD
Corey Hartman, MD

**ARIZONA**
Senait Dyson, MD

**CALIFORNIA**
Susan Amaturo, MD
Nina Botto, MD
Sabrina G. Fabi, MD
Renee M. Howard, MD
Rachel I. Kornik, MD
Haley B. Naik, MD
Roberto R. Ricardo-Gonzalez, MD, PhD
Alan A. Semon, MD
Gregory Van Dyke, MD, PhD
Paul S. Yamachii, MD, PhD

**COLORADO**
Sylvia L. Bricc, MD
Mariah C. Brown, MD

**CONNECTICUT**
Christopher G. Bunick, MD, PhD
Sean R. Christensen, MD, PhD
Peggy S. Myung, MD, PhD
Sanka Ramachandran, MD

**FLORIDA**
David Casper, MD
Clifford W. Lober, MD

**GEORGIA**
Wayne L. Bakotic, DO
Michelle L. Juneau, MD
Jay A. Levin, MD
Brian P. Pollack, MD, PhD
Klaus Sellheyer, MD

**IDAHO**
Gregory L. Wells, MD

**ILLINOIS**
I-Ja Chan, PhD
Lester J. Fahrner, MD
Judith P. Knox, MD
Mark Romanelli, MD
Amy F. Taub, MD

**INDIANA**
Stephen J. Shideler, MD
Brian J. Williams, MD

**IOWA**
David L. Knutson, II, MD
Karolyn A. Wanat, MD

**KANSAS**
David L. Kaplan, MD

**KENTUCKY**
James R. Wharton, MD
Janice W. Yusk, MD

**LOUISIANA**
Kim Bui Drew, MD
Alexis R. Duke, MD
Laurie H. Harrington, MD
Robert A. Koppel, MD
Alan T. Lewis, MD
Dana A. Marshall, MD
Laci Theunissen, MD

**MARYLAND**
Juris Germanas, MD, PhD
Oanh Lauring, MD
Monte S. Meltzer, MD

**MASSACHUSETTS**
Kathryn E. Bowers, MD
Erik Domingues, MD
Daniela Kroshinsky, MD, MPH
Ronald S. Nadel, MD

**MICHIGAN**
Richard J. Ashack, MD
Cynthia Tseng Chow, MD
Jenny Cotton, MD, PhD
Iltefat H. Hamzavi, MD
Marcy L. Street, MD
Kara Walton, MD

**MINNESOTA**
Caleb Creswell, MD
Heidi Foster, MD
Kathryn Gehrig, MD
Lynda S. Kauls, MD
Nancy A. Leitch, MD
Sherri A. Long, MD
Hilary C. Reich, MD

**MISSISSIPPI**
David B. Roy, DO
Sam C. Tumminello, MD
Billy L. Walker, MD

**MISSOURI**
Ramona Behshad, MD
Jaeyoung Yoon, MD, PhD

**NEW HAMPSHIRE**
James G. Dinulos, MD
Andrea Pearson, MD

**NEW JERSEY**
Emily M. Altman, MD
Daniel S. Kessel, MD
Marc Meulener, MD

**NEW YORK**
Chih-Shan Jason Chen, MD, PhD
Paul Chu, MD
David H. Ciocon, MD
Liang Deng, MD, PhD
Lydia M. Evans, MD
Peter C. Friedman, MD
Herbert P. Goodheart, MD
Sherri K. Kaplan, MD
Michael A. Kurzman, MD
Jo-Ann M. Latkowski, MD
Anthony M. Rossi, MD
Alan B. Schlichtman, MD
Jennifer A. Stein, MD
Ida M. Tiongco, MD
Cynthia B. Yalowitz, MD
Ross Zeltser, MD
Stuart M. Zweibel, MD

**NORTH CAROLINA**
William D. Hoover, Jr., MD
Aida M. Lugo-Somolinos, MD
Dean S. Morrell, MD
Phillip M. Williford, MD

**OHIO**
Joshua Arbesman, MD
Benjamin Bogucki, MD
Timothy Chang, MD
Valerie Fuller, DO
Hugh M. Glaster, Jr., MD

**OREGON**
Kyle Horner, MD
Drew Reese, DO
Eric L. Simpson, MD

**PENNSYLVANIA**
Lisa Goldberg, MD
Richard J. Herschaft, MD
Christopher J. Miller, MD
Aimee S. Payne, MD, PhD
Joya Sahu, MD
Stuart Daniel Shanler, MD
 Junko Takeshita, MD, PhD

**RHODE ISLAND**
H. William Higgins, II, MD, MBE

**TEXAS**
Arturo R. Domínguez, MD
Peter D. Hino, MD
Mark D. Koone, MD
Jennifer Krejci-Manwaring, MD
Keagan H. Lee, MD
Vineet Mishra, MD
Gunjan Modi, MD
Amit G. Pandya, MD
Jennifer B. Perone, MD
Christy Riddle, MD
Howard A. Rubin, MD
Amanda Wolthoff, MD
Priya S. Zeikus, MD

**UTAH**
Brad Huber, MD

**VERMONT**
Jamie A. Alpert, MD

**WASHINGTON**
Jennifer Gardner, MD

**WISCONSIN**
Dawn H. Siegel, MD

*Italics=Young Leader (5 years or less out of residency)*
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.

**Cornerstone Benefactor ($500,000 or more)**

Unilever

**Platinum Benefactor ($200,000 or more)**

AbbVie, Galderma, Merz, Valeant Pharmaceuticals North America LLC

**Gold Benefactor ($100,000 or more)**

DUSA Pharmaceuticals

**Silver Benefactor ($50,000 or more)**

Amgen Inc.

Sun Pharmaceuticals
Stuart R. Lessin, MD—Newest DF Fitzpatrick Legacy Fund Member: “What a Gratifying Way to Say Thank You.”

“I have always believed it is our professional responsibility to ensure the future of our specialty,” Dr. Lessin shares. “And the Dermatology Foundation is the ideal organization for enabling us to do that.”

A Foundation member and volunteer during his entire career as a dermato-oncologist, Dr. Lessin made a significant decision to give back still more to the specialty this year by joining the Fitzpatrick Legacy Fund with a gift of $100,000. This exceptional contribution has been on his personal agenda for quite some time, and “now was just the right time for me. It has been very gratifying.”

Dr. Lessin’s relationship with the Foundation began after he completed his dermatology training at the University of Pennsylvania. He received a DF research Fellowship in 1986 and then one of the first Career Development Awards (CDAs) in 1990 that launched his own research career in skin oncology. “My DF research funding allowed me to devote time to research and generate the preliminary data that made me competitive for NIH funding. It was also an enormous validation of my career choice and the work I was doing.” Dr. Lessin emphasizes that since the CDAs were initiated in 1990, “the DF has grown a generation of physician-scientists, and you can connect their body of work to significant progress in patient care.” This list includes biologics for psoriasis, new topical treatments for atopic dermatitis and skin cancers, important gains in laser treatments, and significant advances in public health policy.

Dr. Lessin notes that he is doubly grateful to the DF—for the early funding he received, and for its ongoing efforts to ensure that “dermatology’s scientific base remains strong,” especially during times when support for new investigators is difficult to obtain. “The constant need for new and innovative treatments for patients requires a steady momentum of research progress and an ongoing pipeline—and that is why the DF is so important. It supports the research and careers of new physician-scientists, and ultimately advancements in patient care.” Dr. Lessin encourages all dermatologists to contribute to the work of the DF—“it’s such an important organization.”