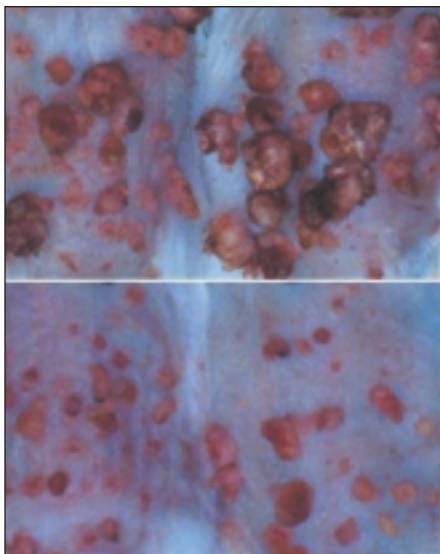


# DERMATOLOGY FOCUS™

## Gamma Delta T Cells— First Responders to Cutaneous Threats

**M**ichael Girardi, MD, Associate Professor and Residency Director in the Department of Dermatology at Yale University School of Medicine, studies T cells in the skin, most especially in the contexts of squamous cell carcinoma and inflammation.

The mention of T cells normally brings to mind CD4<sup>+</sup> and CD8<sup>+</sup> cells, the circulating antigen-responsive lymphocytes that are the centerpiece of adaptive immunity. These immune effector cells evolved with a highly specialized, customizable T-cell receptor (TCR) capable of the infinite



**αβ T cells can promote tumors.** In a two-stage chemical carcinogenesis protocol (initiator followed by promoter) with a high-dose promoter, wild-type mice (*top*)—with all T-cell types present—develop a markedly greater tumor burden than knockout mice missing αβ T cells. (Reprinted with permission from M. Girardi et al. *J Exp Med.* 2003;198, p.752.)

variation necessary to produce T-cell populations individually dedicated to the endless variety of environmental and internal peptide antigens presented for immune recognition by antigen-presenting cells bearing the host's MHC molecules.

Girardi's primary focus, however, is on the little known and poorly understood skin-dwelling  $\gamma\delta$  T cells that are proving to be an important junction between the adaptive and innate immune systems. In contrast to the adaptive response that targets specific antigens, innate immunity recognizes generic molecules on microbes and other invaders or those produced by cells under stress from infection, inflammation, or uncontrolled growth. As an interface between the two, epidermal  $\gamma\delta$  T cells appear to be essential in shaping the cutaneous immune response. Girardi has made some startling discoveries that point to a far greater degree of complexity than currently recognized in the development and control both of skin cancer and of inflammation. These findings suggest that therapeutically stimulating adaptive immunity may, in certain situations, promote pathology rather than resolve it. And the knowledge that Girardi continues to gain is geared toward opening the way to significantly more effective manipulation of immune responses for therapeutic ends.

### $\gamma\delta$ T Cells—An Emerging Portrait

When discovery of the TCR roughly 25 years ago first made T-cell characterization and understanding possible at the molecular level, the T cells that predomi-

(Continued on page 2)



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## Focus on Research

**Cox-2 Inhibition—  
Can it Stop UV-Induced Skin  
Cancers in Their Tracks**

**Alice P. Pentland, MD**

Professor and Chair, Department of Dermatology,  
University of Rochester, Rochester, NY

**P**entland first crossed paths with arachidonic metabolism and the eicosanoids in the early 1980s, during her dermatology residency at the University of



Michigan. Many of the early events in inflammation are extensively influenced by metabolites of arachidonic acid, and at the time, John Voorhees, MD, Chair of the Department of Dermatology, was exploring the role of arachidonic acid in psoriasis. This exposure to arachidonic acid and the inflammatory process peaked Pentland's interest, and she found it sufficiently intriguing to pursue after her residency. In 1983 she began a post-doctoral fellowship in the Department of Pharmacology at Washington University in St. Louis, studying under Philip Needleman, PhD, who was then department chair. Pentland began investigating effects of UV light on the synthesis of prostaglandins and attempting to understand how they are regulated, and after her fellowship she joined the faculty with a joint appointment to Dermatology and Pharmacology.

(Continued on page 11)

nate in the peripheral blood were the first to be identified. They are called  $\alpha\beta$  T cells, reflecting the receptor's bipartite molecular architecture—in this case, with one  $\alpha$ -family molecule and one  $\beta$ -family molecule. The many members of each family gradually came to light, along with the virtually infinite menu of  $\alpha$ - $\beta$  combinations. But there was more to come.

Discovery of  $\gamma\delta$  T cells by Robert E. Tigelaar, MD (then in the Department of Dermatology at University of Texas-Southwestern, now professor of Dermatology and Immunobiology at Yale School of Medicine) and Paul Bergstresser, MD, his colleague then, in mouse epidermis occurred several years later. When these initial observations were first published in 1983, the identity of this newly recognized population of epidermal dendritic cells was a large question mark. They were clearly distinct from Langerhans cells and melanocytes—the two known types of dendritic cells in skin. They expressed a membrane protein identifying them as thymocytes, and Tigelaar began character-

izing them with increasing precision. Collaboration with James P. Allison, PhD (Professor of Immunobiology at UC Berkeley), and an antibody he had developed to a T-cell antigen, finished solving the puzzle. By 1988, Tigelaar had confirmed the T cell identity of these bone marrow-derived dendritic cells, but with a  $\gamma\delta$  TCR—which predominates in fetal thymocytes—where

the  $\alpha\beta$  TCR would otherwise be. He found them strikingly similar to very early stage T cells, and noted their minimal presence in the peripheral circulation and lymphoid tissues but their abundance in certain epithelia, including the epidermis. "Our data imply a role for these epithelial T cells in immune surveillance that is distinct from that of  $\alpha\beta$ - and other  $\gamma\delta$ -bearing T cells," he said, referring to the minuscule number that appear in the peripheral circulation.

Since then, investigators have been identifying the ways in which these epithelial  $\gamma\delta$  T cells—called *intraepithelial lymphocytes (IELs)*—fundamentally differ from their circulating  $\alpha\beta$  T-cell counterparts. They appear before  $\alpha\beta$  T cells do, arising early in fetal development in the thymus and then migrating in large numbers to epithelial tissues in the gut, lungs, skin, and vaginal lining—our barriers in direct con-

tact with the environment—where they remain. The two types of T cells display highly distinct gene expression profiles. IELs do not recirculate between blood and lymph nodes, and their nonvariable TCR does not interact with histocompatibility molecules for antigen recognition. Rather than relying on antigen-presenting cells found in lymph nodes, they encounter antigens on the surface of the epithelial cells surrounding them. In addition, IELs are not dependent on a cytokine-costimulatory molecule combination for activation. "They sit in the tissue already in a semi-activated state," Girardi says, "so it takes relatively less signal to activate them." In sum, these residential T-cell populations have two substantial innate advantages as protective responders: they are right on site—at the barriers—instead of having to migrate there in response to recruitment signals, and they are fast. Their permanently activated state makes them highly sensitive to responding.

Although their abundant epithelial presence, their apparent capacity to respond to a common antigen expressed by their neighboring epithelial cells, and their rapid response capability were intriguing, the biological role of these IELs remained an enigma for a long time.

This mystery is finally yielding to research, as results appearing during the past several years are now pointing to these epidermal  $\gamma\delta$  T cells as critical in maintaining tissue integrity, defending against pathogens, and regulating inflammation.

### Dendritic Epidermal T Cells

Girardi belongs to the handful of scientists who are helping to explore what these *dendritic epidermal T cells*, or *DETC*, do in the skin, and how they do it. He first encountered  $\gamma\delta$  T cells as a medical student at Yale, only a few years after they had been conclusively identified. "I was introduced to them by my mentors," he recalls, referring to Tigelaar, who had just joined the faculty there, and Adrian C. Hayday, PhD, who at that time was in the Department of Immunobiology at Yale and is now at Kings College in London. This collaboration continues today.

"What fascinated me about them was that they are greatly enriched in epithelial tissues, and particularly in the skin," Girardi says. Considering the large surface area of

epithelia, it has been proposed that these IELs comprise somewhere between one-quarter and one-half of the body's T cells. Their dense concentration in the skin—roughly 500 cells per square cm—places them in intimate proximity to neighboring keratinocytes, and their many spiny, elongated projections enable them to contact as many of these keratinocytes as possible. About 95% of this DETC subset of IELs express a single, homogeneous  $\gamma\delta$  TCR.

Girardi had wanted to explore the potential role of these  $\gamma\delta$  T cells in cancer from the start. Attempting to understand and control cancer has been his lifelong holy grail. Having learned about the immune system's effect on cancer and recognizing the skin as the single visually accessible tissue for studying it, Girardi saw these abundant and exquisitely responsive epidermal T cells as a potentially productive avenue for trying to unravel the early forces that come to bear on malignant cells in the skin. Although the cutaneous link between cancer and inflammation—ie, the increased risk of squamous cell carcinoma when mutations (the initiating event) occur in chronically irritated skin (the promotion process)—has led him to explore these  $\gamma\delta$  T cells in this process as well, the focus in this article will be on their role in cutaneous malignancy.

### $\alpha\beta$ and $\gamma\delta$ T Cells— Different Roles in Regulating Cutaneous Malignancy

Girardi's initial premise was that "the localization of  $\gamma\delta$  T cells within epithelia suggests that they may contribute to the control of malignancies." Using human bowel carcinoma as a logical parallel, he noted two observations, that: (1) the tumor-associated antigens MICA and MICB—non-classic MHC class I antigens abundantly expressed on a wide variety of tumors, particularly those of epithelial origin—are strongly up-regulated on these carcinomas, and (2) these tumors are targets for cytotoxicity by intestinal IELs that express a specific receptor—*NKG2d*—for these particular tumor antigens. This receptor was first identified on natural killer lymphocytes, now recognized as part of the innate immune system. Because the capacity of either  $\gamma\delta$  T cells or MICA/B to regulate malignancy in the skin was uncertain, Girardi decided to look for evidence with the aid of three murine models of cutaneous malignancy. Although the MICA/B locus is not conserved in mice, they express counterpart ligands for NKG2d—Rae-1 family proteins and the heat shock protein H60—which were logical candidates for a role in tumor detection.



Michael Girardi, MD

The first mouse model involved cultured squamous cell carcinoma (SCC) cells injected intradermally into two sites per animal. The other two involved chemical carcinogenesis, one by injecting the carcinogen methylcholanthrene (MCA) to produce fibrosarcomas and spindle cell carcinomas, the other via a two-stage topical application that begins with the tumor initiator dimethylbenz[a]anthracene (DMBA) to produce local hyperplasias (some regress, some develop into papillomas), then the tumor promoter phorbol ester (TPA) that can transform papillomas into squamous cell carcinomas. This two-stage sequence mimics the natural incremental progression of malignancies. For the SCC injection, C57BL6 mice (see box, page 7) were engineered to produce 3 types of knockout animals to compare with normal wild-type (WT) animals. The influence of resident  $\alpha\beta$  T cells on tumor development was determined by creating mice that lacked them (TCR $\beta^{-/-}$  mice). Mice without circulating  $\alpha\beta$  T cells (TCR $\beta^{-/-}$  mice) allowed determination of their contribution, and mice unable to produce any T cells (TCR $\beta^{-/-}\delta^{-/-}$  mice) permitted an estimate of their combined impact. A different type of mouse—a cancer-sensitive strain called FVB (see box, page 7)—was used for the other two conditions, comparing WT animals and two knockout mice: TCR $\delta^{-/-}$  and TCR $\beta^{-/-}$ . In all three tumor induction regimens,  $\gamma\delta$  cell deficiency reduced resistance to cutaneous malignancy. Consequences from the loss of  $\alpha\beta$  T cells were unexpectedly varied.

When tumor cells were injected, TCR $\delta^{-/-}$  mice developed more tumors than WT mice by a factor of 3 to 4—37% vs. 10% of injected sites—indicating that the loss of these epidermal T cells had sacrificed potent anti-tumor protection. The other two knockout mice—missing  $\alpha\beta$  T cells or all T cells—experienced equally rampant tumor development, as almost all injected sites became tumors and latency was substantially reduced. Girardi was able to conclude that “ $\alpha\beta$  T cells and  $\gamma\delta$  T cells each regulate the growth of these tumors, and do so in distinct fashions. The lack of  $\gamma\delta$  T cells is not compensated for by the presence of  $\alpha\beta$  T cells and NK cells.” After injecting the chemical MCA, each type of knockout mouse had roughly equivalent tumor counts, which were significantly more than their normal WT counterparts. “Again,” Girardi observes, “the presence of either type of T cell failed to compensate for the absence of the other.”

The two-stage model repeated the process with low and high doses of the promoter TPA. At the low dose, the data showed no significant difference at any point between the WT and TCR $\beta^{-/-}$  mice. In this experimental route to SCC,  $\alpha\beta$  T cell presence or absence made little difference. Loss of  $\gamma\delta$  T cells was a very different story. At 7 weeks, 67% of the TCR $\delta^{-/-}$  mice carried tumors compared to only 16% of the WT mice, and they had also developed more tumors per animal. Presence of resident  $\gamma\delta$  T cells provides critical protection in this paradigm at both doses of the promoter TPA.

Once TPA was delivered at a high dose to TCR $\beta^{-/-}$ , however, the unexpected occurred. Mice *without*  $\alpha\beta$  T cells actually developed substantially *fewer* tumors per animal (see photos on cover and graph, page 7). Their presence was promoting tumor development. “I was floored when I saw this,” Girardi exclaims. “I was so astonished that I repeated this part of the study over and over again, making sure that I hadn’t made a mistake somewhere.” (Girardi revisited this issue in his next study.)

In completing the current study, since  $\gamma\delta$  cells clearly supported resistance to cutaneous malignancy, Girardi and his co-workers looked for—and found—a functional equivalent of human MICA/B that could act as a ligand for the mouse NKG2d receptor. They determined that the SCC tumor line used here expresses a Rae-1 protein, and devised a situation allowing them to observe isolated NKG2d mouse receptors successfully interacting with this human-like tumor antigen. After turning to actual murine epidermal  $\gamma\delta$  T cells and documenting the presence of NKG2d receptors—which increased in number when the cells were activated—Girardi placed them together with SCC cells to see what would happen. The  $\gamma\delta$  T cells—or DETCs—killed cancer cells, and the more DETCs in the mix, the greater the cytotoxicity. To make sure that NKG2d–Rae-1 binding was responsible, Girardi used antibodies or antiserum to shut down either  $\gamma\delta$  T cells, or the NKG2d receptors, or the Rae-1 tumor antigen. “Each reagent significantly inhibited killing,” he notes, “and certain reagent combinations reduced killing by 75% to 95%.”

Girardi’s final step in this series of experiments was designed to assess the general relevance of NKG2d-dependent killing of these SCC cells to the immune surveillance of carcinomas, hoping to show that Rae-1 is up-regulated *in vivo* by chemical carcinogens. As anticipated,

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he and his colleagues found that normal FVB mouse skin contains negligible levels of this tumor antigen and the heat shock protein H60. But the picture changed once skin was painted with DMBA and then TPA. Although levels remained negligible in painted areas where no lesion developed, these NKG2d-binding tumor antigens were significant in most papillomas and in all carcinomas.

**$\alpha\beta$  and  $\gamma\delta$  T Cells—Distinct  
Regulatory Roles: Continued**

Epithelial tissues in which carcinomas develop often contain both systemically derived TCR $\alpha\beta^+$  cells and resident IELs that are commonly enriched in TCR $\gamma\delta^+$  cells, “and murine skin is a striking example of IEL and systemic T cell coexistence,”

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Girardi observes. He had already demonstrated in no uncertain terms that these  $\alpha\beta$  cells “protect the host against chemically induced cutaneous malignancy,” he comments, “but the role of  $\alpha\beta$  T cells emerged as enigmatic, with both protective and tumor-enhancing contributions observed in different systems.” Data from two other groups had also appeared documenting cancer-promoting effects of  $\alpha\beta$  T cells. The laboratory of Hans Schreiber, MD, PhD, who studies the interaction of cancer cells with the immune system at the University of Chicago, had found that these T cells enhance the growth of primary tumors after they are pre-activated by exposure to an antigenic peptide. Lisa M. Coussens, PhD, and co-workers at UC-SF had found that CD4<sup>+</sup>  $\alpha\beta$  T cells responding to bacterial infection can cause tissue disruption that promotes the progression of skin tumors induced by transgenic oncogenes.

So Girardi's next study series—again using cancer-sensitive FVB mice in the two-stage model that had previously uncovered differences—“aimed to clarify the contributions of each T-cell type to the regulation of SCC.” Inducing SCC by topical DMBA initiation, followed by

repetitive application of the tumor promoter TPA, enabled Girardi to monitor the induction of papillomas and then their progression to carcinomas. He repeated the two dose levels of TPA used earlier, ie, a low dose of 5 nmol and a high dose of 40 nmol. And he exposed wild-type FVB mice as well as the three different knockout animals: lacking  $\gamma\delta$  T cells (TCR $\delta$ -/-), lacking  $\alpha\beta$  T cells (TCR $\beta$ -/-), and lacking both (TCR $\beta$ -/ $\delta$ -/-).

Results confirmed his earlier findings for distinctly different T-cell response profiles to these malignant cells in the skin. The least number of tumors per mouse, along with the slowest tumor onset, occurred with both the WT and the TCR $\beta$ -/- mice, ie, those with an intact population of resident  $\gamma\delta$  T cells (aka DETCs) but lacking  $\alpha\beta$  T cells. Tumor incidence and onset both increased substantially in those mice whose  $\alpha\beta$  T cells were intact but could not produce DETCs, and were higher still in TCR $\beta$ -/ $\delta$ -/-, the double knockout mice.

Then Girardi and his colleagues addressed this seemingly harmful effect of  $\alpha\beta$  T cells with a critical test. They restored the TCR $\beta$ -/- mice back to normal. “Whenever one creates mutant mice to

study,” he explains, “the concern is that you have also produced an unintended—and undetected—genetic alteration that is the true cause of the effect you are observing.” So he took a subgroup of TCR $\beta$ -/- mice—which had shown the least sensitivity to tumor occurrence—and reconstituted their  $\alpha\beta$  T cells by adding fetal liver hematopoietic stem cells when they were newborns. This produced mice that were genetically identical to the TCR $\beta$  knockout mice, except they now had both their systemic and epidermal T cells. If these mice behaved like the  $\alpha\beta$  knockout mice under high-dose conditions and produced few tumors, then Girardi could no longer attribute this protective effect to the  $\alpha\beta$  T cells, but to an as yet unidentified and unintended genetic alteration. But if the reconstituted mice were among the high tumor producers, then the tumor-enhancing impact of systemic T cells—under certain conditions—would be confirmed. And that is exactly what happened. “The mice harboring  $\alpha\beta$  T cells were significantly more susceptible to tumor progression than mice of identical genotype that lack  $\alpha\beta$  T cells,” he notes.

The next issue that Girardi and his co-workers tackled was the attempt to identify genetic modifiers that influence the tumor surveillance impact of these  $\gamma\delta$  T cells. This time, they selected two different mouse strains—FVB and C57BL6—cross-bred them, and compared WT and TCR $\delta$ -/- animals within each pure strain and offspring group using the low-dose promoter paradigm. Data confirmed FVB as more susceptible than C57BL6 to chemical induction of SCC, and the greater susceptibility of the FVB.TCR $\delta$ -/- mouse compared to WT. Although 75% of the cross-bred TCR $\delta$ -/- offspring showed the low susceptibility of the C57BL6 parent, when they were backcrossed with FVB mice and a TCR $\delta$ -/- mutant generation was produced, almost 50% of these newest offspring showed enhanced susceptibility.

Now Girardi and his research team are attempting to identify the genes or gene products responsible for this difference in the hope that their results will “elucidate factors that compensate for local T-cell immunosurveillance in highly tumor-resistant hosts,” Girardi says. As for the confusing picture presented by  $\alpha\beta$  T cells—which often display protective anti-tumor activity but clearly promoted chemically induced tumor development with a high-dose promoter—

(Continued on page 7)

# ***DF: Clinical Symposia 2005***

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Plan now to attend the ***DF: Clinical Symposia—Advances in Dermatology***, to be held **March 30–April 3, 2005**, at the Ritz-Carlton, Amelia Island, FL. This Dermatology Foundation peer-reviewed program offers attendees **15 hours of CME credit (AAD Category I)**.

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Refer to the DF website: [www.dermatologyfoundation.org](http://www.dermatologyfoundation.org) for the faculty roster and full topic menu for the 2005 ***DF: Clinical Symposia—Advances in Dermatology***. The *Proceedings* of the 2004 Clinical Symposia are also available on-line.

## Switch to Human Medicine Suits New *Leaders Society* Member and Volunteer



Lindall A. Perry, MD

His commitment led him to join his state's Leaders Society volunteer team because "each new member I recruit, and each current member who gives at a higher level, multiplies my ability to have an impact on the future of our specialty."

"The fact that I am helping to advance my specialty by joining the Leaders Society is a win-win for me," says Lindall A. Perry, MD. Dr. Perry considers himself "blessed to be in dermatology" and dedicated to the Dermatology Foundation's mission.

This midwestern, Mohs-trained clinician may be the only dermatologist on record who began his professional life doing colonoscopies, bronchoscopies, kidney biopsies, and the like on dogs and cats. He had grown up on a livestock farm, enjoyed working summers with his veterinarian uncle, and happily joined the profession. But Dr. Perry's growing desire "to do something for mankind" prompted his shift to human health care.

He first became interested in dermatology because the dermatologists he saw around him as he progressed through medical school always looked happy and energized, Dr. Perry says. His rotation experience confirmed dermatology as right for him.

Dr. Perry's active clinical practice in Columbia, MO, includes Mohs micrographic surgery and general dermatologic surgery. He loves the direct hands-on visual and tactile approach that dermatology requires, the speed and variety of his typical day, and the number of patients he is able to help. These deep satisfactions ignited his desire "to give back to the profession" and do so via the Dermatology Foundation.

Dr. Perry values the continuously growing knowledge base from research funded by the Dermatology Foundation, and Foundation support for research areas inadequately served by government funding. Most especially, he endorses the significant career support enabling talented young investigators to establish their research careers and eligibility for outside funds.

To join Dr. Perry in the Leaders Society, visit the DF website at [www.dermatologyfoundation.org](http://www.dermatologyfoundation.org), or send your \$1,500 dues contribution to the Dermatology Foundation, 1560 Sherman Avenue, Suite 870, Evanston, IL 60201-4808; Phone: 847-328-2256; Fax: 847-328-0509.

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*Annenberg Circle* members  
and their guests.

Girardi says that “it will be important to determine the factors that regulate whether, on aggregate,  $\alpha\beta$  T cells inhibit or promote tumor development. But regardless of the mechanisms involved,” he adds, “the data presented here may aid immunotherapy strategies by emphasizing that enhanced systemic T-cell activation might be most effective against tumors at the early stages of their development. As a tumor progresses,” Girardi continues, “treatments designed to enhance systemic T-cell responses may show more variable efficacy.”

## Final Thoughts

This unexpected discovery of the  $\alpha\beta$  T cell’s potential for cancer promotion “has actually opened up a whole new avenue of investigation for us,” Girardi comments. “Now we are asking: what are the cancer-enhancing cells, what do they look like, what proteins do they express, and how can they be inhibited? And when we intervene and attempt to stimulate the immune system, are we making sure that we are not stimulating those cancer-enhancing immune cells!” On the other hand, Girardi and his research team have also begun to identify the factors associated with their anti-tumor behavior, and have recently shown that this protective response is composed of  $CD8^+$  and interferon- $\gamma$ -producing  $CD4^+$  cells, and that the most overt effects of these components on tumor growth *in situ* are to provoke overt focal necroses and to decrease the stromal bed.

“At the same time,” Girardi observes, “it would seem important not to ignore

the contribution to tumor surveillance of  $\gamma\delta$  T cells, and possibly other locally acting, nonconventional T cells that may resemble them. The efficacy of  $\gamma\delta$  T cells in inhibiting SCC may reflect the fact that these tumors initiate in a region rich in  $TCR\gamma\delta^+$  IELs. Thus, the anatomical site of tumor development will probably dictate the nature of the immune response best equipped to attack the tumor.” Since a unique  $TCR\gamma\delta^+$  repertoire has been identified in human dermis, the protective effects of local T cells docu-

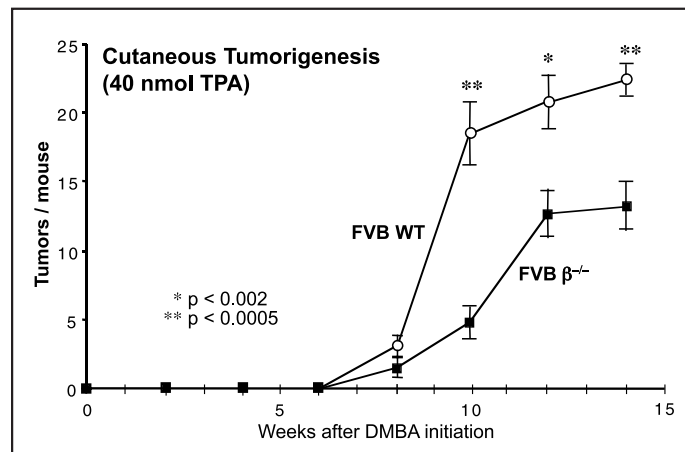
particularly effective against tumors that have lost expression of conventional MHC antigens, a common clinical problem.”

He indicates, in addition, that the effects of local T cells might well be multifaceted. Girardi has also recently documented DETC as potent suppressors of  $\alpha\beta$  T-cell-mediated inflammation of the skin, which he sees as strongly suggesting that local T cells might reduce the potential for  $\alpha\beta$  T cells to promote carcinoma formation, given the link between chronic inflammation and carcinogenesis.

Currently, Girardi and his team are preparing several recent investigations for publication. One concerns progress in identifying factors that lead to the down-regulation of anti-cancer immune responses, which continues to be an ongoing area of research. Another is their recent research on the role of  $\gamma\delta$  T cells in maintaining the barrier integrity of the skin.

And Girardi is also looking forward to the eventual discovery of a rich lode of  $\gamma\delta$  T cells in the human epider-

mis. Although human skin has not yet revealed an extensive presence of these epidermal  $\gamma\delta$  T cells, Girardi points out, most mammals have them, and  $\gamma\delta$  T cells with limited diversity have been identified now in the human dermis. He is confident that cells with homologous functions will eventually be found in the human epidermis as well. “It may be a question of exactly where to look for them,” he says, “or it may be a matter of evolution, and which cells now carry out their function.” So for the time being, Girardi continues to study these critical epidermal immune cells in mouse skin.



**Number of tumors per mouse developing with time after DMBA initiation and promotion with 40 nmol of TPA.** (FVB WT = wild-type mice, with  $\alpha\beta$  T cells; FVB  $\beta^{-/-}$  = knockout mice missing  $\alpha\beta$  T cells.) (Reprinted with permission from M. Girardi et al. *Science*. 2001;294,p.606.)

mented here “may provide a tractable animal model for the surveillance of human carcinomas,” Girardi points out.  $TCR\gamma\delta^+$  are abundant in the human gut—along with systemic T cells and other IELs—and have been reported to attack human bowel carcinomas expressing the MICA tumor antigen. Girardi notes that “the capacity of  $TCR\gamma\delta^+$  IELs to target these nonconventional MHC class I molecules might be

## What’s In a Mouse...

Girardi uses several different strains of mice in his explorations of resident and systemic T-cell behavior in the skin, with choice based on appropriateness for the needs of a particular experimental design.

*FVB mice* have been around for about 15 years. They earned this abbreviation because of their sensitivity to the murine Friend leukemia virus, which was an unplanned by-product of mice initially bred—for histamine sensitivity or resistance following pertussis vaccination—from variants of the “NIH General Purpose Mouse” established there in 1935. These FVB mice turned out to be extremely useful in the chemical induction of SCC because a relatively high proportion of the papillomas that develop progress to carcinomas. “It’s a terrific strain to work with for my purposes,” Girardi explains, “because we can manipulate the system gently and they will be highly prone to cancer.”

*C57BL6 mice* are a popular, widely used inbred strain of laboratory mice, and—for Girardi’s purposes—highly resistant to carcinogenesis.

## Suggested Readings

Girardi M, Oppenheim DE, Steele CR, et al. “Regulation of cutaneous malignancy by  $\gamma\delta$  T cells.” *Science*. 2001;294:605–9.

Girardi M, Glusac E, Filler B, et al. “The distinct contributions of murine T cell receptor ( $TCR$ ) $\gamma\delta^+$  and  $TCR\alpha\beta^+$  T cells to different stages of chemically induced skin cancer.” *J Exp Med*. 2003;198:747–55.

Girardi M, Oppenheim DE, Glusac EJ, et al. “Characterizing the protective component of the  $\alpha\beta$  T cell response to transplantable squamous cell carcinoma.” *J Invest Dermatol*. 2004;122:699–706. ■



## Annenberg Circle Growing

### New Annenberg Circle Members in 2004

(As of November 15, 2004)

#### FROM THE SPECIALTY

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Alan R. Berlin, DO  
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Susan H. Weinkle, MD  
Jonathan S. Weiss, MD  
Daniel B. Yarosh, PhD

#### FROM THE PUBLIC

Wayne Traub

**“As a modern day practitioner and educator, I will always be grateful to those who came before me and laid the foundation for what we know today. My gift to the Dermatology Foundation represents my own commitment to making certain that this wonderful medical specialty continues to make great strides by promoting both research and education.”**



Clarence W. Brown, Jr., MD  
Chicago, Illinois

The most generous level of giving to the Dermatology Foundation has gained the commitments, so far this year, of 42 new members—recognized at the left—expanding the roster to 247. Quotes from three of these new members are included here, each reflecting on his or her recent decision to join the **Annenberg Circle**.



Angela Yen Moore, MD  
Arlington, Texas

**“The Dermatology Foundation’s Career Development Award helped launch me into an active clinical and research practice. Now, more than ever, research needs support from all dermatologists, not just those in academics, and I am thankful to be in the position to contribute to the future of dermatology.”**

Each member’s lifetime \$25,000 contribution further strengthens the DF’s critical mission of developing the careers of future thought leaders. Up to \$10,000 of accrued Leaders Society membership may be applied to the \$25,000 **Annenberg Circle** commitment. Membership dues may be paid over as many as five years, at a minimum commitment of \$5,000 per year, until the pledge is completed.

**“When Steve Shama, Dick Scher, and Jerry Krueger called me to join the Annenberg Circle, Steve told me he’d give me the opportunity to wear a nicer ribbon at the AAD meeting; Dick told me he was going to make me an offer I couldn’t refuse; and Jerry told me that research is the future of our specialty. All three were right! It is an honor to be able to join this illustrious group of leaders of our specialty.”**



Mark Lebwohl, MD  
New York, NY

**To join the Annenberg Circle, contact Joe Flint, Manager, Individual Giving, at 847-328-2256 or by email at [dfgen@dermatologyfoundation.org](mailto:dfgen@dermatologyfoundation.org).**

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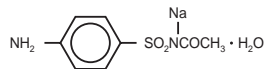
Safety Information:

Although rare, local irritation has been reported with topical sodium sulfacetamide and sulfur therapy. Plexion® Cloths are contraindicated for use by patients with hypersensitivity to sulfur or sulfonamides, and patients with kidney disease.



#### Rx ONLY

**DESCRIPTION:** Sodium sulfacetamide is a sulfonamide with antibacterial activity while - sulfur acts as a keratolytic agent. Chemically sodium sulfacetamide is N-[(4-aminophenyl) sulfonyl]-acetamide, monosodium salt, monohydrate. The structural formula is:



Each gram of Plexion, (sodium sulfacetamide USP 10% and sulfur USP 5%) Cleanser contains 100 mg of Sodium Sulfacetamide USP and 50 mg of Sulfur USP in a cleanser base containing: Purified Water USP, Sodium Methyl Oleoyltaurate, Sodium Cocoyl Isethionate, Disodium Oleamido MEA Sulfosuccinate, Cetyl Alcohol NF, Glyceryl Stearate (and) PEG-100 Stearate, Stearyl Alcohol NF, PEG-55 Propylene Glycol Oleate, Magnesium Aluminum Silicate NF, Methylparaben NF, Edetate Disodium USP, Butylated Hydroxytoluene NF, Sodium Thiosulfate USP, Fragrance, Xanthan Gum NF, and Propylparaben NF.

Each cloth of Plexion, (sodium sulfacetamide USP 10% and sulfur USP 5%) Cleansing Cloths is coated with a cleanser-based formulation. Each gram of this cleanser-based formulation contains 100 mg of sodium sulfacetamide USP and 50 mg of sulfur USP. The cleanser base consists of: Purified Water USP, Sodium Methyl Oleoyltaurate, Sodium Cocoyl Isethionate, Disodium Laureth Sulfosuccinate (and) Sodium Lauryl Sulfoacetate, Disodium Oleamido MEA Sulfosuccinate, Glycerine USP, Sorbitan Monooleate NF, Glyceryl Stearate (and) PEG-100 Stearate, Stearyl Alcohol NF, Propylene Glycol (and) PEG-55 Propylene Glycol Oleate, Cetyl Alcohol NF, Edetate Disodium USP, Methylparaben NF, PEG-150 Pentaerythrityl Tetrastearate, Butylated Hydroxytoluene NF, Sodium Thiosulfate USP, Aloe Vera Gel Decolorized, Allantoin, Alpha Bisabolol Natural, Fragrance, Propylparaben NF.

Each gram of Plexion SCT<sup>®</sup> (sodium sulfacetamide USP 10% and sulfur USP 5%) contains 100 mg of Sodium Sulfacetamide USP and 50 mg of Sulfur USP in a cream containing: Purified Water USP, Kaolin USP, Glyceryl Stearate (and) PEG-100 Stearate, Witch Hazel USP, Silicon Dioxide NF, Magnesium Aluminum Silicate NF, Benzyl Alcohol NF, Water (and) Propylene Glycol (and) Quillaja Saponaria Extract, Xanthan Gum NF, Sodium Thiosulfate USP, Fragrance.

Each gram of Plexion<sup>®</sup> (sodium sulfacetamide USP 10% and sulfur USP 5%) Topical Suspension contains 100 mg of Sodium Sulfacetamide USP and 50 mg of Sulfur USP in a suspension containing: Purified Water USP, Propylene Glycol USP, Isopropyl Myristate NF, Light Mineral Oil NF, Polysorbate 60 NF, Sorbitan Monostearate NF, Cetyl Alcohol NF, Hydrogenated Coco-Glycerides USP, Stearyl Alcohol NF, Fragrances, Benzyl Alcohol NF, Glyceryl Stearate (and) PEG-100 Stearate, Dimethicone NF, Zinc Ricinoleate, Xanthan Gum NF, Edetate Disodium USP, and Sodium Thiosulfate USP.

**CLINICAL PHARMACOLOGY:** The most widely accepted mechanism of action of sulfonamides is the Woods-Fildes theory, which is based on the fact that sulfonamides act as competitive antagonists to para-aminobenzoic acid (PABA), an essential component for bacterial growth. While absorption through intact skin has not been determined, sodium sulfacetamide is readily absorbed from the gastrointestinal tract when taken orally and excreted in the urine, largely unchanged. The biological half-life has variously been reported as 7 to 12.8 hours. The exact mode of action of sulfur in the treatment of acne is unknown, but it has been reported that it inhibits the growth of Propionibacterium acnes and the formation of free fatty acids.

**INDICATIONS:** PLEXION Cleanser, PLEXION Cleansing Cloths, PLEXION SCT and PLEXION TS are indicated in the topical control of acne vulgaris, acne rosacea and seborrheic dermatitis.

**CONTRAINDICATIONS:** Plexion Cleanser, PLEXION Cleansing Cloths, PLEXION SCT and PLEXION TS are contraindicated for use by patients having known hypersensitivity to sulfonamides, sulfur or any other component of this preparation. These PLEXION<sup>®</sup> brand products are not to be used by patients with kidney disease.

**WARNINGS:** Although rare, sensitivity to sodium sulfacetamide may occur. Therefore, caution and careful supervision should be observed when prescribing this drug for patients who may be prone to hypersensitivity to topical sulfonamides. Systemic toxic reactions such as agranulocytosis, acute hemolytic anemia, purpura hemorrhagica, drug fever, jaundice, and contact dermatitis indicate hypersensitivity to sulfonamides. Particular caution should be employed if areas of denuded or abraded skin are involved.

**FOR EXTERNAL USE ONLY.** Keep away from eyes. Keep out of reach of children. Keep container tightly closed.

**PRECAUTIONS:** General - If irritation develops, use of the product should be discontinued and appropriate therapy instituted. Patients should be carefully observed for possible local irritation or sensitization during long-term therapy. The object of this therapy is to achieve desquamation without irritation, but sodium sulfacetamide and sulfur can cause reddening and scaling of the epidermis. These side effects are not unusual in the treatment of acne vulgaris, but patients should be cautioned about the possibility.

**Information for Patients:** Avoid contact with eyes, eyelids, lips and mucous membranes. If accidental contact occurs, rinse with water. If excessive irritation develops, discontinue use and consult your physician.

**Carcinogenesis, Mutagenesis and Impairment of Fertility -** Long-term studies in animals have not been performed to evaluate carcinogenic potential.

**Pregnancy Category C -** Animal reproduction studies have not been conducted with PLEXION Cleanser, PLEXION Cleansing Cloths, PLEXION TS or PLEXION SCT. It is also not known whether these PLEXION brand products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. These PLEXION<sup>®</sup> brand products should be given to a pregnant woman only if clearly needed.

**Nursing Mothers -** It is not known whether sodium sulfacetamide is excreted in the human milk following topical use of Plexion Cleanser, Plexion Cleansing Cloths, PLEXION SCT or PLEXION TS. However, small amounts of orally administered sulfonamides have been reported to be eliminated in human milk. In view of this and because many drugs are excreted in human milk, caution should be exercised when these PLEXION brand products are administered to a nursing woman.

**Pediatric Use -** Safety and effectiveness in children under the age of 12 have not been established.

**ADVERSE REACTIONS:** Although rare, sodium sulfacetamide may cause local irritation.

**DOSAGE AND ADMINISTRATION:** PLEXION Cleanser: Wash affected areas once or twice daily, or as directed by your physician. Avoid contact with eyes or mucous membranes. Wet skin and liberally apply to areas to be cleansed, massage gently into skin for 10-20 seconds working into a full lather, rinse thoroughly and pat dry. If drying occurs, it may be controlled by rinsing cleanser off sooner or using less often.

**PLEXION Cleansing Cloths:** Wash affected areas with cleansing cloth once or twice daily, or as directed by your physician. Wet face with water. Wet cloth with a little water and work into a full lather. Cleanse face with cloth for 10-20 seconds avoiding eyes. Rinse thoroughly and pat dry. Throw away cloth. Do not flush.

**PLEXION SCT:** Use once daily or as directed by your physician. Wet skin. Apply in a film to entire face, avoiding contact with eyes or mucous membranes. Wait 10 minutes or until dry. Rinse thoroughly with water and pat dry.

**PLEXION TS:** Cleanse affected areas. Apply a thin film of PLEXION TS to affected areas 1 to 3 times daily, or as directed by a physician.

**HOW SUPPLIED:** Plexion<sup>®</sup> (sodium sulfacetamide 10% and sulfur 5%) Cleanser is available in 6 oz. (170.3 g) tube (NDC 99207-741-06) and 12 oz. (340.2 g) bottle (NDC 99207-741-12). Plexion<sup>®</sup> (sodium sulfacetamide 10% and sulfur 5%) Cleansing Cloths are available in boxes of 30 cloths (3.7 g) (NDC 99207-745-30). Plexion SCT<sup>®</sup> (sodium sulfacetamide 10% and sulfur 5%) is available in a 4 oz. tube (NDC 99207-744-04). Plexion<sup>®</sup> (sodium sulfacetamide 10% and sulfur 5%) Topical Suspension is available in 30 g tube (NDC 99207-743-30).

Store at 15° - 25°C (59° - 77°F).

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Patent Pending  
74530-08C



# Focus on Research

(Continued from cover)

By the mid-1980s, several labs—including Needleman's—were progressing toward identifying the two distinct cyclooxygenase (COX) enzymes. "The COX-2 enzyme was actually discovered at other laboratories," Pentland notes, "and as soon as it became known, I immediately looked at it in keratinocytes and realized that, in these cells, it is regulated by UV light." UV light, keratinocytes, and COX-2 have been her active focus ever since, through a decade at Washington University, and since 1996 at the University of Rochester. (Needleman went on to develop celecoxib, and eventually moved from academia to industry.)

## Eicosanoids: The ABCs

Pentland explains that arachidonic acid and its metabolites—the eicosanoids—are ubiquitous bioactive mediators formed from the unsaturated fatty acids present in cell membranes. The release of arachidonic acid from membrane phospholipids by a phospholipase is key in initiating eicosanoid synthesis. The eicosanoids function as local lipid hormones, with potent biologic effects in picomolar amounts that regulate many important physiologic and pathologic processes.

The fatty acid metabolism of arachidonic acid is the most common substrate for cyclooxygenase as well as lipoxygenase and monooxygenase enzymes. Cyclooxygenase metabolism leads to the synthesis of prostaglandins—the focus here—and thromboxanes. Recognition and study of these compounds began back in the 1930s, when Swedish physiologist Ulf von Euler described acidic lipid extracts from the prostate secretions of humans and sheep—abundant in seminal vesicles—that could contract smooth muscle. Having found these secretions in the prostate gland, he named them prostaglandins. Current eicosanoid terminology reflects the number of double bonds present in the substrate fatty acid, eg, prostaglandin PGE<sub>2</sub>, derived from arachidonic acid, has two double bonds remaining in its side chain.

Prostaglandins—produced in response to numerous growth factors and environmental stimuli—act through dedicated G-protein-linked receptors, also called seven-transmembrane receptors because they pass through the cell membrane seven times. The prostaglandins active in—although not limited to—the skin are PGD<sub>2</sub>, PGE<sub>2</sub>, PGF<sub>2α</sub>, and PGI<sub>2</sub>. The

E-series prostaglandins—important modulators of normal cell proliferation and apoptosis, with an important role in wound repair—are the most prominent.

The two COX isoforms share 60% homology. COX-1 is considered primarily a housekeeping form, while COX-2 is highly regulated and induced by inflammation. Pentland's early discovery of the intimate relationship between UV light and the regulation of COX-2 in the skin eventually led her to investigate and document its role in UV-induced basal cell (BCC) and squamous cell (SCC) carcinomas, and then begin to explore the protective possibilities of COX-2 inhibition.

## COX-2 and UV-Induced Skin Tumors

UV light has been well documented as a complete carcinogen—responsible for both initiation and promotion of BCC and SCC—and tumors produced by exposure to UV light constitute nearly 50% of cancers diagnosed in the US today. Approximately 90% of the 90,000 to 1,200,000 new cases of skin cancer each year are attributable to UV light irradiation. The UV light spectrum comprises UVA (320–400 nm), UVB (290–320 nm), and UVC (200–290 nm). Because UVC is filtered out by the earth's ozone layer, it has little biological relevance in skin tumor formation. Although UVB is clearly the most effective in causing SCC, the oxidative stress induced by UVA—the most abundant wavelength segment of the solar spectrum—has also been associated with photocarcinogenesis.

UV exposure of the skin induces prostaglandin synthesis by increasing synthesis and activity of cytosolic phospholipase A<sub>2</sub>, which liberates arachidonic acid from membrane phospholipids to free it for COX conversion to prostaglandins. This prostaglandin synthesis was eventually determined to play a role in UV injury. Exposure to three times the minimal erythema dose of UV radiation produces a prolonged increase in the release of several E-series prostaglandins, including PGE<sub>2</sub>. Early treatment with the broad-spectrum COX inhibitor indomethacin was found to inhibit this erythema, clearly demonstrating the role of prostaglandins in the process.

Pentland had begun to suspect that "the acute up-regulation of COX-2 by UV radiation may contribute to photocarcinogenesis in the same way it had recently been shown to contribute to

colon cancer." Her suspicion was strengthened by the evidence she had found supporting the potential involvement of COX-2 in human actinic keratosis and SCC of the skin.

## COX-2 Inhibition Impairs UV-induced Tumor Promotion

To test this possibility, Pentland designed a study in which albino hairless mice—the standard model for UV photocarcinogenesis work—were chronically exposed to broad-band UV (ie, UVA + UVB), then fed a COX-2 inhibitor. Irradiation was 5 days a week, initially representing 70% of an edema dose and equivalent to 30 minutes of noonday autumn sun in Rochester, NY, then increasing by 10% each week for weeks 2 through 13. After radiation, when at least 90% of the animals had one tumor, they were separated into two groups with equivalent tumor number and multiplicity. Then from weeks 19 through 28, one group ate a diet of standard chow and the other ate chow supplemented with celecoxib (a final concentration of 1500 ppm). Throughout both stages of this protocol, papilloma and tumor incidence and size were determined and photographed weekly.

Although existing tumors were unaffected in the celecoxib group after medication began, their rate of new tumor appearance began to slow at four weeks and was substantially less by 10 weeks. Size and weight of their new tumors were also significantly less. By 10 weeks, tumor burden in the control mice had become large enough to end the experiment. More than 95% of the tumors in both groups were SCC, the most common type of tumor induced by UV irradiation in hairless mice. Pentland and her co-workers tested to make sure that COX-1 had not inadvertently been inhibited, and they also found evidence of increased COX-2 in the right places. COX-2 staining was intense in papillomas in the areas of dysplastic epidermis. Carcinomas also showed intense staining, and contained an infiltrate of intensely stained inflammatory cells. Pentland verified that this COX-2 presence in irradiated skin correlated with increases in prostaglandin synthesis, especially PGE<sub>2</sub>, the predominant product formed in skin. Areas of UV-protected skin on these same animals showed equal activity of both COX isoforms.

Because celecoxib was not begun dur-

## In Memoriam: Jeffrey S. Schechner, MD, Yale Dermatologist

The Dermatology Foundation is deeply saddened to announce the sudden and untimely death of Dr. Jeffrey Schechner in early September, at age 39. Dr. Schechner was a superb clinician and an insightful and productive scientist about to test a novel bioengineered skin equivalent in clinical trials. Dr. Schechner was funded by the Dermatology Foundation in the early stages of his career. In 1997 he received DF support as a recipient of the Dermatologist Investigator Research Fellowship, followed by a three-year Clinical Career Development Award from 1998 through 2000.

At the time of his death, Dr. Schechner was an Associate Professor in the Department of Dermatology at Yale University and Chief of Dermatology at the West Haven Veterans Administration Medical Center. "As a scientist," Richard L. Edelson, MD, Chairman of Dermatology at Yale, says, "he led the effort to create an improved tissue-engineered skin that, by incorporating human endothelial cells, would work significantly better than currently available options. He was in the midst of designing a clinical trial to bring this work to fruition. Dr. Schechner also studied functional roles of skin endothelial cells in inflammatory

diseases and cutaneous malignancies, and he played a key role in the development of human skin grafting onto immunodeficient mice. This provided a novel system for the study of living human skin," Dr. Edelson says, a model that has since facilitated significant progress in cutaneous research at Yale and elsewhere.



Dr. Jeffrey S. Schechner

In expressing the reactions of colleagues and friends, Dr. Edelson says: "We are stunned by the loss of Jeff Schechner. We have been robbed of our cherished colleague and the many more years of friendship and partnership we had all looked forward to, but all that we are—and can become—will remain immeasurably enriched by his invaluable contributions to our programs and environment. And his family's loss dwarfs our own."

Dr. Schechner is survived by his wife Christina Herrick, MD, PhD, also a dermatologist, and two children.

The family has requested that memorial contributions be made to the Dermatology Foundation, 1560 Sherman Avenue, Suite 870, Evanston, IL 60201-4808.

ing irradiation, it cannot have acted via tumor initiation events—such as thymine dimer formation and UV-mediated production of free radicals—associated with UV exposure. "These results suggest that COX-2 induction in dysplastic epidermis, combined with PGE<sub>2</sub> formation by nearby inflammatory cells, is a potent proliferative stimulus that is able to overcome the normal cellular commitment to differentiation," Pentland points out. "The fact that no existing tumor was affected suggests that this PGE<sub>2</sub> effect is most important in the early stages of tumor promotion," she adds.

On the one hand, this study pointed to the importance of COX-2 in UV-induced tumorigenesis of skin in mice, and on the other, it documented oral administration of the selective COX-2 inhibitor celecoxib as a potent agent for reducing UV-induced tumor multiplicity in hairless mice. The key mechanism suggested is an effect on local proliferation of the epidermis. Pentland spoke of the frequent requests from patients diagnosed with a SCC or actinic keratoses for something to prevent the development of new lesions, and commented that her study suggested the

possible clinical utility of such an approach in at-risk individuals. Whether this inhibitory effect also occurs in human populations remained to be examined.

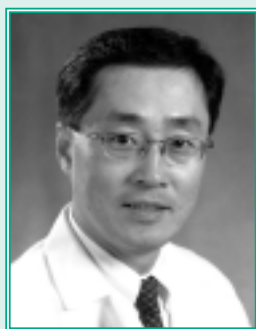
### PGE<sub>2</sub> and its Receptor in Human Skin: The Dynamics of Prostaglandin Surges

Considerable evidence continued to accumulate from various laboratories pointing to the ability of PGE<sub>2</sub> to promote tumor growth as a consequence of its mitogenic activity, pro-angiogenic activity, and inhibition of apoptosis. It appeared likely that understanding the benefit produced by COX-2 inhibition required demonstration of a distinct receptor-based mechanism. To provide this missing link, Pentland designed an experiment based on her awareness that prostaglandin receptors typically "undergo ligand-induced receptor down-regulation." This means that when a prostaglandin receptor receives substantially increased stimulation because its respective prostaglandin has suddenly surged, the cell—attempting to restore balance—stops expressing the receptor. This dynamic creates the phar-

macologic equivalent of a knockout mouse for that particular receptor, which reverses once prostaglandin production returns to normal levels. Malignant lesions are a different story. COX-2 expression and PGE<sub>2</sub> production generally increase as lesions progress from normal to benign papillomas, and from benign papillomas to frank malignancy. The marked increase in prostaglandin production becomes the normal state of affairs, and thus so does the receptor loss.

Pentland and her research team used HaCat cells—a human keratinocyte cell line that is immortalized but noninvasive—and transfected them with either a sense or anti-sense construct of EP<sub>2</sub>, one of the four main PGE<sub>2</sub> receptor types. The sense construct provided these cells with a high level of receptor expression. The anti-sense construct prevented receptor expression, the equivalent of the pharmacologic knockout. Each engineered cell line was cloned, and assays ensured that the receptors in the EP<sub>2</sub>-sense cells were functioning properly. To evaluate the invasive behavior of these two groups of clones, Pentland and her co-workers used

## Sewon Kang, MD, MPH: New Medical & Scientific Committee Chair



Sewon Kang, MD, MPH

Dr. Sewon Kang has been chosen to chair the DF Medical & Scientific Committee for 2004–2005 after serving for two years as a committee member. This committee of scientific experts reflects the full breadth of the specialty, and is charged with the peer review of applications to the Research Awards Program and recommendations for funding.

Dr. Kang brings his strong background to this challenging responsibility. He is now Professor of Dermatology and Director, Dermatopharmacology Unit in the Department of Dermatology at the University of Michigan Medical Center, and the Principal Investigator for both a substantial RO1 Grant and K24 Mid-Career Investigator Award from the NIH. In addition to his previous participation on the Medical & Scientific Committee, Dr. Kang brings over 10 years of extensive grant review experience with other entities that include the NIH.

“This committee is really the core of what the Foundation does year after year,” Dr. Kang observes. “And just as important as the content of the proposals we evaluate are the investigative dermatologists who have submitted them. **We are investing in people as well as research,**” he explains, **“and attempting to identify those who are going to become the next generation of leaders in our specialty. Through this Research Awards Program, our goal is to ensure the continued advancement of our specialty by developing and nurturing the next cadre of leaders in investigative dermatology. This is broadly defined,”** he adds, **“and includes top level clinicians, inspiring teachers, fine skin surgeons, and insightful medical**

**economics outcomes researchers in addition to laboratory-based scientists.”** Dr. Kang will be putting these goals into practice as he guides the committee during the review and deliberation process.

Dr. Kang himself is an example of this success. He has fulfilled the promise implicit in the three-year DF Clinical Career Development Award awarded to him in the mid-1990s, after completing his education (a degree in chemistry from Williams College, MPH and MD from the University of Michigan, dermatology residence at Harvard Medical School) and joining the Department of Dermatology at the University of Michigan Medical Center in 1992. Now, as one of today’s leaders in investigative dermatology, he is playing a crucial role in establishing the next generation.

### DF: Shaping Medical Dermatology

The urgent need for research progress and commitment in medical dermatology is addressed by the DF’s multiyear **Medical Dermatology Career Development Award** designed specifically to support the career development of dermatologists who want to advance the understanding and treatment of patients with systemic disease. *Medical dermatology, which involves “patients who are notably challenging to manage,” Bruce Wintroub, MD, President of the DF, points out, “encompasses serious skin disorders that are part of a generalized medical illness, such as lupus of the skin, and severe skin disorders requiring complex, high-risk systemic therapy.”*

The very first recipients of this three-year award—David F. Fiorentino, MD, PhD, at Stanford for research in scleroderma (Vol. 23, No. 2) and Lindy Fox, MD, at Yale University for research in consultative medical dermatology—are now in the initial year of their research projects.

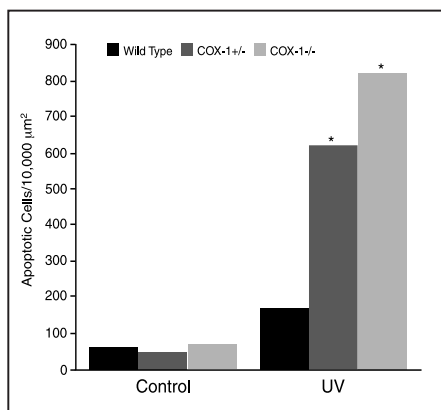
a three-dimensional organ culture model of normal skin. The anti-sense clones “all demonstrated extensive deep invasion with marked branching and networking into the dermal compartment,” Pentland notes. All told, there was more than a twofold increase in depth of invasion compared to the sense clones and to control HaCat cells that had been transfected with just the empty vector.

The fact that molecular intervention, as in this experiment, and pharmacologic down-regulation, as in the living organism, both result in a marked increase in

cell invasiveness “strongly suggests that increased COX-2 and PGE<sub>2</sub> production in advanced malignancy may lead to a more aggressive tumor,” Pentland points out, adding that “these data strongly support the EP<sub>2</sub> receptor as key in this process.” She also identified an accompanying loss of expression of paxillin, a structural protein involved in focal adhesions. This loss is also seen in mouse keratinocytes after malignant conversion, and Pentland speculates that its loss facilitates the ability of these malignant keratinocytes to leave the integrated structure of the epidermis.

### How COX-2 Inhibition Photoprotects

Having established the role of the PGE<sub>2</sub> receptor in the prostaglandin-driven UV-induced malignant process in the skin, and the efficacy of COX-2 inhibition in impairing UV-induced tumor promotion (Susan Fischer, PhD, at UT-MD Anderson Cancer Center had shown similar efficacy against initiation as well, in hairless mice), Pentland turned her attention to learning what UV-induced COX-2 expression achieves in the skin. She hoped to identify a mechanism



**In COX-1 knockout mice (COX-1<sup>-/-</sup>), keratinocyte apoptosis after UV irradiation is greatly increased.** A significantly higher number of apoptotic cells were detected in this group versus wild-type (WT) controls. An intermediate number were present in the COX-1<sup>+/-</sup> genotype. \* =  $P < 0.05$ . (Reprinted with permission from AP Pentland et al. *Cancer Res.* 2004;64,p.5589.)

explaining the photoprotective impact of COX-2 inhibition.

She used hairless mice to characterize early events in the epidermis following acute UV exposure with sunlamps that mimic natural sunlight. Three groups were studied: a control group, mice dosed with the broad-spectrum COX inhibitor indomethacin, and mice dosed with the experimental COX-2 inhibitor SC-791, which was more selective than previously reported inhibitors. Evaluating control animals, Pentland showed that basal keratinocytes express COX-2, and that the resulting local prostaglandin synthesis affects these keratinocytes by both reducing apoptosis and stimulating their proliferation. Both inhibitors resulted in minimizing these effects—apoptosis increased, proliferation was reined in, and keratinocyte differentiation showed a slight increase.

Although initially Pentland had tentatively regarded the primary COX-2/prostaglandin impact to be reduced apoptosis of UV-damaged keratinocytes and the benefit of COX-2 inhibition as enabling these damaged cells to be destroyed, she has come increasingly “to focus on the fact that the prostaglandins regulate proliferation, and less and less on any effect on apoptosis,” she says. She regards this immediate proliferative impact as one aspect of a menu of protective responses to UV damage. “Because an injury like that from light damages many things, many repairs are needed,” Pentland points out. “There are numerous checkpoints for identifying the thymine dimers that UV light creates in DNA, and various processes for removing them once they are identified. But this repair process takes time,” she continues,

“which means there is also a need for immediate photoprotection. And one way of achieving that is by producing a much larger number of keratinocytes. Keratinocytes themselves contain a number of light-absorbing substances in addition to melanin,” she explains, “including endogenous amino acids, and they contain proteins that consume oxygen radicals. This makes thickening the epidermis an excellent preventive photoprotective strategy for the short term.” But this protective proliferation is in reality a double-edged sword, because it intersects with the fact that just a single afternoon in the sun creates about six billion photoproducts. Damaged cells that occasionally escape DNA repair and/or apoptosis become potential candidates for amplification via the immediate protective strategy of proliferation.

Pentland’s speculation was strongly supported in her next investigation.

### One Study With Several Fundamental Lessons

This next study was motivated by evidence from other model systems in mice—intestinal cancer and two-stage chemically induced SCC—that COX-1 inhibition can also offer anti-tumor protection. In a mouse that spontaneously develops intestinal polyps, knocking out the COX-1 gene resulted in a 77% reduction in intestinal polyps. In a chemically induced skin cancer protocol applying the initiator DMBA followed by the promoter TPA to NMRI mice, COX-1 knockout animals were substantially more resistant to tumor development.

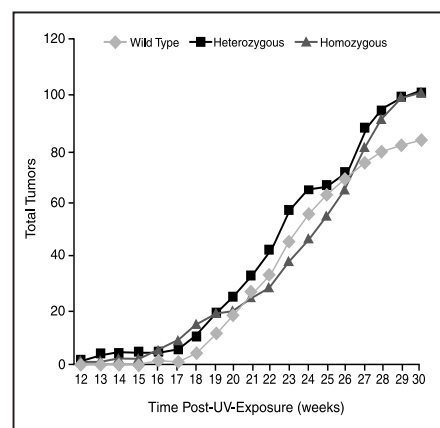
Pentland and her co-workers used hairless mice with a selective COX-1 deletion to examine its role in epidermal responses after UV irradiation. Three groups of animals were put through their paces—wild-type controls, mice heterozygous for the COX-1 deletion and thus producing less of the enzyme, and knockout mice producing no COX-1 at all. The light source combined UVA and UVB wavelengths, closely resembling the UV spectrum of sunshine through the mid-UVA range. Some mice were irradiated with an acute protocol—an environmentally relevant dose, ie, equivalent to 60 minutes of noonday summer sun in Rochester, NY—and examined 24 and 72 hours after exposure. Typical findings of UV irradiation were observed, including a modest increase in epidermal thickness. The chronic protocol involved 15 weeks of incrementally increasing exposure, with a weekly exposure schedule of 3

times/week. Tumor development was observed, and after sacrifice samples of exposed skin were taken for measurement of epidermal thickness, histologic analysis, measurement of prostaglandins, keratinocyte proliferation, and keratinocyte apoptosis.

Pentland found that the absence of COX-1 in the skin increased apoptosis four-fold in chronically irradiated knockout animals (see graph at left), at least twice the levels that are considered therapeutically important in anti-cancer treatments. But despite this impressive achievement, the three mouse groups were identical in regard to both epidermal proliferation and susceptibility to UV-induced tumor formation (see graph, below). Tumor number, average tumor size, and time of tumor onset in COX-1 knockout mice were the same. Unlike her results with COX-2 inhibition, “results here indicated that selective COX-1 deletion is not helpful, despite strongly positive evidence of protection in other model systems,” Pentland observes.

These results may, at least in part, reflect genetic differences in tumor susceptibility between different mouse strains. It may also be a function of how cancer is induced or promoted in these different models. Chemically induced skin tumors are the exception in the real world, as nearly all skin cancers are caused by repeated exposure to sunlight, and extensive endogenous systems are present to repair the effects of this chronic environmental insult.

Pentland concludes that a causal relationship between induced COX-2 expression and UV-induced development of skin cancer has been demonstrated in the hairless mice used in her initial study,



**COX-1 knockout mice showed a 4-fold increase in apoptosis after UV exposure, but tumor development was unaffected.**

WT mice, those heterozygous for the deletion, and mice lacking COX-1 were identical in tumor number and time of onset. (Reprinted with permission from AP Pentland et al. *Cancer Res.* 2004;64,p.5590.)

## Post-Residents Receive Discounted Member Rate

The Dermatology Foundation—recognizing the challenges of getting started in a career—offers **a discounted membership rate for the first two years after a dermatologist's residency, allowing members to receive full benefits for just \$100 a year.**

### Member benefits include:

- Complimentary subscriptions to two widely respected quarterly publications, ***Dermatology Focus*** and the members-only ***Progress in Dermatology***.
- The opportunity to **network** with today's leaders—and tomorrow's—at Foundation-sponsored events.
- Reduced-fee registration for the Foundation's annual ***Clinical Symposia***. Each Symposia registrant receives 15 hours of AAD Category I credit to use toward the CME Award of the AAD.
- **Recognition** ribbon given at the AAD Annual Meeting and other major dermatology meetings.

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If you completed residency in 2002, 2003, or 2004, please join in shaping the future of dermatology.

Visit the DF website at [www.dermatologyfoundation.org](http://www.dermatologyfoundation.org) or mail your \$100 membership dues to Dermatology Foundation, 1560 Sherman Avenue, Suite 870, Evanston, IL 60201-4808. For questions, call 847-328-2256.

in Fischer's investigation, and in a later study by Ida F. Orenge, MD, an investigative dermatologist at Baylor College of Medicine. "In these studies," she says, "selective COX-2 inhibition suppressed tumor formation in response to chronic UV exposure. The clear implication is that selective COX-2 inhibition may be a useful intervention for populations at risk for non-melanoma skin cancer, and the fact that NSAIDs have already been shown to be effective in reducing the incidence of breast and colon cancer in humans lends excitement to this possibility." Two clinical trials are in progress. One—sponsored by the National Cancer Institute and Pharmacia—involves six centers under the overall direction of Craig Elmetts, MD, at the University of Alabama. A randomized, double-blind placebo-controlled study of 240 patients is assessing the effect on the emergence of actinic keratoses over a 9-month period. Patient assessment should be completed before the summer of 2005, but it will be some time before the results are fully analyzed and ready for publication. Another multicenter study—headed by Ervin Epstein, MD, at the University of California—San Francisco—is examining the chemopreventive potential of selective COX inhibitors for BCC carcinoma in patients with basal cell nevus syndrome. "If the effects are as dramatic as in mouse models of tumorigenesis—which most closely resemble squamous cell carcinoma—one can imagine the incidence of basal cell cancer in high-risk individuals dropping by half," Pentland states.

Along with this potential optimism, Pentland cautions that "such an intervention for skin cancer prevention would likely be very broad-based, making it

extremely important to be certain of the associated risks and benefits." In the case of traditional NSAIDs and aspirin, one clear problem is the incidence of gastrointestinal effects, particularly ulcers and gastritis. Selective inhibitors are thought to minimize this, but the issue is not clearcut. These drugs are also a common cause of renal failure, which would make it contraindicated for individuals who have undergone renal transplantation and begun to develop many squamous cell cancers. And given the commonness of renal problems among older patients, the risk-benefit ratio for such treatment in this context must be established before the broad-based use of NSAIDs can be recommended.

The importance of considering risk and benefit in detail is highlighted by the recent withdrawal of Vioxx from the market due to that drug's capacity to increase the risk of stroke in patients taking the drug long term. Re-study of FDA data on celecoxib has not revealed a similar problem for this chemically distinct drug.

### Final Conclusions

Pentland's final conclusions from this most recent study in her laboratory range from specific to broad relevance. In regard to the target for decreasing tumor initiation or progression in photocarcinogenesis, apoptosis clearly is not the key method that it had been conceived of as being. Despite a fourfold induction of apoptosis in COX-1 knockout hairless mice, no substantive protection against skin cancer was evident.

But "more important than the implication of these findings for skin cancer," Pentland emphasizes, "are the more generalizable conclusions that can be drawn.

One relates to previous work, in which the efficacy of a cancer treatment or prevention strategy is usually linked with its capacity to enhance apoptosis," she points out. "The ability to separate induction of apoptosis from protection against tumorigenesis is clearly demonstrated here, suggesting that although increased apoptosis may be helpful, it is not sufficient to provide cancer prevention. And," she continues, "these results also confirm that tumorigenesis is specifically linked to the carcinogenic stimulus. Although ample evidence supports the unique mutational profile of various carcinogenic exposures, studies to develop treatments or chemoprevention strategies are often tested in models that may not replicate the etiology of the human cancer of interest," Pentland notes, concluding that "because substantial resources must be invested in human chemoprevention studies, our recent investigation indicates that models to test chemoprevention strategies must specifically consider cancer etiology in their design."

### Suggested Readings

Pentland AP, Schoggins JW, Scott GA, et al. "Reduction of UV-induced skin tumors in hairless mice by selective COX-2 inhibition." *Carcinogenesis*. 1999;20:1939-44.

Tripp CS, Blomme EAG, Chinn KS, et al. "Epidermal COX-2 induction following ultraviolet irradiation: Suggested mechanism for the role of COX-2 inhibition in photoprotection." *J Invest Dermatol*. 2003;121:853-61.

Pentland AP, Scott G, Van Buskirk J, et al. "Cyclooxygenase-1 deletion enhances apoptosis but does not protect against ultraviolet-induced tumors." *Cancer Res*. 2004;64:5587-91. ■

## PROFILES OF SUPPORT

*The Dermatology Foundation is deeply grateful for industry's substantial and ever-growing confidence and generosity. Continuing our profiles of our Corporate Honor Society partners—companies contributing at least \$50,000 annually to the Foundation (see page 4 for this roster)—we are pleased to feature Unilever Home & Personal Care – U.S.A.*

**Anthony W. Johnson, BSc, PhD, DipRCPath**, is Director of Skin Clinical Evaluation at **Unilever Home & Personal Care – U.S.A.** He joined Unilever 34 years ago in the area of skin toxicology and product safety, eventually moving into skin research, then skin product development, and now clinical evaluation for the past 12 years.

Although Unilever does not have a pharmaceutical arm, the products they develop and manufacture for personal and home care clearly affect the skin and engendered their early awareness of the need to understand the skin and how best to study it. That perception was the origin of Unilever's partnership with the Dermatology Foundation.

Dr. Johnson vividly recalls this beginning, "over 20 years ago, when we recognized the importance of the DF's goal to advance dermatologic research and became one of their early corporate supporters." As Unilever has witnessed the tremendous growth in the development of research and teaching careers enabled by the DF, their own support has grown accordingly, to Gold Benefactor in the Corporate Honor Society at the \$100,000 to \$200,000 level. Stacie Bright, Unilever's Public Relations Manager, expresses



Anthony W. Johnson

their pride in being a sponsor at this level, and the company-wide value placed on this long-term partnership to shape the future of dermatology by developing the research and teaching careers of emerging leaders in medical and surgical dermatology.

Dr. Johnson personally finds that "the major advances in skin research and understanding over the past 10 years have come primarily from work in departments and divisions of dermatology around the United States. There are some phenomenal research groups led by outstanding

scientists and educators," he points out, "and the DF brings all of these people together."

Building on this, Unilever organizes an annual day-long seminar at their research laboratory in New Jersey at which young DF award recipients make a series of presentations. This event is attended by people throughout the company, "including our business colleagues and people from development as well as our young research scientists," Dr. Johnson explains. "It is inspirational for the younger scientists here at Unilever, as well as elsewhere, to realize the exciting discoveries coming out

of dermatologic research and teaching today. And the DF is a conduit for doing that," Dr. Johnson says.

Recognizing that the skin's profound complexity precludes Unilever's ability to meet all of its own research needs despite their top level internal program, Dr. Johnson observes that "our support of the DF's programs to build research and teaching careers throughout dermatology is our way of making a significant contribution to the specialty."



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