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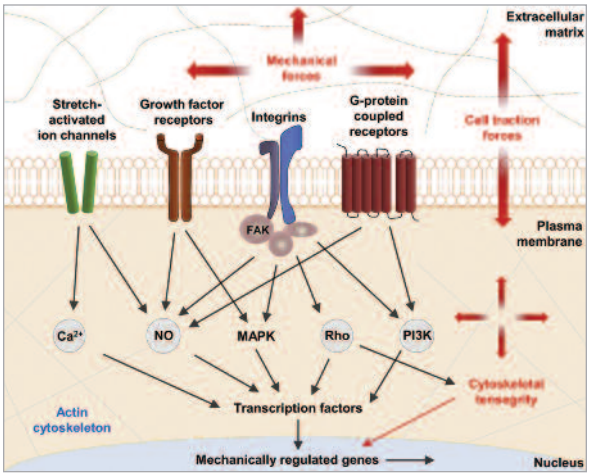
DERMATOLOGY FOCUS™

Changing the Wound Healing Landscape—Offloading Stress, Aiding Stem Cells

The clinical and economic burdens caused by wounds—those that heal with impairing scars and those that heal slowly or not at all—are substantial, global, and continue to grow (see box on page 8). Strides in delineating the myriad molecular factors involved in normal and pathological tissue repair have not translated to significant advances in patient care. Despite the use of multimodality regimens to treat hypertrophic scar formation—including corticosteroid injections, laser and radiation therapies, and scar revision surgeries—outcomes remain poor. And chronic wounds remain notoriously challenging.

Rising to the Challenge

Two plastic and reconstructive surgeon–scientists—Michael T. Longaker, MD, and Geoffrey Gurtner, MD, at Stanford University—are determined to transform this picture. They each have an abiding, passionate determination to understand and resolve the high-impact problems of scars and chronic wounds, and formed a high-energy collaboration roughly eight years ago to launch a coordinated program of basic and translational research dedicated to achieving this goal. (They are professors in the Department of Surgery/Plastic & Reconstructive Surgery and affiliated with the Institute of Stem Cell Biology and Regenerative Medicine at Stanford and with the Cancer Center. Longaker, co-director of the Institute and director of their program in Regenerative Medicine, is also a professor by courtesy in the departments of Bioengineering and of Materials Science and Engineering, and is director of Children's Surgical Research and of research in the Division of Plastic & Reconstructive Surgery. Gurtner, a microvascular surgeon and associate member of the Institute, is associate chair of Surgery and also a professor by courtesy in the Department of Materials Science and Engineering.)



Mechanotransduction pathways. At least 5 major overlapping cellular pathways link physical force with fibrogenic responses: integrin–matrix interactions, cytoskeletal strain responses, stretch ion channels, cell traction forces, and G protein-coupled receptors. (Reprinted with permission from VW Wong et al. *Sem Cell Dev Biol.* 2012;23:981–6.)

"Our goal is improvements that have a direct impact in patients," Gurtner says. "So our focus has been on the two extremes of normal wound healing. We search for the molecular signals that tell a healing wound to continue depositing collagen and create fibrosis, especially the fibrosis we see in burns. We are

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Focus on Research

The Skin Microbiome—Our Partner(s) in Health

Richard L. Gallo, MD, PhD
Dermatology Division Chief, Professor of Medicine and Pediatrics, University of California, San Diego


Richard L. Gallo, MD, PhD

Gallo has been deeply intrigued with the relationship between skin and microbes for many years, and the perspective that drew him in from the start became the overarching framework for his expanding body of research. "I became fascinated with our ability to survive in dangerous environments," he recalls. "There are literally billions of pathogens on the earth, and the skin is very frequently damaged and broken. Yet relatively few of the organisms in our environment have any potential to be skin pathogens, and the ability of a microbe to cause an infection is an infrequent event. So," he continues, "I've always been more interested in understanding why we are healthy than why we are sick. I believe that a better understanding of how we maintain our health will improve our ability to control and improve it."

Gallo first documented the presence of antimicrobial peptides in the skin. They had been found in the gut, and he was convinced they also formed part of the skin's innate immune system. He found the cathelicidins about 20 years ago, then provided

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also searching for the molecular mechanisms behind impaired wound healing. And throughout," he emphasizes, "our focus is on translational approaches that can make a difference for patients and enter the clinic in a reasonable time frame."

They have advanced most rapidly in understanding and controlling fibrosis. From the start, Longaker and Gurtner were convinced that mechanical stress plays a critical and underappreciated role in human wound healing and scar formation, and that this could hold significant translational potential. Their well-placed suspicion quickly began to pay off, enabling them to create the first small-animal models that mimic human wound healing and bring productive *in vivo* studies into the lab. Their molecular exploration—aiming at therapeutic targets—has produced surprises. This research has progressed side by side with their development of a simple stress-offloading device to minimize fibrosis in healing wounds. Recent human data are highly encouraging. Strategies to improve the survival and impact of stem cells for treating difficult wounds are in preclinical studies. This discussion will summarize Gurtner's and Longaker's progress.

They are extremely grateful to the interdisciplinary resources at Stanford that have enabled their progress, and to the hands-on involvement of Victor W. Wong, MD, currently a resident in plastic surgery, whose three-year fellowship in Gurtner's lab was critical to making many of these studies happen (and who, in the process, was incurably bitten by the research bug).

Fetal Wound Healing Points the Way

Longaker's early experience with fetal surgery after his internship was a profound turning point. It gave rise to his fascination with wound healing and his awareness of mechanical stress as a factor in scar formation, led to his meeting Gurtner, and to choosing a surgery residency. At the start of his four-year post-doc research fellowship at UCSF in 1987, Longaker was assigned to the groundbreaking Fetal Treatment Program that had recently been established there by pediatric surgeon Michael Harrison, MD. "We were surprised to discover that when these infants were born, there was very little evidence of the surgery," Longaker recalls. "And one day Dr. Harrison suggested that I look into the way fetuses heal."

Working on sheep, mice, and rabbits, Longaker learned that scarless healing lasts only until the third trimester, when the fetus's skin quickly assumes its barrier structure and function. Until then, it was a gelatinous tissue enabling the continuous absorption of needed molecules from amniotic fluid. Cutting it was like cutting into jello, with no residual strain. These different material properties of skin appeared to have very different effects on scarring. Longaker went on to train in surgery, plastic surgery, and craniofacial surgery, and ultimately settled at Stanford.

Gurtner's medical studies at UCSF coincided with Longaker's research fellowship, and he became one of Gurtner's most important mentors. Gurtner's ensuing interest in scars intensified significantly during his surgery residency and the time he spent at the Shriners Burn Hospital. After a residency in plastic surgery and further training in microvascular surgery, he eventually joined Longaker at Stanford.

Conceptualizing the First Step

The repair of wounds is one of the most complex biological processes that occur during human life. After an injury, multiple biological pathways immediately become activated and are synchronized to respond. Although some organisms maintain the ability—shown by the human fetus—to regenerate tissue throughout adult life, in humans the wound repair process commonly leads to a nonfunctioning mass of fibrotic tissue known as a scar. "Why can't we do a better job of repairing ourselves?" Longaker wanted to know. He was intrigued by the disparity with fetal wound healing.

Michael T. Longaker, MD, MBA

Geoffrey C. Gurtner, MD, FACS

Gurtner was puzzled by the human–mouse disparity. In humans, re-epithelialization and granulation tissue formation are the major wound closure mechanisms and the scar is significant. In the mouse, wound closure proceeds via contraction and results in only a fine scar. Thus this normally ideal lab animal was a poor model for studying human wounds *in vivo*. Pig skin is the most comparable to human skin, but pigs are costly and challenging to handle. Gurtner wanted to find a way to make mouse skin more "human" in the lab. One difference between mouse and human skin is the inherent amount of stress—mouse skin is loose, and human skin is not. Mouse skin has a thin layer of muscle—the panniculosus carnosus—which exists in humans only in the platysma of the neck. Gurtner hoped that finding a way to endow mouse skin with a human-like tension would create human-like scars in healing wounds.

Making Mouse Skin More Human: Adding Mechanical Stress

To test this, Gurtner came up with a way to prevent the mouse wound from contracting. He borrowed a basic tool—a distraction device—from reconstructive plastic surgery, placing it across a mouse wound to tighten the skin artificially (see illustration on page 7) and achieve the levels of mechanical stress normally experienced by human

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DF Honors the Specialty's Finest

The Dermatology Foundation pays yearly tribute to dermatologists whose exemplary capabilities and dedication have helped to make the specialty what it is today. Presentation of the 2013 awards will be a highlight of the DF Annual Meeting on Saturday, March 22 in Denver. The leaders and role models honored by their peers are:

Lifetime Career Educator Award—Stephen I. Katz, MD, PhD
Clark W. Finnerud Award—Peggy S. Crawford, MD
Practitioner of the Year—Z. Charles Fixler, MD

(Drs. Crawford and Fixler will be highlighted in the Spring issue.)

2013 Lifetime Career Educator Award:
Stephen I. Katz, MD, PhD

Recognizing an academic dermatologist who has a lifelong history of dedicated service as a mentor, role model and inspirational teacher to many generations of residents and fellows.

Immunodermatologist Dr. Stephen I. Katz, after joining the Dermatology Branch of the National Cancer Institute in 1974, quickly became and has remained an important teacher and mentor in the specialty.

He was chief of the Dermatology Branch from 1977 to 2001 and has been director of the NIAMS (National Institute of Arthritis and Musculoskeletal and Skin Diseases) since 1995. From the very start, the centerpiece of this highly accomplished scientist's career has been his immunodermatology lab and the fertile, hands-on mentoring environment he created there. In addition to Dr. Katz's fundamental contributions to the immunobiology of the skin over the years, his lab functions as a vital training center for students and fellows who have become outstanding physician-scientists and leaders in investigative dermatology across the U.S. and abroad. His fundamental contributions to the immunobiology of the skin included the characterization of Langerhans cells and dendritic cells, and epidermally expressed cytokines.

"It is very fitting that Steve Katz be recognized by the DF with the Lifetime Career Educator Award," says a former mentee and long-time dermatology department chair. "His curiosity, enthusiasm, and lifelong commitment to science and scholarly activities have had a profound and durable impact on his trainees and the specialty in this country and others. *His candle has lit many fires."*

Dr. Katz learned the importance of good mentors in his own early experiences. His first, and still most important, mentor was his older brother, Rockville, MD, dermatologist Dr. Robert Katz. "Bob helped open my eyes to the world, to medical school, to dermatol-

wounds. A distraction device is normally used to lengthen bone by slowly moving two segments apart in a way that enables new bone to fill this gap. And applying it to mouse wounds to augment mechanical stress during the one-week proliferative phase of wound healing produced "a dramatic increase in the amount of scar formation," Longaker says. The resulting scars—which were histopathologically and structurally identical to hypertrophic scars in humans—persisted for more than six months.

Mechanical Loading—Explaining its Impact

How does this mechanical load produce human-like hypertrophic scars in mouse skin? Normal human wound healing requires the orchestrated recruitment and expansion of different cells in healing wounds, then their rapid disappearance and a return to homeostasis during the transition from proliferation to the remodeling phase of wound healing. Apoptosis in the wound environment—specifically in fibroblasts—was believed to be important in restoring cell balance and enabling the newly deposited matrix to re-establish a homogeneous mechanical environment. Evidence pointed to the prosurvival marker Akt as the upstream regulator of proliferation in the wound environment through its direct inhibition of proapoptotic signals. In Gurtner's mice, the antiapoptotic milieu was prolonged when wounds were mechanically stressed and resulted in hyperproliferative scars. Even two weeks after wounding, cell counts were 20-fold the numbers in unloaded skin. Akt activation increased and cellular apoptosis plummeted. Gurtner and Longaker knew that Akt is regulated by FAK (*focal adhesion kinase*), and that FAK activation was thought to be mechanically induced. And this fit their mouse model like a glove.

To make sure that diminished fibroblast apoptosis was not simply a bystander in this stress-induced hypertrophic scar formation in mouse skin, Longaker and Gurtner repeated their study with genetically altered mice. They knocked out either a promoter (p53) or an inhibitor (*Bc*/ll) of apoptosis. With apoptosis eliminated in the wound, cellularity increased and scars were significantly more hypertrophic. When apoptosis was promoted, cellular density and scar hypertrophy diminished significantly.

Gurtner and Longaker had demonstrated that mechanical loading prevents needed apoptosis in the proliferative wound environment, and does this by activating the Akt pathway. And they concluded that "the presence of a narrow temporal window for

ogy, and to a research-oriented residency program. This last choice transformed me," Dr. Katz says. Among his valued mentors, Dr. Katz also notes Dr. Harvey Blank, the former Chair of Dermatology at the University of Miami where Dr. Katz trained, and British immunologist Dr. John Turk with whom he did a post-residency research fellowship. This experience ignited his passion for research, and he returned to the U.S. and joined the NIH in 1974 as a Senior Investigator in the Dermatology Branch of the National Cancer Institute.

Crucial to Dr. Katz's ability to accept this fellowship were the combined support of the GI Bill (he was in the Army after his residency) and a Research Fellowship awarded by the Dermatology Foundation in 1972, the sixth year of DF awards. "So if you call me a success," Dr. Katz wryly notes, "the Dermatology Foundation had something to do with it."

Ironically, when Dr. Katz joined the Dermatology Branch it was for "a three- to four-year adventure. The NIH seemed like a candy store where one could choose from seemingly myriad possible research pursuits with extraordinary potential for collaboration." He had no idea that he would be there 40 years later, as enthusiastic as ever, nor that the Dermatology Branch would rapidly become a magnet for residents and medical students who would—alongside their mentor—become movers and shakers in the specialty's progress.

Another of his early mentees—who went on to transform a dermatology department as chair, and then a medical school as its dean—points out that "Steve has inspired and educated a generation of academic leaders in dermatology in the U.S. and internationally. He is an outstanding role model and friend in all ways who has had an enormous influence on dermatology worldwide."

Dr. Katz has received an exceptional number of national and international honors and awards. He is particularly proud of his honorary memberships in both American and foreign dermatology organizations, and of the Presidential Executive Meritorious Rank Award from President Clinton. He is also thrilled with the Japanese government's bestowal of the Order of the Rising Sun in 2011 for his "great contribution to the education of Japanese dermatologists."

Dr. Katz acknowledges that the essence of his satisfaction with his career in dermatology has been "in teaching, and in developing a core of scientists who went on to develop their own independent leadership positions in the U.S. and around the world. That is tremendously satisfying and gives me great joy."

this suggests a critical period for therapeutic intervention in humans." They point out that traditional anti-inflammatory therapeutics for hypertrophic scarring are not only looking in the wrong direction, they are actively interfering with physiologically necessary inflammation and neovascularization. These treatments also begin too late, at a time when the process of hypertrophic scarring is already well established. Minimizing mechanical signaling or the downstream signal that delays apoptosis would be useful therapeutic strategies for eliminating hypertrophic scar formation without compromising the ultimate strength of the healing wound. Gurtner and Longaker turned their short-term focus to mechanical signaling—ie, mechanotransduction.

Mechanotransduction in the Skin

Mechanotransduction—the conversion of physical stimuli into biochemical responses—occurs via complex mechanoresponsive elements that often blur the distinction between physical and chemical signaling (see illustration on cover). "Human skin is a highly specialized mechanoresponsive interface separating our bodies from the external environment," Longaker and Gurtner point out. Every major cell type in the skin is mechanoresponsive. "And it is hard to imagine that life evolved in an environment characterized by gravity and physical forces without them becoming very important levers in development and disease," Gurtner observes. A critical role for mechanotransduction in determining how wounds heal holds compelling logic.

The German anatomist Karl Langer had published his carefully documented observations of the skin's intrinsic tensions back in 1861 when he established Langer's lines, which correspond to the orientation of native collagen fibers in the dermis. Although surgeons since then routinely strive to keep incisions parallel to Langer's lines to minimize tension across the wound, the basis of this connection between mechanical stress and scarring had remained intuitive. The underlying molecular mechanisms were still unclear.

Looking to the future, Gurtner and Longaker set their sights on identifying the molecular mechanisms in the context of human wounds and eventually manipulating them therapeutically. The Akt pathway has been their entry to this molecular exploration.

Simultaneously looking for more immediate clinical benefit, they have developed a tension offloading device for wound application during the critical week of proliferative activity to reduce pressure—and thus scarring. It is a counterpart, in a way, of the topical device they used on mouse skin to increase tension and thus induce significant scarring.

Annenberg Circle: New in 2013

The Dermatology Foundation is pleased to welcome its newest Annenberg Circle members. Their substantial commitment is an effective investment in the future, strengthening the specialty's scientific foundation for years to come. The Foundation's Board of Trustees is grateful to each new AC member who joined over 600 colleagues who have pledged $25,000 over five years to support the critical early research of tomorrow's leaders.

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Inflammation: The Big Surprise

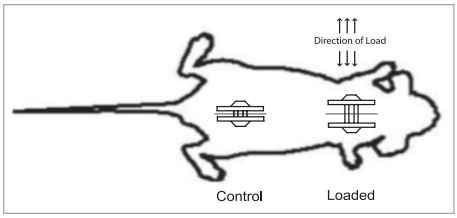
Gurtner and Longaker performed a focused microarray analysis, comparing the expression of mechanically regulated genes in mechanically loaded vs unloaded mouse wounds at 14 days after injury. They expected to see very simple, straightforward relationships—the mechanical forces directly causing fibroblasts to deposit more collagen and increasing scar formation. "But it wasn't that simple!" Gurtner says. The small changes in the expression of collagen genes were not nearly enough to explain the gross and histologic observations in their mouse studies. Even more unexpected was a gene subset highly enriched for T-cell–regulated pathways. When Longaker and Gurtner compared scar formation in T-cell–deficient and wild-type animals, scar formation was reduced almost 9-fold in mice lacking T cells. These mice also failed to recruit systemic inflammatory cells and fibroblast precursors. But mechanical stimulation—and pronounced scarring—in wild-type mice was highly associated with sustained Th2 (IL-4, IL-13) cytokine activity and signaling of the potent profibrotic chemokine MCP-1 (monocyte chemoattractant protein-1), with a known link to human fibrotic disorders.

"It turns out that inflammation is the primary way that mechanical forces increase fibrosis and scar formation," Gurtner says. "It is *not* through a direct effect on cells." A certain minimal level of temporary inflammation is necessary for good wound healing. It is the prolonged high level of inflammatory stimuli precipitated by mechanical forces that results in fibrosis.

Just Give Me the FAKs Please

Longaker and Gurtner began their molecular journey by examining Akt-mediated mechanotransduction in fibroblasts *in vitro* and *in vivo*. Exposing cultured fibroblasts to mechanical strain increased their motility, which was blocked once an Akt inhibitor was added to the mix. But although inhibiting Akt significantly restored apoptosis, hypertrophic scarring continued. Mechanically stressing fibroblasts turns on Akt signaling, which reduces apoptosis, but it was not the critical pathway for the hypertrophic scar itself.

So they turned their attention upstream to FAK, the multitasking protein upstream from Akt that has been highly implicated in mechanotransduction processes, that is important to fibroblast function (regulating survival, motility, inflammatory signaling, and collagen production), and also induces Akt activation. Gurtner and Longaker demonstrated clearly in mice that fibroblast-specific FAK mediates the stress-induced production of both collagen and the profibrotic chemokine MCP-1.



Biomechanical loading device replicates human skin stiffness. This novel device—engineered from expansion screws and titanium surgical Luhr plates—placed over 2-cm linear incision on the mouse dorsum replicates the greater tensile force of human skin. The control wound is left unloaded. (Reprinted with permission from S Aarabi et al. *FASEB J.* 2007;21:3250–61.)

Knocking out fibroblast-specific FAK in mice blunted inflammatory cell recruitment after injury and substantially reduced fibrosis. MCP-1 knockout mice also formed minimal scars. And adding a small-molecule FAK inhibitor to cultured human fibroblasts blocked FAK's impact on their fibrosis-related behavior.

"These findings strongly suggest that FAK is a critical mechanosensor during scar formation," Gurtner and Longaker commented. Because physical force regulates fibrosis through inflammatory FAK-stimulated pathways, molecular strategies targeting FAK should be able to uncouple mechanical force from pathologic scar formation.

Although FAK is a critical element, they realize that there may be more to this story. "The field of wound mechanobiology is young," Longaker and Gurtner point out, "and we anticipate that ongoing and future research will continue to elucidate the intimate relationship between mechanical and chemical signaling following injury."

In the Here and Now—A Device to Offload Wounds

Hints of potential benefit from reducing the mechanical tension on wounds were apparent in the very modest improvements achieved with silicone sheeting and compression bandages, and even with paper tape application. And botulinum toxin, used primarily in facial esthetic surgery, has been reported to reduce scar formation after surgical revision of facial scars—an effect attributed to reduced wound tension during early remodeling.

"But our concept of shielding the healing wound as it becomes a scar until it has reached its maximum strength—this was a novel concept," Longaker says. "And it was not a solution that came entirely from molecular research, or from mouse studies, or from clinical manipulation. It was the interface of materials and surgery," Longaker points out. And that concept required working with a material that would pull the surrounding tissue to offload the wound underneath it during the critical 8-week period.

The Right Stuff

First came the search for the right material. Gurtner subjected various material substrates—combinations of polymer backing materials, pressure-sensitive adhesives, and strain applicators—to biomechanical testing and observed their ability to modulate skin behavior. A polymer device was eventually developed and tested in red Duroc swine, which are considered the ideal large animal model for studying human-like wound healing—especially for hypertrophic scarring.

Full-thickness excisional wounds of graduated dimensions were created, then sutured closed under high tension. Increasing wound size required increasingly greater tension to close it, and the degree of scar formation correlated directly with the amount of tension required. These scars had all the features of human hypertrophic scarring.

The results of stress-shielded incisions were very different, with significantly reduced matrix deposition, epithelial thickening, and scar hypertrophy. The healed tissue actually recapitulated the histologic architecture of unwounded skin, including restoration of epithelial rete pegs and return of skin adnexae. Gurtner and Longaker's experimental device had effectively offloaded high tension wounds, blocked profibrotic pathways and excess scar formation, and allowed regeneration of normal tissue. And it was determined to be safe.

From Pigs to People

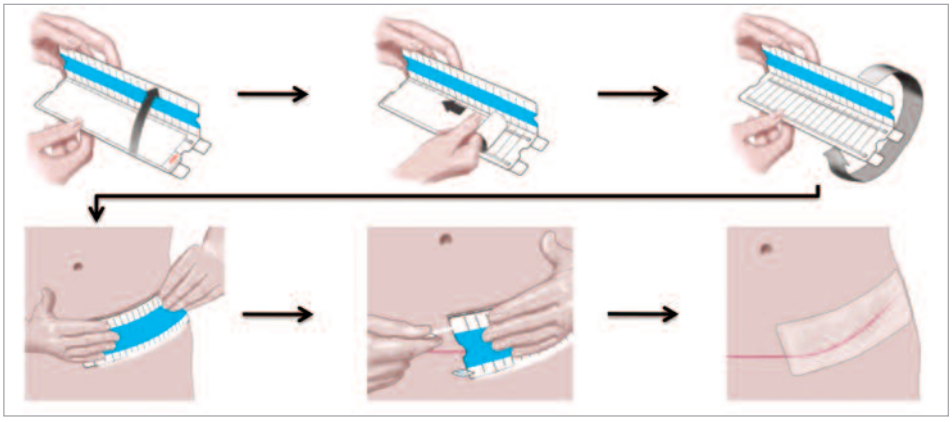
This prototype device has undergone extensively tested modifications, and is now a single-use book-type applicator (see illustration below). The polymer sheet is incorporated in the device, which exerts a consistent strain on the polymer when opened. This silicone elastomeric dressing (16 cm x 5 cm or 6 cm x 4 cm) adheres to the skin with a pressure-sensitive silicone adhesive. Human feedback confirms a device that is comfortable and easy to use, and clinical results have been gratifying.

A phase I trial in 9 patients undergoing abdominoplasty surgery confirmed safety and efficacy. Each incision served as its own control, with the device applied to one half and the other half given standard postoperative wound care. Based on professional photographs taken 8–12 months after surgery, evaluated using a visual analog scale (VAS), the device improved scar appearance by ≤63%, which was maintained for ≥12 months.

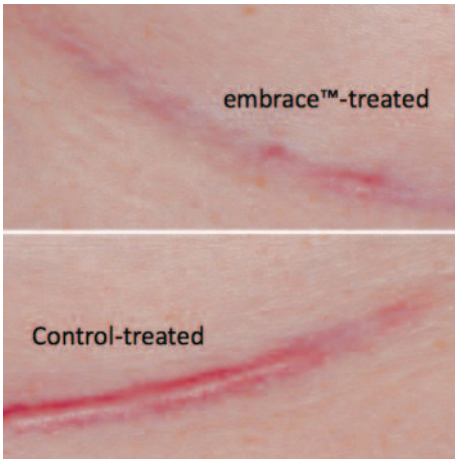
A just-published trial involved patients undergoing scar revision surgery on abdomen, breast, or neck. The 10 (of 12) patients completing the trial were 1 man and 9 women (including 4 African-Americans and 1 Asian) aged 29–51 years. Each scar was its own control. The device was applied between 1 and 4 days after revision, then patients returned weekly for a replacement device for ≤12 weeks. At 6 months, four independent surgeons carried out a blinded evaluation of each scar comparison. The mean VAS score for treated scars was significantly less than that for control scars (3.78 vs 5.58; $p<0.005$) (see photos on page 8). Patients were evenly split between *satisfied* and *very satisfied* with the comparative appearance of their treated scar segment. "The highly statistically significant difference between the device-treated and control-treated scars strongly supports the difference as real and not due to chance, despite the small study size," Longaker says.

Protecting Stem Cells

Stem cells are, ultimately, the most desirable solution to both overhealing and underhealing because they provide everything that is needed in one neat package. "They retain the ability to elaborate the full complexity of biological signaling, together with the environmental cues that are needed to regulate the differentiation and proliferation of these cells," Longaker explains. "And they



Application of the offloading device. The applicator containing the FDA-approved device is opened to strain the silicone elastomeric dressing, then the device is applied directly over the center of the closed incision 1–4 days postoperatively and adheres through a pressure-sensitive silicone adhesive. (Reprinted with permission from AF Lim et al. See *Suggested Readings* for citation.)



Device-treated vs control-treated scar-revision incision. Photographs taken 6 months after scar revision surgery show significantly improved appearance of device-treated portion of the scar (*top*). (Reprinted with permission from AF Lim et al. See *Suggested Readings* for citation.)

The Impact of Wounds

Scars—and the clinical problems they create—appear to reflect an evolutionary trade-off in the interests of survival. A wound that closed quickly prevented fatal blood loss, minimized the risk of infection, and enabled a swift return of mobility for escaping predators. But accelerated wound closure does not allow sufficient time for perfecting the architecture of regenerated tissue. Thus the new collagen is less well organized and the tissue is somewhat weaker, ie, the nonfunctioning mass of fibrotic tissue that we call a scar.

In healthy people, this repair process—an intricately choreographed, efficient interplay of biological pathways—becomes overly exuberant in roughly 15% of healing wounds. It is most often a hypertrophic scar, remaining within the boundaries of the original wound, and may partially regress. A keloid scar develops after the healing process and invades normal skin. These excessively fibrotic scars produce severe functional and esthetic defects. Many "normal" scars are also aesthetic problems. People with chronic diseases, most notably diabetes, involve the counterpart scenario—a dysfunctional repair process creating wounds that require months or years to heal, or may not heal at all. Chronic wounds pose a serious infection risk as well as impairment and cosmetic concerns.

Without significant progress in minimizing and repairing scars and in treating chronic wounds, the prospects are daunting. Worldwide, the annual number of surgical incisions—each one generating a scar—has reached 200 million. Scar revision is among the top procedures in the U.S. for improving abnormal structures (171,000 carried out in 2012). The worldwide prevalence of chronic wounds—pressure ulcers, venous/arterial ulcers, and diabetic wounds—is estimated at over 40 million. They affect roughly 2% of the general population in the U.S., translating to well over 6 million patients and a conservative estimate of $50 billion per year to care for them.

also serve as vehicles for growth factor and cytokine delivery to the wound bed."

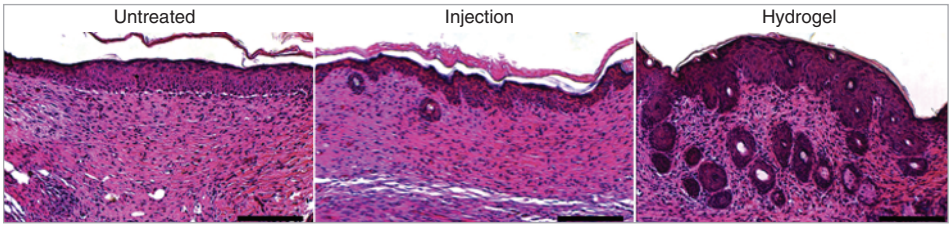
In theory the delivery of stem cells provides the simplest, most elegant solution, eliminating the need to identify and manipulate molecular targets with devices and/or drugs, modify for individual differences, etc. In practice, though, experimental attempts to use mesenchymally derived stem cells in wound healing are plagued by low engraftment. Typical long-term engraftment rates hover below 3%, delivered systemically or by local injection. Yet a hint of therapeutic efficacy continues to drive the search for a better way.

The direction Longaker and Gurtner took emerged when they took into account the harsh inflammatory environment—with high levels of reactive oxygen species—that confronts stem cells when they enter wounds. They believe that stem cells need to be delivered in a supportive microenvironment that protects them well enough and long enough to enable them to survive. And to do this, Longaker and Gurtner envision seeding stem cells onto a soft collagen hydrogel that mimics the architecture of fetal skin.

The material they chose to work with is pullulan—a natural, inexpensive, edible, bland, and tasteless glucan gum that is used in breath fresheners, some oral hygiene products and cosmetics, and skin and hair care products. This polysaccharide polymer, produced from starch by the fungus *Aureobasidium pullulans,* has good adhesive properties and is an effective, stable carrier for active skin care ingredients. Pullulan can thus be easily and rapidly seeded with stem cells. And most especially, glucans such as pullulan are very good at quenching free radicals.

In vitro and *in vivo* comparisons of their biomimetic hydrogel to standard local injection—the current gold standard for stem cell delivery—have been highly encouraging. Their hydrogel proved highly capable of free-radical protection, possibly by functioning as a sacrificial substrate. Wounds treated with seeded hydrogels showed long-term stem cell survival, significantly accelerated healing, and a return of skin appendages (see photos below).

While these studies continue, Longaker and Gurtner are also attempting to isolate stem cells from human adipose tissue. Liposuction waste creates a plentiful and easier to obtain inexpensive supply of stem cells compared with extracting mesenchymal cells from bone marrow. Because adipose tissue contains multiple stem cell subtypes, they are refining a technique for isolating and purifying the specific population desired. The factors needed in a wound that resists healing are very different from the requirements in a healthy healing environment. This ability to enrich for a specific stem cell subtype "opens the door for what Dr. Gurtner and I call *bedside tissue engineering,*" Longaker explains. "We envision harvesting a patient's fat tissue, enriching for the type of stem cells we want, seeding them on the hydrogel, and delivering them right back to that patient in the OR. This is truly personalized medicine," he adds.



MSC-seeded biomimetic hydrogel improves regenerative healing. Wounds treated with mesenchymal stem cells (MSC) in a protective pullulan–collagen hydrogel showed significantly improved skin architecture compared to injected MSC ($p<0.05$), including greater return of hair follicles and sebaceous glands. (Reprinted with permission from KC Rustad et al. See *Suggested Readings* for citation.)

Suggested Readings

Wong VW, Akaishi S, Longaker MT, Gurtner GC. "Pushing back: Wound mechanotransduction in repair and regeneration." *J Invest Dermatol.* 2011;131:2186–96.

Lim AF, Weintraub J, Kaplan EN, Januszyk M, et al. "The embrace device significantly decreases scarring following scar revision surgery in a randomized controlled trial." *Plast Reconstr Surg.* 2014;133:398–405.

Rustad KC, Wong VW, Sorkin M, Glotzbach JP, et al. "Enhancement of mesenchymal stem cell angiogenic capacity and stemness by a biomimetic hydrogen scaffold." *Biomaterials.* 2012;33:80–90. ■

(Continued from cover)

the first demonstration that mammals depend on them for defense against infection. And this is what started Gallo thinking about the skin microbiome—years before it appeared on the radar in 2007 as a tentative component of the Human Microbiome Project (see *Dermatology Focus*, 2012: Fall).

"Once we discovered that the skin could produce natural antibiotics," he explains, "I began to wonder—if our skin is producing endogenous antibiotics that are so effective at killing pathogens, then how and why do we permit so many bacteria to be normal residents on the skin surface?" The tools for exploring this question, however, would not exist for some time.

When bacteria were first easily culturable from the skin, back in the early part of the 19th century, the one-dimensional and enduring perception was that these skin residents posed a constant threat. Thus these microbial skin residents were considered an enemy across the border, and the border had to be defended. The first cracks in this conviction came in the 1980s and culminated in the "hygiene hypothesis," which suggested that being too clean could actually be detrimental. That launched a wave of unscientific work claiming benefits from probiotics and other products until finally, "in the last five years or so, technology has advanced to the point at which we can show for animal models—mechanistically and in a controlled way—that harboring many of these microbes clearly benefits the host," Gallo says. The ability to characterize the 16S rRNA (ribosomal RNA) gene—present in all bacteria and archaea but not in eukaryotes—has revolutionized the ability to identify and quantify microbes.

Getting Started—Conceptualizing an Agenda

Once these tools came into being, Gallo and his colleagues defined the questions they felt would enable a productive start to their research. "We asked ourselves: If the microbiome does indeed help us as people seem to think it does, let us make a list of likely ways it *could* help us, and then test them to see if our hypotheses are true."

They came up with two basic questions. Can microbes that reside on the skin produce their own antibiotics the way we do, ie, do the good bacteria fight the bad bacteria directly? Can microbes that reside on the skin influence the immune system? And the answer to both was *yes*.

Microbial Antimicrobials: *S. epidermidis* and Phenol-soluble Modulins

Phenol-soluble modulins (PSMs)—small secreted peptides produced by most staphylococci, especially *Staphylococcus aureus* and *S. epidermidis*—are a newly recognized family of toxins. Their multiple functions include killing competing microbes and acting as weapons in interbacterial warfare. But at the time Gallo and his team were just beginning their studies, little was known about them other than that the γ and δ forms expressed by *S. aureus* exerted membrane-disruptive effects. Despite relevant hints that these PSMs could be antimicrobial, their action as AMPs (antimicrobial peptides) had not been extensively studied.

This is where Gallo and his team jumped in. They turned to *S. epidermidis* because it is one of the most abundant microbes on healthy human skin, and sought to investigate whether the unique peptides PSMγ and PSMδ found in this microbe could be beneficial to the host, and thus serve as an additional AMP on normal skin surface. They hypothesized that peptides produced by a normal microbial resident of human skin might also act as an antimicrobial shield and contribute to normal defense at the epidermal interface.

Gallo et al. were able to show a strong architectural and functional resemblance between the PSMγ (also called δ-toxin) and PSMδ produced by *S. epidermidis* mammalian AMPs such as LL-37. They all have an α-helical character and strong lipid membrane interaction. These PSMs directly induced lipid vesicle leakage in pathogenic bacteria, and functionally partnered both with each other and with LL-37 to enhance antimicrobial action. The PSMγ and PSMδ expressed by *S. epidermidis* exhibited a unique and highly desirable function for selective removal of pathogenic organisms on the skin such as *S. aureus* and group A Streptococcus (GAS), boosting innate immune defense in an immediate and selective way. Equally important is that they brought no harm to the *S. epidermidis* community or other normal flora on the skin.

Gallo commented at the time that "this finding presents the possibility for a topical antimicrobial strategy to kill common pathogens while the microbiome is preserved, and would be likely to extend the duration of maximal immune defense and thus prevent repopulation by pathogens." He added that "this selective activity could become an important part of a normal microbial defense strategy against colonization and transmission of hospital-acquired bacterial pathogens, and could also be exploited for a role in future anti-infective therapeutics."

S. epidermidis—Homing in on δ-toxin

Gallo and his co-workers extended their observations that the antimicrobial PSMs contribute to host innate immunity through interacting with and amplifying the cutaneous antimicrobial response.

Their first step in this sequel study assessed δ-toxin in human skin. Immunohistochemistry showed it normally present in the epidermis and sparse in the dermis. A synthetic version of this toxin interacted with NETs (*neutrophil extracellular traps*, which are one of the ways in which neutrophils kill bacteria), induced further NET formation, and colocalized with cathelicidins. In antimicrobial assays against GAS, δ-toxin cooperated with three different human AMPs. In whole blood, adding δ-toxin had a bacteriostatic effect on GAS and increased the killing capability of NETs against GAS, and the toxin bound to four host AMPs. The final step moved to an *in vivo* setting. Fresh full-

Antibiotic-resistant Microbes—A Growing Menace

In the U.S., *S. aureus* is responsible for an estimated 12 million outpatient visits and 292,000 hospitalizations a year. Of the latter, 126,000—43%—are due to MRSA (methicillin-resistant *S. aureus*). Community-acquired MRSA (CA-MRSA) is reported as the most common cause of purulent skin and soft tissue infections. Hospital-acquired bacterial infections cause >90,000 deaths annually, according to the CDC. All of these infections are particularly challenging to treat because these bacteria have become resistant to many commonly used antibiotics.

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thickness mouse wounds were pretreated with either δ-toxin or PBS (phosphate-buffered saline) control before GAS was added to mimic an infected wound, then the wounds and surrounding fascia were harvested. GAS survival was significantly decreased only in mouse wounds pretreated with δ-toxin, with a parallel decrease of Mip-2, a proinflammatory cytokine that can serve as a marker for infection. This indicated an increase in bacterial clearance and general reduction of an inflammatory infection.

This was the first demonstration that AMPs from the resident *S. epidermidis* interact physically with the host AMPs, and the functional reduction of GAS survival in a mouse model of wound infection suggests a beneficial and mutual innate immune role for this common constituent of the skin microbiome.

Microbial Antimicrobials and Fermentation—Probiotics for the Skin

Fermentation is, most simply, metabolic processing by bacteria or yeast that anaerobically transforms a sugar to an acid, gas, and/or alcohol. Beer is a product of fermentation. So is yogurt, which contains live probiotic strains and has been used for centuries to restore and maintain the digestive microbial ecosystem. This is an excellent example of *bacterial interference*—also called *bacteriotherapy*—the use of commensal bacteria to prevent host colonization by pathogens. Observations in plants and humans suggest this as a promising and broader modality for preventing and treating infections. There are microorganisms both on and within fruits, for example, that metabolize sugars during ripening and produce short-chain fatty acids (SCFAs)—the principal end products of bacterial fermentation—which turn out to inhibit activity of bacterial competitors in the fruit. This would use a dynamic that has been in play for untold millenia, and thus minimize both the selective pressure for antibiotic resistance and the troublesome side effect profiles that are encountered with antibiotic drugs.

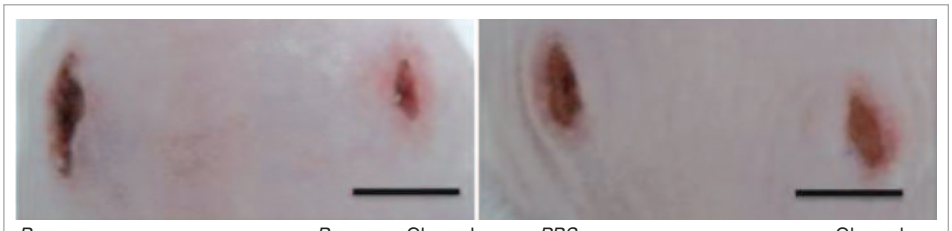
This takes on particular interest for the skin, given that one of the most prevalent skin commensals—*Propionibacterium acnes*—is a master of fermentation. It is a facultative anaerobe, as it can live in an environment with or without oxygen, and earned its name because of its pronounced ability to ferment carbohydrates to propionic acid. And propionic acid is an SCFA with known antimicrobial activity.

Microbial Antimicrobials and Fermentation: *S. aureus* Control

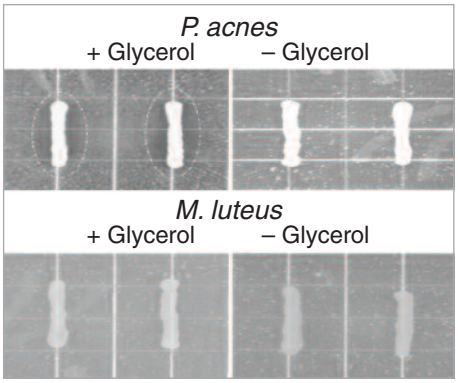
Gallo and his collaborator Eric (Chun-Ming) Huang, PhD, a colleague in the Division of Dermatology at UCSD with a special interest and expertise in studying *P. acnes*, have begun exploring the possibility that this common skin-residing microbe may provide a gateway to a radically different approach to prevention and treatment of skin infections—*pro*biotics rather than *anti*-biotics. They have begun with *S. aureus*. An effective approach that avoids this microbe's facility for developing drug resistance would be an important achievement (see box on page 9).

Although *P. acnes* resides on the skin surface, this facultative anaerobe has been co-isolated with *S. aureus* from shoulder sepsis and prosthetic hip infections in adults. Gallo and Huang hypothesized that *P. acnes* enters the dermis when a deep wound is created by pathogen infection, that the anaerobic wound microenvironment triggers it to begin fermenting such naturally available sugars as glycerol and glucose, and then the propionic acid helps to prevent *S. aureus*, in this case, from entering the bloodstream and becoming a systemic infection.

Huang and Gallo's first steps in putting this to the test carefully documented *in vitro*, and then with wounds in mouse skin, that *P. acnes* does indeed ferment glycerol, that this produces SCFAs and that propionic acid is one of them, that this fermentation inhibits *S. aureus* (see photos on page 11), that wounds pretreated with *P. acnes* and glycerol heal significantly faster (see photos below) and show up to 80% reduction in *S. aureus* colonization. They worked with USA300, a major source of CA-MRSA infections and particularly antibiotic-resistant. And Huang and Gallo were also able to show that propionic acid acts on USA300 by lowering its intracellular pH—known to be a lethal antibacterial mechanism of SCFAs. They plan to develop anti-*S. aureus* skin probiotics containing live *P. acnes* with glycerol and/or SCFAs, apply them to skin wounds over several days, and determine what does or does not happen. Gallo and Huang will also assess biopsies of deep anaerobic (cellulitis) and superficial (impetigo) *S. aureus*-infected wounds to assess the relative abundance of *P. acnes*, *S. aureus*, and SCFAs.



***P. acnes* fermentation in USA300-infected skin wounds improved healing.** USA300-infected wounds pretreated for 3 days with *P. acnes* and glycerol healed more quickly than pretreatment with each component alone, or with PBS alone. Bar = 0.5 cm. (From M Shu et al. See *Suggested Readings* for citation.)

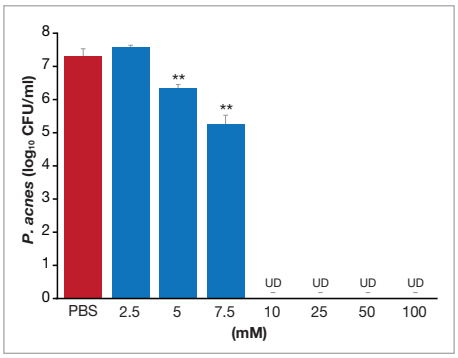


***P. acnes* interferes with USA300 growth in the presence of glycerol.** When USA300 (a major source of CA-MRSA infections) is grown in agar plates under anaerobic conditions at 30°C, it is inhibited in the zone surrounding the combined presence of *P. acnes* and glycerol (*top left*). There is no inhibitory effect from *P. acnes* without glycerol (*top right*), or from *Micrococcus luteus* with (*bottom left*) or without (*bottom right*) glycerol. (From M Shu et al. See *Suggested Readings* for citation.)

Fermentation: A New Direction Toward *P. acnes* Control

With increasing evidence that skin commensal organisms actively maintain homeostasis within their microbial community, Gallo and Huang wanted to see if they could harness this capability to address the frequent overgrowth of the common commensal *P. acnes*, strongly associated with acne vulgaris. Acne lesions, especially a closed comedone or deep-seated abscess in an open comedone, provide the anaerobic microenvironment that is particularly hospitable to *P. acnes* growth. *S. epidermidis* and other skin microflora coexist in these lesions. Huang and Gallo suspected their function is *P. acnes* control, with the anaerobic microenvironment triggering fermentation behavior. They focused on *S. epidermidis*, the other predominant skin commensal. First they confirmed that it can ferment glycerol and that this combination creates inhibition zones within an overgrown colony of *P. acnes*. Succinic acid, one of the SCFAs produced when *S. epidermidis* ferments glycerol, was the active product (see graph at right). It inhibited the growth of *P. acnes in vitro* and then markedly suppressed *P. acnes*-induced inflammation in mice by intralesional injection and by topical application.

This first demonstration that one member of the skin microbiome can rein in the overgrowth of another—and do so by fermenting a local sugar molecule—"opens up a new area of study for understanding how the skin microbiome functions to promote human health," Huang and Gallo observe. "In addition, these observations can potentially be applied to develop probiotics—not only against acne vulgaris—but to treat other skin diseases as well."



Fermentation product of *S. epidermidis* interferes with *P. acnes* growth. *P. acnes* was effectively suppressed by succinic acid (a SCFA produced when *S. epidermidis* ferments glycerol) at concentrations of ≥5–7.5 mM in PBS, and completely killed at a concentration ≥10 mM. Incubation with PBS alone is the control. *UD = undetectable.* ***p*<0.01. (Reprinted with permission from Y Wang et al. *Appl Microbiol Biotechnol.* 2014;98:411–24.)

Skin Commensals Influence the Immune Response: Part 1

With research on the gut microbiome already underway for some time, "we knew that it influences some aspects of the overall immune system," Gallo says, "either through the availability of specific nutrients or through a direct modification of immune function." The skin—independent of that but also part of the larger system—has its own microbiome and local set of immunocytes to interact with. Nothing was known about it, and Gallo knew it needed to be explored.

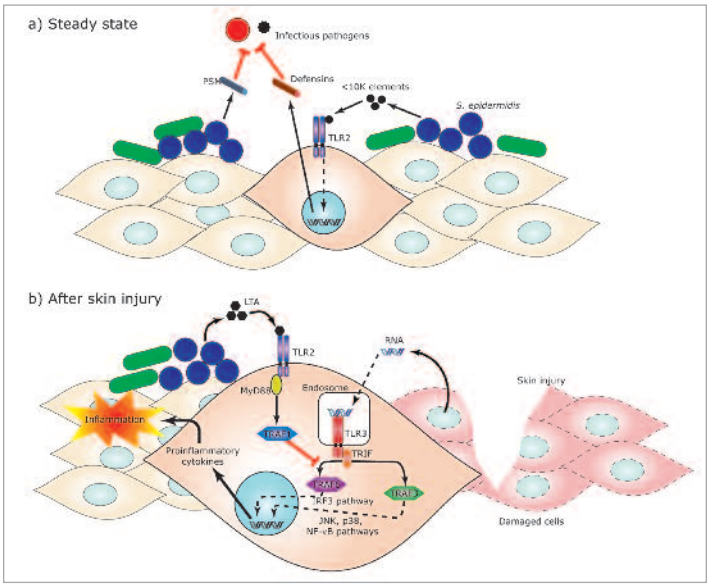
Inflammation on the skin—usually due to infection or injury—is undesirable when it is uncontrolled. During wound repair it may cause dysfunction, and when this occurs after minor trauma it will exacerbate several human skin diseases, eg, psoriasis. Good im-

mune defense requires a balance—sufficient inflammation for a rapid response to injury while avoiding excessive inflammation. Maintaining this balance becomes very intricate at epithelial surfaces that are in contact with the external environment, with frequent trauma and exposure to the products of the microbiome.

"We hypothesized right from the start that the skin microbiome might be influencing immunocytes' function," Gallo recalls. But there was little information for shaping the specifics of their hypothesis. Although the cutaneous immune response to infection had been well defined, the operative mechanisms in response to skin injury—in part involving the Toll-like receptors (TLRs)—were poorly understood. For their immune system focus, Gallo and his group chose the TLRs on keratinocytes. In addition to their known involvement in gut inflammatory processes, the epidermis uses TLR3 for recognition of injury to self. For their microbiome focus, they chose staphylococcal species because they are the most frequently cultured normal inhabitant of healthy human skin "and had been hypothesized to serve a role in human health," Gallo says.

Their results were the first step in mapping the terrain of skin microbiome–immune system interaction. Working in small progressive steps *in vitro* and *in vivo*, including use of various neutralizing antibodies and knockout mouse models, Gallo et al. identified a previously unknown mechanism by which a product of staphylococci—staphylococcal lipoteichoic acid (LTA), a known molecular signal for recognition of staphylococci—damps down skin inflammation that has been triggered by injury-activated TLR3 cells. "When the keratinocyte recognizes this product of *S. epidermidis*, it downregulates some inflammatory events," Gallo notes (see illustration at right). This process begins with wounding and the abundant numbers of damaged cells in the wound, which includes necrotic keratinocytes. The RNA they release activates TLR3 on healthy keratinocytes, which in turn induce the keratinocytes to express the highly inflammatory cytokines TNF-α and IL-6. Adding *S. epidermidis* to the equation activates TLR2, triggering a complex series of events that attenuates TLR3 activity and thus diminishes release of TNF-α and IL-6. The molecule initiating this anti-inflammatory counterbalance is the LTA that *S. epidermidis* produces, which is the ligand/activator for TLR2.

Gallo's study revealed for the first time that TLR3 is critical in the induction of inflammation after skin injury, and that an anti-inflammatory balance is accomplished by specific staphylococcal LTAs and mediated by TLR2 on keratinocytes. Looking ahead, Gallo suspects that using products of bacterial commensals at the site of injury might be a beneficial therapeutic strategy for managing wound healing that is complicated by excessive inflammation, or possibly to control other inflammatory disorders. "The trick," he says, "will be to evoke an adequate reduction in the detrimental aspects of inflammation without increasing the risk of wound infection."



***S. epidermidis*-produced factors modulate the skin immune system.** *Steady state (a):* its antimicrobial peptides act against infectious microbes, and a small molecule increases defensin expression through TLR2 signaling. *After skin injury (b):* uncontrolled inflammation can delay wound healing. Staphyloccal LTA works through TLR2 to inhibit excess inflammatory cytokine release. *IRF (IFN-regulatory factor); JNK (C-Jun N-terminal kinase); LTA (lipoteichoic acid); MyD88 (myeloid differentiation primary response gene 88); TRAF (tumor necrosis factor receptor-assisted factor); TRIF (TIR-domain-containing adapter-inducing IFN-β).* (Reprinted with permission from RL Gallo et al. See *Suggested Readings* for citation.)

Skin Commensals Influence the Immune Response: Part 2

Gallo et al.'s next discovery was that some resident bacteria not only produce their own antibiotics, but can express molecules that upregulate our endogenous antibiotics—our defensins in this case. Exposing undifferentiated human keratinocytes to sterile, nontoxic *S. epidermidis*-conditioned culture medium enhanced mRNA expression of two human β-defensins—hBD2 and hBD3—and increased the capacity of cell lysates to inhibit the growth of GAS and *S. aureus*. Similar preparations from other bacteria had no effect. Administering this *S. epidermidis* medium to mice decreased their susceptibility to infection by GAS. TLR2 was found to be a central mediator in this process.

These findings add further support to the potential use of *S. epidermidis* to activate TLR2 signaling. In addition to controlling injury-induced inflammation, it simultaneously induces antimicrobial peptide expression to improve the skin's defense against infection. "Understanding this relationship provides a new direction for the study of the skin immune response," Gallo observes. "And it further highlights concerns related to indiscriminant use of both systemic and topical antimicrobial products."

The Skin Microbiome—Down in the Dermis

The skin appears to regulate which microbes populate its surface, and we know that some of these microbes affect the development of the immune system in the skin as well as the physical characteristics of the epidermal barrier. "It is becoming increasingly accepted that a dynamic interaction takes place between these surface bacteria and the host," Gallo points out, "but it has been unclear how this can take place if the microbial community resides only on top of a physical barrier devoid of live cells, while the many cell types well equipped to detect and respond to these microbes are only below the stratum corneum."

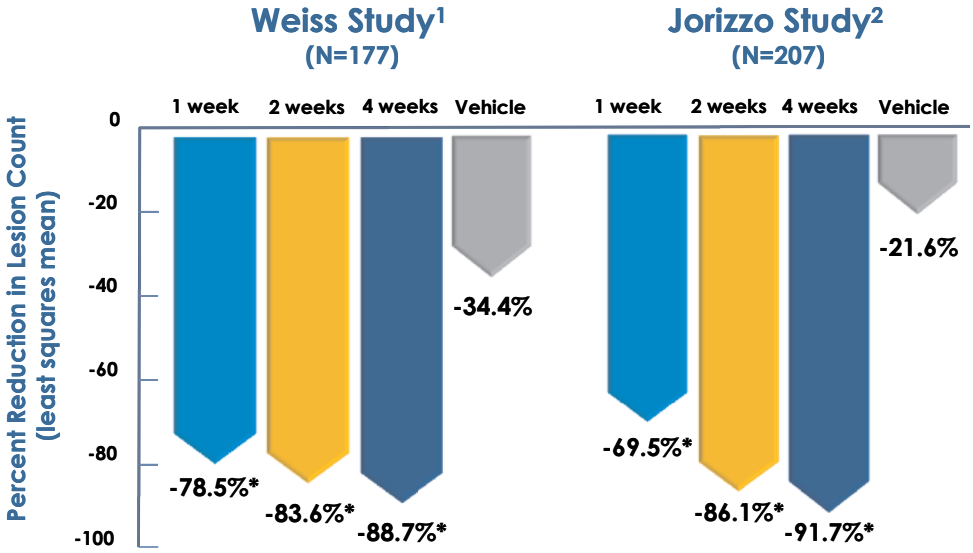
So he and his co-workers began to question the long-held assumption that the skin maintains a complete barrier to bacterial entry. Instead, they hypothesized that some microbes or their products do penetrate below the stratum corneum, perhaps even below the epidermal basement membrane.

The newest technologies for identifying bacteria enabled Gallo and colleagues to put their hypothesis to the test. They were able to assess the DNA from any microbes found below the stratum corneum in the skin they sampled, which means that all of the microbes present would be recognized

(Continued on page 15)

once-a-day Carac® fluorouracil cream 0.5%

Significant AK lesion reduction at 1, 2, and 4 weeks



*P<.001 vs vehicle.

Results from two Phase 3 vehicle-controlled, randomized, double-blind, multicenter studies of patients (N=384) with actinic keratoses. Secondary endpoint of percent reduction (least squares mean) in AK lesions at 1, 2 and 4 weeks compared active to vehicle.

Significant mean reduction in the number of AK lesions with 1 week of treatment compared to vehicle[1,2]

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Carac is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

Important Safety Information

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Rarely, unexpected, systemic toxicity (e.g., stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase "DPD" activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills.

Carac should be discontinued if severe abdominal pain, bloody diarrhea, vomiting, fever, or chills develop when using the product.

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In clinical trials, the most common drug-related adverse events were application site reactions (94.6%), which included: erythema, dryness, burning, erosion, pain, and edema, and eye irritation (5.4%).

Patients using Carac should avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction maybe increased.

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. Weiss J, Menter A, Hevia O, et al. Effective treatment of actinic keratosis with 0.5% fluorouracil cream for 1, 2, or 4 weeks. *Cutis.* 2002;70(suppl 2):2229. **2.** Jorizzo J, Stewart D, Bucko A, et al. Randomized trial evaluating a new 0.5% fluorouracil formulation demonstrates efficacy after 1-, 2-, or 4-week treatment in patients with actinic keratosis. *Cutis.* 2002;70:335-339.

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Carac® Cream, 0.5%

Rx Only

(fluorouracil cream)

BRIEF SUMMARY

IMPORTANT NOTE: This information is a BRIEF SUMMARY of the complete prescribing information provided with the product and therefore should not be used as the basis for prescribing the product. This summary has been prepared by deleting information from the complete prescribing information such as certain text, tables, and references. The physician should be thoroughly familiar with the complete prescribing information before prescribing the product.

FOR TOPICAL DERMATOLOGICAL USE ONLY (NOT FOR OPHTHALMIC, ORAL, OR INTRAVAGINAL USE)

INDICATIONS AND USAGE

Carac is indicated for the topical treatment of multiple actinic or solar keratoses of the face and anterior scalp.

CONTRAINDICATIONS

Fluorouracil may cause fetal harm when administered to a pregnant woman. Fluorouracil is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

No adequate and well-controlled studies have been conducted in pregnant women with either topical or parenteral forms of fluorouracil. One birth defect (ventricular septal defect) and cases of miscarriage have been reported when fluorouracil was applied to mucous membrane areas. Multiple birth defects have been reported in the fetus of a patient treated with intravenous fluorouracil.

Animal reproduction studies have not been conducted with Carac. Fluorouracil, the active ingredient, has been shown to be teratogenic in mice, rats, and hamsters when administered parenterally at doses greater than or equal to 10, 15 and 33 mg/kg/day, respectively, [4X, 11X and 20X, respectively, the Maximum Recommended Human Dose (MRHD) based on body surface area (BSA)]. Fluorouracil was administered during the period of organogenesis for each species. Embryolethal effects occurred in monkeys at parenteral doses greater than 40 mg/kg/day (65X the MRHD based on BSA) administered during the period of organogenesis.

Carac should not be used in patients with dihydropyrimidine dehydrogenase (DPD) enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme dihydropyrimidine dehydrogenase (DPD). DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities.

Carac is contraindicated in patients with known hypersensitivity to any of its components.

WARNINGS

The potential for a delayed hypersensitivity reaction to fluorouracil exists. Patch testing to prove hypersensitivity may be inconclusive.

Patients should discontinue therapy with Carac if symptoms of DPD enzyme deficiency develop.

Rarely, unexpected, systemic toxicity (e.g. stomatitis, diarrhea, neutropenia, and neurotoxicity) associated with parenteral administration of fluorouracil has been attributed to deficiency of dihydropyrimidine dehydrogenase "DPD" activity. One case of life threatening systemic toxicity has been reported with the topical use of 5% fluorouracil in a patient with a complete absence of DPD enzyme activity. Symptoms included severe abdominal pain, bloody diarrhea, vomiting, fever, and chills. Physical examination revealed stomatitis, erythematous skin rash, neutropenia, thrombocytopenia, inflammation of the esophagus, stomach, and small bowel. Although this case was observed with 5% fluorouracil cream, it is unknown whether patients with profound DPD enzyme deficiency would develop systemic toxicity with lower concentrations of topically applied fluorouracil.

Applications to mucous membranes should be avoided due to the possibility of local inflammation and ulceration.

PRECAUTIONS

General

There is a possibility of increased absorption through ulcerated or inflamed skin.

Information for the Patient

Patients using Carac should receive the following information and instructions:

1. This medication is to be used as directed.
2. This medication should not be used for any disorder other than that for which it was prescribed.
3. It is for external use only.
4. Avoid contact with the eyes, eyelids, nostrils, and mouth.
5. Cleanse affected area and wait 10 minutes before applying Carac.
6. Wash hands immediately after applying Carac.
7. Avoid prolonged exposure to sunlight or other forms of ultraviolet irradiation during treatment, as the intensity of the reaction may be increased.
8. Most patients using Carac get skin reactions where the medicine is used. These reactions include redness, dryness, burning, pain, erosion (loss of the upper layer of skin), and swelling. Irritation at the application site may persist for two or more weeks after therapy is discontinued. Treated areas may be unsightly during and after therapy.
9. If you develop abdominal pain, bloody diarrhea, vomiting, fever, or chills while on Carac therapy, stop the medication and contact your physician and/or pharmacist.
10. Report any side effects to the physician and/or pharmacist.

Laboratory Tests

To rule out the presence of a frank neoplasm, a biopsy may be considered for those areas failing to respond to treatment or recurring after treatment.

Carcinogenesis, Mutagenesis and Impairment of Fertility

Adequate long-term studies in animals to evaluate carcinogenic potential have not been conducted with fluorouracil. Studies with the active ingredient of Carac, fluorouracil, have shown positive effects in *in vitro* and *in vivo* tests for mutagenicity and on impairment of fertility in *in vivo* animal studies. *Fluorouracil* produced morphological transformation of cells in *in vitro* cell transformation assays. Morphological transformation was also produced in an *in vitro* assay by a metabolite of fluorouracil, and the transformed cells produced malignant tumors when injected into immunosuppressed syngeneic mice.

Fluorouracil has been shown to exert mutagenic activity in yeast cells, *Bacillus subtilis,* and *Drosophila* assays. In addition, fluorouracil has produced chromosome damage at concentrations of 1.0 and 2.0 mcg/mL in an *in vitro* hamster fibroblast assay, was positive in a microwell mouse lymphoma assay, and was positive in *in vivo* micronucleus assays in rats and mice following intraperitoneal administration. Some patients receiving cumulative doses of 0.24 to 1.0 g of fluorouracil parenterally have shown an increase in numerical and structural chromosome aberrations in peripheral blood lymphocytes.

Fluorouracil has been shown to impair fertility after parenteral administration in rats. Fluorouracil administered at intraperitoneal doses of 125 and 250 mg/kg has been shown to induce chromosomal aberrations and changes in chromosome organization of spermatogonia in rats. In mice, single-dose intravenous and intraperitoneal injections of fluorouracil have been reported to kill differentiated spermatogonia and spermatocytes at a dose of 500 mg/kg and produce abnormalities in spermatids at 50 mg/kg.

Pediatric Use

Actinic keratosis is not a condition seen within the pediatric population, except in association with rare genetic diseases. Carac should not be used in children. The safety and effectiveness of Carac have not been established in patients less than 18 years old.

Geriatric Use

No significant differences in safety and efficacy measures were demonstrated in patients age 65 and older compared to all other patients.

Pregnancy

Teratogenic Effects: Pregnancy Category X

See CONTRAINDICATIONS

Nursing Women

It is not known whether fluorouracil is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from fluorouracil, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

The following were adverse events considered to be drug-related and occurring with a frequency of ≥1% with Carac: application site reaction (94.6%), and eye irritation (5.4%). The signs and symptoms of facial irritation (application site reaction) are presented below.

Summary of Facial Irritation Signs and Symptoms - Pooled Phase 3 Studies

Clinical Sign or Symptom	Active One Week N=85	Active Two Week N=87	Active Four Week N=85	ALL Active Treatments N=257	Vehicle Treatments N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
Erythema	76 (89.4)	82 (94.3)	82 (96.5)	240 (93.4)	76 (59.8)
Dryness	59 (69.4)	76 (87.4)	79 (92.9)	214 (83.3)	60 (47.2)
Burning	51 (60.0)	70 (80.5)	71 (83.5)	192 (74.7)	28 (22.0)
Erosion	21 (24.7)	38 (43.7)	54 (63.5)	113 (44.0)	17 (13.4)
Pain	26 (30.6)	34 (39.1)	52 (61.2)	112 (43.6)	7 (5.5)
Edema	12 (14.1)	28 (32.2)	51 (60.0)	91 (35.4)	6 (4.7)

During clinical trials, irritation generally began on day 4 and persisted for the remainder of treatment. Severity of facial irritation at the last treatment visit was slightly below baseline for the vehicle group, mild to moderate for the 1 week active treatment group, and moderate for the 2 and 4 week active treatment groups. Mean severity declined rapidly for each active group after completion of treatment and was below baseline for each group at the week 2 post-treatment follow-up visit.

Thirty-one patients (12% of those treated with Carac in the Phase 3 clinical studies) discontinued study treatment early due to facial irritation. Except for three patients, discontinuation of treatment occurred on or after day 11 of treatment.

Eye irritation adverse events, described as mild to moderate in intensity, were characterized as burning, watering, sensitivity, stinging and itching. These adverse events occurred across all treatment arms in one of the two Phase 3 studies.

Summary of All Adverse Events Reported in ≥ 1% of Patients in the Combined Active Treatment and Vehicle Groups - Pooled Phase 3 Studies

	9721 and 9722 Combined				
Adverse Event	Active One Week N=85	Active Two Week N=87	Active Four Week N=85	ALL Active Treatments N=257	Vehicle Treatments N=127
	n (%)	n (%)	n (%)	n (%)	n (%)
BODY AS A WHOLE	7 (8.2)	6 (6.9)	12 (14.1)	25 (9.7)	15 (11.8)
Headache	3 (3.5)	2 (2.3)	3 (3.5)	8 (3.1)	3 (2.4)
Common Cold	4 (4.7)	0	2 (2.4)	6 (2.3)	3 (2.4)
Allergy	0	2 (2.3)	1 (1.2)	3 (1.2)	2 (1.6)
Infection Upper Respiratory	0	0	0	0	2 (1.6)
MUSCULOSKELETAL	1 (1.2)	1 (1.1)	1 (1.2)	3 (1.2)	5 (3.9)
Muscle Soreness	0	0	0	0	2 (1.6)
RESPIRATORY	5 (5.9)	0	1 (1.2)	6 (2.3)	6 (4.7)
Sinusitis	4 (4.7)	0	0	4 (1.6)	2 (1.6)
SKIN & APPENDAGES	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	85 (66.9)
Application Site Reaction	78 (91.8)	83 (95.4)	82 (96.5)	243 (94.6)	83 (65.4)
Irritation Skin	1 (1.2)	0	2 (2.4)	3 (1.2)	0
SPECIAL SENSES	6 (7.1)	4 (4.6)	6 (7.1)	16 (6.2)	6 (4.7)
Eye Irritation	5 (5.9)	3 (3.4)	6 (7.1)	14 (5.4)	3 (2.4)

Adverse Experiences Reported by Body System

In the Phase 3 studies, no serious adverse event was considered related to study drug. A total of five patients, three in the active treatment groups and two in the vehicle group, experienced at least one serious adverse event. Three patients died as a result of adverse event(s) considered unrelated to study drug (stomach cancer, myocardial infarction and cardiac failure).

Post-treatment clinical laboratory tests other than pregnancy tests were not performed during the Phase 3 clinical studies. Clinical laboratory tests were performed during conduct of a Phase 2 study of 104 patients and 21 patients in a Phase 1 study. No abnormal serum chemistry, hematology, or urinalysis results in these studies were considered clinically significant.

DOSAGE AND ADMINISTRATION

Carac cream should be applied once a day to the skin where actinic keratosis lesions appear, using enough to cover the entire area with a thin film. Carac cream should not be applied near the eyes, nostrils or mouth. Carac cream should be applied ten minutes after thoroughly washing, rinsing, and drying the entire area. Carac cream may be applied using the fingertips. Immediately after application, the hands should be thoroughly washed. Carac should be applied up to 4 weeks as tolerated. Continued treatment up to 4 weeks results in greater lesion reduction. Local irritation is not markedly increased by extending treatment from 2 to 4 weeks, and is generally resolved within 2 weeks of cessation of treatment.

OVERDOSE

Ordinarily, topical overdosage will not cause acute problems. If Carac is accidentally ingested, induce emesis and gastric lavage. Administer symptomatic and supportive care as needed. If contact is made with the eye, flush with copious amounts of water.

HOW SUPPLIED

Cream - 30 gram tube NDC 0187-5200-30

Store at Controlled Room Temperature 20° to 25° C (68° to 77° F) [see USP].

Prescribing Information as of November 2012

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CRC 13-006 6/30/2014

instead of only those that could be grown in culture. The genetic material they extracted was the 16S rRNA found in supposedly sterile areas. 16S rRNA comes only from bacteria, and distinctive sequences enable identification of the different groups. Gallo's team was also able to benefit from such recent developments as *pyrosequencing*, which enabled them to work with extremely minute quantities of DNA, expanding and then sequencing them very rapidly. Gallo and his lab team used multiple independent detection techniques rather than just one or two, to strengthen their observations.

Donor facial and palm skin was thoroughly sterilized before biopsy, and then careful sterilization procedures at every step ensured that results could not possibly reflect even the slightest contamination. Multiple samples were taken from each of five donors and the locations, quantities, and identities of bacteria found below the stratum corneum were determined.

"Our procedures detected the existence of DNA encoding for bacterial 16S rRNA genes at various depths in subcutaneous tissues," Gallo says. Notably, they were detected beneath the maximal depth of follicles in facial skin (3.0 mm) and below the eccrine glands that extended 1.5 mm below the surface in palm skin. Microbial DNA was found in all skin compartments—epidermis, follicle, dermis, and subcutaneous adipose tissue—and consisted primarily of members of the phylum Proteobacteria with a small presence of such phyla as Actinobacteria, Firmicutes, and Bacteroidetes (see profile below). So diverse elements of the skin microbiome are present in subcutaneous regions of normal human skin—including the deep dermal stroma and superficial adipose tissue, always regarded as inherently sterile in the absence of skin injury—and they are directly positioned to influence host behavior. This surprising finding helps explain the interactions that Gallo had found between factors produced by commensal microbes and cells below the physical barrier of the skin's stratum corneum.

Many questions remain to be explored, but these groundbreaking initial results are already "expanding our understanding of the complexity of symbiotic interactions between our microbial community and human health, and provide the basis for an entirely new approach to understanding skin disease," Gallo points out.

Rethinking the Host

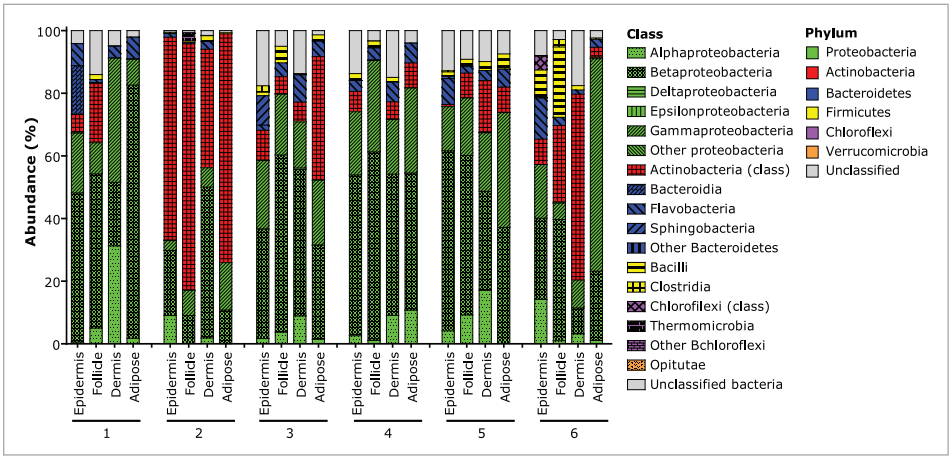
Studies have begun illuminating the intimate relationships shared between the human host and resident microbes. Host immunologic factors and behaviors shape the composition of these communities, while microbes present on the skin greatly impact the functions of human immunity. Gallo believes that the skin immune system should be reconsidered a collective mixture of elements from the host and elements from the microbes that are acting in a mutualistic relationship.

"I feel very strongly that in the next few years, this will be redefining what we mean when we talk about *self*," he muses. "We will no longer see ourselves as a single organism existing separately and independently, but as a team that relies on different cell types to carry out functions. Some of those cell types may be bacteria. And they may also be viruses or fungi, which currently we know much less about."

Rethinking Antibiotic Therapy

Discovering now how interactive the normal skin microbiome and host are in maintaining skin health, it is apparent that the use of topical and systemic antibiotic treatments has to be rethought. Conventional antibiotics nonspecifically kill a variety of bacteria, which risks impairing the microbiome's homeostasis. The indiscriminate use of antibiotics has a long-term impact on the microbiome—and thus on health—that can take years to recover from. Even the short-term appropriate application of antibiotics risks creating dysbiosis, and any short-term improvement comes at the cost of a long-term risk of subsequent colonization by

(Continued on page 17)



The subcutaneous microbiome is diverse. The relative abundance of bacterial classes associated with each skin compartment is shown for each of the 6 skin biopsies. (Reprinted from T. Nakatsuji et al. *Nat Commun.* 2013;4: doi:10.1038/ncomms2441.)

"Thank You" to the *Leaders Society* Volunteers

The DF Board of Trustees expresses heartfelt gratitude to each and every campaign volunteer. These dermatologists volunteered substantial time and effort to participate in the 2013 *Leaders Society* campaign to benefit the specialty's future. Their valuable efforts have a direct impact on making early career support available to tomorrow's leaders in dermatology, enabling their contributions to advance patient care in all areas of the specialty.

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Mark P. Seraly, MD— New Annenberg Circle *Sustaining* Member:

"I am a strong believer in giving back."

"I love dermatology and I want it to be viable and accessible in the future," Dr. Seraly says. "It is more important than ever to show we are truly the experts in skin, hair, and nail health. That means continuing to push forward and develop new therapies—and that requires investment. That is why I support the DF at the highest level I can."

Dr. Seraly is a long-term supporter of the Foundation's work to provide research funding to new investigators beginning their careers. He became a *Leaders Society* member in 1998, just four years after completing his residency and joining the faculty at the University of Pittsburgh. Dr. Seraly shares that he was inspired to join by three former mentors—Drs. Brian Jegasothy, Michael Tharp, and Arthur Rhodes—whose teaching, guidance, and leadership he credits for making him the dermatologist he is today.

Mark P. Seraly, MD

In 2000, Dr. Seraly established his private practice in McMurray, PA, integrating medical and procedural dermatology, and enjoys having residents and medical students rotating through his office. More recently, he notes, he developed a telemedicine platform that directly connects the dermatologist and patient, providing a new access point for care. His support for the DF is based on his experience that "it takes innovation, capital, and hard work" to advance patient care. In 2010 Dr. Seraly increased his participation in the DF to the *Annenberg Circle* and, this past year, made the decision to become an AC *Sustaining* member by increasing his $25,000 AC contribution with a pledge to give $5,000 annually for the next six years.

"I am a strong believer in giving back. Dermatologists are a small group, representing about 1% of all physicians nationally," Dr. Seraly points out, "and we all have to make a special effort to maintain our credibility and to merit patient confidence as the physician experts of the skin—and this requires exploration and innovation."

harmful bacteria. The treatment for such infectious skin diseases as acne vulgaris and atopic dermatitis are in this category.

Gallo believes that restoration and maintenance of the skin's normal microflora—ie, probiotic therapy—is needed for reversing dysbiosis created by antibiotic treatment, and also for treating many skin diseases themselves. Almost any skin disease is potentially a target for probiotic therapy, including those with genetic causes. An obvious one is atopic dermatitis, where there is a well-known dysbiosis. The genetic abnormality may act by altering the host's natural environment and thereby generating an altered microbiome, which then participates in causing the actual disease. "Once we understand this well enough, we can design a way to change the environment so that it will maintain normal microbes," Gallo states." And that in a nutshell is the hope for a probiotic." When antimicrobial therapy is warranted for treating skin infections, Gallo is hopeful about the development of endogenous peptides. These AMPs exert precisely targeted activity only against skin pathogens, and do not affect commensals.

Currently, Gallo and his team are pursuing several directions. They are discovering new endogenous antimicrobials. They are progressing in their understanding of how an abnormal microbiome could cause skin diseases. They are working to understand new functions they have uncovered for the microbiome. And they are gearing up to do autologous bacterial transplantation on the skin with therapeutic intent, replacing an abnormal bacterial composition with a balanced microbiome developed from it. They plan to expand the subject's own skin-resident bacteria in a beneficial direction, then return this normalized commensal community to the subject.

"This is a very rapidly evolving field," Gallo notes, "and it's very exciting to be part of it."

Suggested Readings

Gallo RL, Nakatsuji T. "Microbial symbiosis with the innate immune defense system of the skin." *J Invest Dermatol.* 2011;131:1974–80.

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Lai Y, Di Nardo A, Nakatsuji T, Leichtle A, et al. "Commensal bacteria regulate TLR3-dependent inflammation following skin injury." *Nat Med.* 2009;15:1377–82.

Shu M, Wang Y, Yu J, Kuo S, et al. "Fermentation of *Propionibacterium acnes*, a commensal bacterium in the human skin microbiome, as skin probiotics against methicillin-resistant *Staphylococcus aureus*." *PLOS ONE.* 2013;8:e55380. ■

Gallo was awarded a DF Research Grant in 1997 that led to the discovery of antimicrobial peptides on mammalian skin.

203 New *Leaders Society* Members Support the Future

The Foundation is pleased to welcome its newest Leaders Society members. Their annual contribution of $1,500 demonstrates their confidence in the DF's ability to effectively support the development of tomorrow's leaders. The DF Board of Trustees sincerely appreciates the support demonstrated by all its *Leaders Society* members who help make the work of the Foundation possible.

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Richard J. Havens

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

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Giving Back—Profile of a DF Volunteer

Seemal R. Desai, MD— "Support Our Specialty's Future"

Seemal R. Desai, MD

"I became a *Leaders Society* member and volunteer because the Dermatology Foundation effectively supports research of the skin and skin disease—and this is how we will improve our ability to care for our patients," says Dr. Seemal R. Desai, a dermatologist in Plano, Texas.

Dr. Desai made his commitment in 2013, within five years of completing his resident training at the University of Alabama, earning him the *Young Leader* membership designation. A few months later, he joined the national *Leaders Society* campaign and was extremely successful in furthering participation in his state.

Dr. Desai's private practice centers on complex medical dermatology. His primary clinical interest is in the diagnosis and management of challenging pigmentary disorders, including vitiligo, melasma, postinflammatory hyper- and hypopigmentation, and the exacerbated problems in skin of color. He is also a clinical assistant professor at UT Southwestern Medical Center. Dr. Desai's choice of dermatology and clinical focus reflect the formative influence of a family member's experience with vitiligo at an early age. He is keenly aware of the need for significant progress in understanding and treating these diseases—and clearly states that research is the only way to get there.

An energetic DF member and volunteer, Desai is also active in the Dallas Dermatological Society, the AAD, and the AMA. "I love practicing and seeing patients, and I'm grateful every day that I became a dermatologist," he says. "But I also want to be involved."

He emphasizes that dermatologists represent a small group in medicine and there is a "continual need to demonstrate that we are the experts. So we should all stand up and support the specialty through community service and research. That's why I support the Dermatology Foundation."

The DF is exceptionally grateful to its many volunteers who give generously of their time and inspiration to keep dermatology at the forefront of medicine.

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