

# Highlights from the 68th Annual Meeting of the Society of Investigative Dermatology

Heather Yarnall Schultz<sup>1</sup>

*Journal of Investigative Dermatology* (2007) **127**, 2073–2076. doi:10.1038/sj.jid.5701016

During the 68th Annual Meeting of the Society of Investigative Dermatology,\* more than 900 papers were presented via oral and poster presentations. The abstracts for the presentations were published in the *Journal of Investigative Dermatology* Supplement 1, in April 2007. One of the most remarkable features of this society meeting is the melding of both basic science and clinical research from a vast range of topics, including immunology, genetics, epidemiology, structure and developmental biology, infectious diseases, photobiology, and cancer biology. The following review of the meeting highlights a mere sampling of notable presentations.

## IMMUNOLOGY

### Antimicrobial peptides

Because the skin is the first defense against infectious and environmental agents, advances in understanding the immune response are critical for tackling common skin disorders such as atopic dermatitis (AD). Robert Modlin (University of California, Los Angeles, CA) presented findings regarding the dependence of human vitamin D<sub>3</sub>-induced antimicrobial activity against *Mycobacterium tuberculosis* on the antimicrobial peptide cathelicidin. Although his group has previously published findings indicating that the activation of monocyte human Toll-like receptors (TLRs) induced cathelicidin expression and subsequent vitamin D receptor-dependent antimicrobial activity against this pathogen, Dr. Modlin furthered this remarkable story by describing the role of interleukin (IL)-15 in the process. IL-15 is sufficient to induce the vitamin D synthesis path-

way. This cytokine is an important mediator of TLR activation of the vitamin D receptor and cathelicidin and, as such, may be a great target for *M. tuberculosis* treatment. In addition, Jürgen Schaubert (University of California, Davis, CA) presented evidence that injury enhances TLR2 function and antimicrobial peptide expression through a vitamin D-dependent mechanism. Again, the pathway involved IL-15.

Tissa Hata (University of California, Davis, CA) explored the function of cathelicidin in AD and psoriasis patients. Although AD patients are particularly susceptible to infection and inflammation, expression of antimicrobial peptides is low in lesional skin from AD patients. In lesions from psoriasis patients, the peptide is expressed at high levels. Dr. Hata's group probed the systemic expression of cathelicidin. They found no correlation among cathelicidin expression levels in skin, saliva, and blood, thereby supporting clinical observations of increased infection only in the skin of AD patients. These results support the manipulation of antimicrobial peptides in the skin for the treatment of AD.

### Barrier dysfunction

Additional insight into AD, a disease at the interface of allergy and immunology, was provided by Donald Leung (National Jewish Medical and Research Center, Denver, CO) in the Julius Stone Lectureship. Dr. Leung described the complex interplay among genetics, immunology, and environmental factors that affect barrier dysfunction. Furthermore, he described the challenge presented by this common disease (17% of children are affected) to the potential

of a mass smallpox vaccination campaign. In normal patients, IL-37 selectively kills vaccinia; however, in AD skin, dysregulated Th2 cytokines suppress the expression of IL-37 and promote vaccinia growth. Thus, treatment with anti-IL-4 or anti-IL-13 may stimulate the expression of IL-37 and permit effective immune response against vaccinia virus in AD skin.

### Toll-like receptors and cancer

Damia Tormo (University of Bonn, Germany) described the therapeutic efficacy of antigen-specific vaccination and TLR stimulation against transplanted and autochthonous melanoma in mice. Stimulation of both the adaptive immune response via adenovirus transduction of antigen and the innate immune response via TLR ligand injection resulted in tumor rejection in a mouse model for invasive melanomas following neonatal carcinogen treatment. Although the treatment delayed the growth of autochthonous primary melanomas in the mice, the tumors did not regress. These studies offer promising insights into the orchestration of an immune response for tumor immunity.

The protective effect of TLR4 against carcinogen-induced cutaneous tumorigenesis in mice was described by Nabiha Yusuf (University of Alabama at Birmingham, AL). TLR4-deficient mice were treated with a carcinogenic polycyclic aromatic hydrocarbon (DMBA). The mice developed contact hypersensitivity associated with carcinogenesis and exhibited increased IL-17, a proinflammatory cytokine often associated with allergies, as well as decreased interferon- $\gamma$ , a Th1 proinflammatory cytokine.

<sup>1</sup>Freelance medical writer, Durham, North Carolina, USA

Correspondence: Heather Yarnall Schultz, 920B Martin Luther King Jr Blvd. Ste. 216 Chapel Hill, NC 27514. E-mail: hyschultz@yahoo.com

DMBA served as both an initiator and a promoter for tumorigenesis in these mice by increasing tumor number, incidence, and size. Interestingly, DBMA treatment resulted in lower levels of IL-12, a cytokine that mediates tumor regression by inhibiting angiogenesis and promoting Th1 cytokine release and T-cell cytotoxicity. These results suggest that efforts to divert the cell-mediated immune response from IL-17 to interferon- $\gamma$  may ultimately prove beneficial in the prevention of skin tumors.

### Interleukin-1 $\beta$ in the inflammasome

Lloyd Miller (University of California, Los Angeles, CA) discussed the role of IL-1 $\beta$  and the inflammasome in IL-1 receptor–dependent neutrophil recruitment during *Staphylococcus aureus* skin infection. Methicillin-resistant *S. aureus* is the most common cause of emergency room visits for skin infections and thus a critical health problem. This group previously reported that the IL-1 receptor was required to recruit neutrophils for clearance of this infection. The response was further examined in IL-1 $\alpha$ -, IL-1 $\beta$ -, and IL-1 $\alpha/1\beta$ -deficient mice. IL-1 $\beta$  was found to be responsible because deficient mice displayed larger lesions, defects in bacterial clearance, and impairment of neutrophil abscess. Thus, generation of IL-1 $\beta$  is a critical component for promotion of neutrophil clearance in *S. aureus* infection.

### Interleukin-23 and psoriasis

In the inaugural Eugene Farber Lecture to honor the late renowned Stanford University professor of dermatology, Brian Nickoloff (Loyola University of Chicago Medical Center, IL) commemorated his colleague's dedication to the combination of clinical and basic research on psoriasis with a description of his work on cytokine networking in psoriasis. The notion of a vast cytokine network and the nonrandom trafficking of immunocytes in psoriasis, a chronic inflammatory disease, was initially proposed by Nickoloff more than a decade ago; however, recent efforts in multiple labs have supported this idea. Cytokines comprise the language that orchestrates the cross-talk between immunocytes and keratinocytes. In psoriasis, both IL-23 and Th17 responses play a

role. Interestingly, healing of psoriatic plaques does not result in scar formation. Thus, the mechanism for termination of inflammation mediated by IL-23 and Th17 remains an area for future scrutiny. In addition, Frank Nestle (King's College London) described genetic and functional evidence for a role of the IL-23 pathway in the pathogenesis of psoriasis. Whole genome–association scans covering 300,000 markers were employed to identify genetic markers of psoriasis. A specific variation in IL-23 receptor (R381Q) was found to be associated with psoriasis. To validate these data, IL-23 blockade was shown to prevent psoriasis in a humanized mouse skin graft model. As a result of the identification of the same IL-23 receptor variant in irritable bowel syndrome, another inflammatory disease, this signaling pathway is clearly earmarked as a therapeutic target.

## GENETHERAPY

### Therapy for epidermolysis bullosa

Gene therapy is a promising avenue for correction of defective genes implicated in a variety of skin diseases. Genetic defects in collagen VII are responsible for recessive dystrophic epidermolysis bullosa (RDEB). J. Burnett (University of Southern California, Los Angeles, CA) described the use of a minigene encoding the intact noncollagenous domains NC1 and NC2 and one half of the central collagenous domain of type VII collagen. The protein made from this minigene is very stable and retains the full function of collagen VII. In RDEB mice, injection of the short protein or lentiviral therapy with the minigene resulted in correction of blister formation, abrogation of basement membrane separation, and restoration of the anchoring fibrils. The protein therapy was found to be very promising and safe because treatment actually increased the survival of the mice. In addition, William Buitrago (Baylor College of Medicine, Houston, TX) presented his work on gene therapy to correct mutations in keratin 14 that disrupt filament integrity and cause Dowling-Meara epidermolysis bullosa simplex (EBS), an autosomal dominant severe blistering disease. A mouse model that mimics EBS with expression of mutant keratin 14 in a small area of the skin

via treatment with a topical inducer was developed. In these mice, mutant epidermal stem cells suffered a growth disadvantage compared with epidermal stem cells in which the keratin 14 mutation had been corrected via lentiviral gene therapy. Moreover, the transduced cells were able to correct the EBS phenotype *in vivo*.

### Systemic gene therapy via the skin

Jean-Philippe Therrien (National Cancer Institute, National Institutes of Health, Bethesda, MD) described a novel approach for the systemic delivery of genes by genetically modified human skin equivalents. A bicistronic vector containing the therapeutic antihypertensive atrial natriuretic peptide gene linked to a multidrug-resistance selectable marker was used. Transduced human skin equivalents were grafted to immunocompromised mice and subjected to topical selection with colchicine to select keratinocytes that express the marker. The atrial natriuretic peptide showed remarkable long-term expression, validating the use of this system for long-term systemic delivery of therapeutic molecules via the skin.

## UV DAMAGE, DNA REPAIR, AND GENOMIC INSTABILITY

### Genotyping of melanomas

In the canonical DNA damage model, ultraviolet (UV) light damages DNA, and these lesions activate programs of cell cycle arrest, DNA repair, or apoptosis. If one of the checkpoints is bypassed due to error or mutation in a key factor, the cell may proliferate abnormally. Thus, cancer research has focused on understanding the implications of DNA damage. In a state-of-the-art plenary lecture, Boris Bastian (University of California, San Francisco, CA) described somatic alterations in melanomas based on sites of sun exposure. Classifications of melanomas from chronically sun-damaged, non-chronically sun-damaged, acral, or mucosal sites revealed differences in genotype, with mutations in oncogenic BRAF occurring in non-chronically sun-damaged sites and mutations in the oncogene Kit occurring at the other sites. In addition, melanomas at sites protected from chronic sun exposure were more likely to exhibit genomic

instability. These interesting findings suggest that clinical melanomas result from different molecular mechanisms.

#### NF- $\kappa$ B induction in SCC

David Bickers (Columbia University, New York, NY), who specializes in studying the role of carcinogens such as UV radiation in skin cancer, demonstrated that the blockade of nuclear factor kappa B (NF- $\kappa$ B), which typically drives proliferation and resistance to apoptosis, inhibits UVB-induced photocarcinogenesis in murine skin. Squamous-cell carcinomas (SCCs) and basal-cell carcinomas (BCCs) are induced by UVB concomitant with inactivation of p53. Activation of NF- $\kappa$ B is a common feature of SCC in human skin. When Bickers' group blocked NF- $\kappa$ B with a specific inhibitor (pyrrolidine dithiocarbamate), NF- $\kappa$ B did not translocate to the nucleus. Following UVB exposure, the mice exhibited delayed tumor formation, decreased incidence of tumors, and decreased tumor size. Diminished expression of NF- $\kappa$ B downstream targets and proliferation markers and increased expression of apoptosis executor caspase-3 indicated that UVB-induced NF- $\kappa$ B is critical for the pathogenesis of SCCs.

#### Telomeres in genetic stability

Telomeres have also been a hot topic for research lately because faulty replication of these terminal chromosomal sequences may result in senescence, elicit a DNA damage response, or cause genomic instability. Advances in understanding the pathways involved in maintaining this fidelity have aided our understanding of DNA repair, aging, and tumorigenesis. Thomas R nger (Boston University, MA) presented work on the role of the Fanconi anemia/BRCA1 pathway in telomere loop opening and closing. Although the Fanconi anemia pathway is activated in response to DNA damage, the pathway is interestingly activated in the absence of damage in late S phase. The addition of oligonucleotides with homology to telomere ends (T-oligos) also induces this activation and elicits formation of foci containing the DNA damage/repair factors, FANCD2, BRCA1,  $\gamma$ -H2AX, and RAD51. These complexes may play a role in telomere D loop opening to complete replication.

Mark Eller (Boston University, MA) described a mechanism for protection of genomic integrity in the face of telomere replication. Telomeres employ a loop structure to cap chromosome ends in order to protect the ends from recognition by DNA damage sensors. Because T-oligos mimic free telomeric ends, these sequences induce a DNA damage response and generate foci that include typical DNA damage responders. WRN is the helicase mutated in Werner's syndrome, a disease characterized by premature aging and predisposition to cancer. This helicase, which preferentially binds to DNA hairpins, G quadruplexes, and telomere loop structures, is required for the foci formation. In fact, knockdown of WRN activity reduces T-oligo activity. Taken together, the evidence implicates WRN in recognition of uncapped telomere ends, signaling of replicative stress, initiation of proliferation arrest, and recruitment of DNA repair complexes to telomeres.

#### Telomere sequences affect angiogenesis

In addition to activating a DNA damage response, T-oligos have been implicated in inhibition of tumor angiogenesis and melanoma growth. D. Levine (Boston University, MA) demonstrated that T-oligo treatment of mice bearing human melanoma cell xenografts significantly decreased the potent angiogenic factor VEGF and the expression of the VEGF receptor. In addition, T-oligo treatment also increased the transcription factor E2F1, which is known to promote apoptosis and negatively regulate proangiogenic factors. The treatment also decreased endothelial tube formation, invasion by melanoma cells, and tumor volume. Thus, T-oligos negatively regulate tumor angiogenesis and cooperate with proapoptotic factors to reduce melanoma growth *in vivo*. Although the exact mechanism of this effect is not completely clear, T-oligos may provide a novel therapy for melanomas.

### CELL SIGNALING AND DEVELOPMENT

#### Wnt signaling

Complex regulatory cell signaling drives cell proliferation, differentiation, and function. In a state-of-the-art plenary lecture, Sarah Millar (University of Pennsylvania, Philadelphia, PA) pre-

sented evidence for Wnt signaling in the development of skin appendages including hair follicles, teeth, and mammary glands. Not only is this pathway required for the initiation of postnatal development of hair follicles and mammary glands, but this signaling is also critical for embryonic tooth and tongue taste-papillae development. Moreover, in the William Montagna Lecture, George Cotsarelis (University of Pennsylvania, Philadelphia, PA) presented new findings regarding hair-follicle stem cells and hair regeneration. Despite contrary findings published more than 50 years ago, the central dogma in cutaneous biology asserts that hair follicles form only during development and thus adult hair-follicle loss is permanent. However, hair-follicle regeneration was recently observed following re-epithelialization after wounding in mice. Although cells from the hair bulge contributed to the re-epithelialization, genetic labeling experiments revealed that the new hair follicles derive exclusively from the interfollicular epidermal cells. In addition, this hair follicle neogenesis was found to be dependent on the Wnt signaling pathway. These exciting results herald a novel regenerative potential for mammals and offer promise for clinical management of alopecia and tissue engineering.

In addition, E. Moore (University of Washington, Seattle, WA) revealed that Wnt/ $\beta$ -catenin signaling plays a very different role in melanoma than in colon cancer. Murine and human melanoma cell lines overexpressing Wnt3a or -5a showed that activation of this pathway negatively regulates tumor growth and decreases proliferation. These findings are in stark contrast with the deleterious effects observed with  $\beta$ -catenin activation in colon cancer. In the future, the Wnt/ $\beta$ -catenin pathway may be targeted for melanoma treatment or serve as prognostic markers.

#### Hedgehog signaling in BCC

In a state-of-the-art plenary lecture, Andrzej Dlugosz (University of Michigan, Ann Arbor, MI) discussed hedgehog signaling, a pathway critical for both development and regulation of hair follicles. Activation of the hedgehog pathway is important and perhaps

sufficient for development of BCC. In a "gene switch" mouse model, hedgehog signaling deactivation resulted in robust regression of BCCs. Thus, hedgehog signaling antagonists, including cyclopamide, may serve as a treatment target for both BCC and medulloblastomas.

#### Lipid biosynthesis in epidermal barrier function

Yoshikazu Uchida (University of California, San Francisco, CA) presented work honored by the Nature Publishing Group as the most outstanding abstract in the basic sciences. Ceramides are critical components for epidermal permeability barrier function. Mutations in ELOVL4, a fatty acid elongation enzyme, are associated with macular degeneration. Because this gene is also expressed in the skin, the group examined mice homozygous for these mutations and found that they exhibit compromised epidermal permeability barrier, deficient epidermal lamellar body content, significant decreases in very-long-chain fatty acids, and a lack of epidermal  $\omega$ -O-acylceramide and its immediate precursor. The results demonstrate that ELOVL4 is required for generation of very long fatty acids that are critical not only for epidermal barrier formation but also for mammalian survival.

#### DIAGNOSTICS AND CLINICAL RESEARCH

##### Prenatal diagnostics

In a state-of-the-art plenary lecture, John McGrath (King's College London) described the state of prenatal diagnostic testing for inherited skin disorders. Fetal skin biopsy, chorionic villi sampling, and preimplantation genetic diagnosis have been employed to diagnose EB at earlier and earlier stages of development. Noninvasive embryo testing is on the horizon as researchers learn more about collecting and analyzing short fragments of fetal DNA and RNA present in maternal blood as early as 18 days after embryo transfer.

##### Noninvasive diagnostics for melanoma

William Wachsmann conveyed a pioneering effort to differentiate melanoma from dysplastic nevi in suspicious pigmented

skin lesions using a novel noninvasive tape stripping method. This work was also honored by the Nature Publishing Group for innovative research in the clinical research sector. Although the gold standard of melanoma diagnosis is histopathology of biopsied tissue, these researchers employed their Epidermal Genetic Information Retrieval system (EGIR) to analyze stratum corneum RNA from pigmented lesions. This simple noninvasive method provided RNA for amplification and microarray analysis. In trials, approximately 88 genes were discriminators between melanoma and dysplastic nevi. This study demonstrated that EGIR-harvested RNA can be used to differentiate melanoma from dysplastic nevi and that the stratum corneum gene profile is, in fact, altered in melanoma.

##### Novel wound-closure method

Irene Kochevar (Harvard University, Boston, MA) presented evidence supporting photochemical tissue bonding as an alternative to sutures or glue for closure of skin excisions and incisions. Photochemical tissue bonding involves application of Rose Bengal dye to the wound site and subsequent exposure to green light. The resultant watertight seal stems from chemical linkage of surface collagen molecules. Although Rose Bengal is known to generate phototoxic singlet oxygen molecules, this method produced no thermal damage, no cell toxicity, and no increased inflammation. Together these attributes suggest that this method may be useful for wound closure and may even lead to reduced scarring.

##### UVA photoadaptation

Another method of phototherapy is employed to treat scleroderma, a condition involving increased collagen deposition in the dermis. This therapy is remarkably successful in some patients, but others do not respond. Frank Wang (University of Michigan, Ann Arbor, MI) demonstrated that photoadaptation diminishes the *in vivo* antifibrotic response to UVA1 phototherapy. By testing the effects on tanning and matrix metalloproteinase 1 induction, this group found that the

lightest skin responds well to UVA1 treatment with upregulation of the proteinase; however, treatment results in darkening of the skin and a subsequent diminished response. Clinically, the findings support further investigation to determine whether UVA1 is, in fact, better suited to light-skinned individuals or whether lower doses may minimize increased pigmentation in response to phototherapy.

#### Conclusions

Two speakers gave futuristic presentations. Stuart Schreiber (Harvard University, Boston, MA), who presented the Herman Beerman Lecture, described the building of a small-molecule drug-discovery pipeline. In addition, the remarkable data-sharing network of ChemBank (<http://chembank.broad.harvard.edu>), which focuses on target identification via comparative analysis of small molecules in biological assays, was demonstrated. In the Naomi Kanof Lecture, which emphasizes scientific achievement outside the skin, Thomas Pearson (University of Rochester, NY) chronicled the global pandemic of cardiovascular disease from the standpoints of epidemiology and preventive medicine. This presentation depicted cardiovascular disease in developed and developing countries and highlighted trends in risk factors and prevention.

The primary goals of the Society for Investigative Dermatology are to promote the science relevant to skin health and disease and to provide education and scholarly exchange of scientific data. The annual meeting of the Society furthers these objectives by bringing together diverse researchers and engaging them in critical assimilation of the state-of-the-art results in the field. Combining invited lectures and submitted presentations from around the world with sponsored satellite symposia, educational tracks for residents and fellows, and breakout symposia, this meeting clearly met the goals.

*\*The 68th Annual Meeting of the Society of Investigative Dermatology was held at the Hyatt Regency Century Plaza Hotel in Los Angeles, California, USA, 9–12 May 2007.*