Montagna Symposium on the Biology of Skin

Montagna Symposium 2017—Precision Dermatology: Next Generation Prevention, Diagnosis, and Treatment

Jakub Tolar[1], Johann W. Bauer[2], Daniel H. Kaplan[3], Sancy A. Leachman[4,5], John A. McGrath[6], Amy S. Paller[7], Kelly A. Griffith-Bauer[8], Clara E. Stemwedel[4] and Molly F. Kulesz-Martin[4,9]

Journal of Investigative Dermatology (2018) **138,** 1243–1248; doi:10.1016/j.jid.2018.02.039

The Annual Montagna Symposium on the Biology of Skin is a unique event in the scientific world, inspired by the passion for knowledge and collegiality of the late William Montagna, PhD. He was a great scientist in an age of giants, with interests as broad as ornithology, primatology, histology, entomology, taxidermy, and the French horn. It was this breadth of knowledge and willingness to share it that marked the early meetings (once known as the Brown Meeting, after Brown University, and then the Green Meeting, after the verdure of the Pacific Northwest). Every meeting is imbued with the sense of responsibility to live up to the extraordinary life and ideals of Dr. Montagna, and the results resonate far beyond the meeting itself.

The goal of the 66th Annual Meeting was to combine molecular understanding of disease and health with clinical applications of big data by exploring a progression of topics—from genes to cells to tissues to devices and ending with people—focused on the future of personalized dermatology. "Precision Dermatology: Next Generation Prevention, Diagnosis, and Treatment" was held October 12–16, 2017, in Stevenson, WA. Jakub Tolar (University of Minnesota, Minneapolis) served as Program Chair, with John McGrath (King's College London, UK), Daniel Kaplan (University of Pittsburgh, PA), Johann Bauer (Paracelsus Medical University, Salzburg, Austria), Sancy Leachman (Oregon Health and Science University, Portland, Orgeon), and Amy Paller (Northwestern University, Evanston, IL) serving as Session Chairs.

GENES: DIGITAL CODE

The advent of next-generation sequencing has had an immense impact on gene discovery and the identification of disease mutations, germline and somatic. In the era of precision medicine, attention is turning toward the predictive value of data in both clinical care and understanding disease behavior. John McGrath chaired and introduced the "Genetically Defined Diagnosis and Therapy" session with a presentation on "gene hunting" for Mendelian genodermatoses. Examples are emerging of useful reductionist dissection of genetic traits, often into more than one disease entity in the same individual, such as the occurrence of inherited hair and nail abnormalities clinically categorized as a form of ectodermal dysplasia but genetically reduced to two separate autosomal recessive hair and nail gene disorders (Hsu et al., 2017). Regarding clinical care, preemptive management is now alive in the clinic, improving physician astuteness and precision, for example, in anticipating the future clinical course in infants with seemingly nonspecific forms of ichthyosis (Saito et al., 2017) or in more complex genetic disorders like inherited poikilodermatous syndromes with potential for life-threatening complications (Takeichi et al., 2017). Such advances have an immediate benefit for patients and families, extending the goal of making an accurate genetic diagnosis into improving clinical management.

In tumors, molecular dissection of mutational events is also reworking models of cancers such as melanoma. Boris Bastian (University of California, San Francisco) discussed the revision of classic models of oncogene activation based on the timing of events such as activation of telomerase expression (Chiba et al., 2017), underscoring new dynamic models of pre-neoplastic lesions that reflect an equilibrium state of slow proliferation and attrition. Understanding this state—and dissecting key underlying mechanisms—is set to herald the development of new biomarkers for diagnosis and prognostication (Shain and Bastian, 2017).

Precision at a gene level is also fundamental to dissecting human epidermal reprogramming, with relevance

[1]*Division of Blood and Marrow Transplantation, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota, USA;* [2]*EB House Austria, Research Program for Molecular Therapy of Genodermatoses, Department of Dermatology, University Hospital of the Paracelsus Medical University, Salzburg, Austria;* [3]*Departments of Dermatology and Immunology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA;* [4]*Department of Dermatology, Oregon Health and Science University, Portland, Oregon, USA;* [5]*Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon, USA;* [6]*St. Johns Institute of Dermatology, King's College London, Guys Campus, London, UK;* [7]*Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA;* [8]*Department of Dermatology, University of California, San Francisco, School of Medicine, San Francisco, California, USA; and* [9]*Department of Cell, Developmental and Cancer Biology, Oregon Health and Science University, Portland, Oregon, USA*

Correspondence: Molly Kulesz-Martin, Departments of Dermatology and Cell, Developmental and Cancer Biology, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, L468R, Portland, Oregon 97239, USA. E-mail: kuleszma@ohsu.edu

Abbreviations: AhR, aryl hydrocarbon receptor; CAAR, chimeric autoantibody receptor; i, inhibitor

Received 13 December 2017; revised 2 February 2018; accepted 5 February 2018; accepted manuscript published online 14 March 2018; corrected proof published online 2 May 2018

Figure 1. Group photo. Courtesy of Jeremy Bauer.

to aging, cancer, and inflammation. Raymond Cho (University of California, San Francisco) presented new work on advances in single-cell RNA sequencing technologies that have allowed for transcriptomic profiling of thousands of keratinocytes from different anatomic sites. These studies have identified more detailed and complex coordinate transcriptional changes during keratinocyte differentiation, identifying discrete regulatory programs on a genome-level scale. Understanding keratinocyte behavior in such a detailed manner provides a compendium for precision dissection of hundreds of disease states, with grand openings for future preventative or novel therapeutic interventions.

Johann Bauer and Mark Osborn (University of Minnesota, Minneapolis) presented other approaches to precise, personal therapeutics, already in preclinical phases. These include the application of spliceosome-mediated RNA trans-splicing and gene editing technologies, particularly use of the clustered regularly interspaced short palindromic repeats (i.e., CRISPR)-Cas9 nuclease system, both of which are in development for testing in recessive dystrophic epidermolysis bullosa associated with mutations in the type VII collagen gene, *COL7A1* (Peking et al., 2017; Perdoni et al., 2016). At a gene level, precision medicine is making its clinical mark.

CELLS: BIOBRICKS

At a cellular level, also, the increased understanding of how cells and their mechanisms interact with their environments is creating improved treatment options. One of the critical aspects for the success of precision medicine is the accurate identification of specific pathways driving pathogenesis in disease states and the development of selective approaches to interfere with these processes. The path to translation relies on a solid understanding of disease mechanisms. Past success stories include psoriasis and atopic dermatitis for which IL-23/IL-17 and IL-4, respectively, were found to be central components of each disease, and new biologic therapies targeting these cytokines have revolutionized the therapy of both diseases. Building on these successes, the goal of the "Cells as Living Medications" session was to explore (i) novel aspects of skin biology that may ultimately provide novel therapeutic targets and (ii) new translational approaches that capitalize on recent discoveries.

Kenji Kabashima (Kyoto University, Japan) described, in the setting of the elicitation phase of contact hypersensitivity, a murine model of contact dermatitis, a structure of sequential leukocyte clusters forming along postcapillary venules through a coordinated chemokine-driven process. This structure does not exist in the steady state but is "induced" in response to local inflammatory condition. He terms it "inducible SALT (iSALT)," reminiscent of the skin-associated lymphoid tissue (SALT) initially proposed by Streilein (1978). This tissue's lymphoid structure is likely key to maintaining chronic inflammation (Kogame et al., 2017).

Paola Di Meglio (King's College London, UK) presented data on the aryl hydrocarbon receptor (AhR), an environmental sensor and transcription factor activated by the environmental pollutant dioxin but also by physiological ligands of dietary and microbial origin. AhR is a critical regulator of homeostasis at barrier organs (gut, skin, lung). In the skin, physiological AhR ligands in keratinocytes decrease their responsiveness to inflammatory stimuli. Thus, AhR acts as an anti-inflammatory brake to constrain chronic inflammation and maintain skin homeostasis.

Daniel Kaplan presented his group's ongoing work on the importance of pain-sensing nerves in the skin for the development of innate resistance to epicutaneous infection with *Candida albicans*. He showed that nerves are required to elicit IL-23 from dermal dendritic cells that then promote a type 17 immune response required for host defense. He also showed how *C. albicans* directly activated two subsets of nerves that can be distinguished