Melanoma to Vitiligo: The Melanocyte in Biology & Medicine—Joint Montagna Symposium on the Biology of Skin/PanAmerican Society for Pigment Cell Research Annual Meeting

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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Introduction

Melanoma to Vitiligo: The Melanocyte in Biology & Medicine generated and amplified a growing understanding of the scientific basis of and clinical and pathologic relationship between melanoma, a bi-product of uncontrolled growth of melanocytes, and vitiligo, a disorder of undesirable death of melanocytes. This meeting, held Oct. 17–22, 2018, at Salishan Resort on the Oregon Coast, incorporated the full spectrum of pigment cell biology and chemistry, as well as the biological underpinnings of clinical disease. Each of seven sessions, incorporating session keynote and established and junior investigator talks, endeavored to (1) present cutting-edge pigment cell biology/chemistry; (2) emphasize the application of science to melanoma, vitiligo, and other medical disorders; (3) bring together widely divergent disciplines to enhance transdisciplinary discussion on these topics; and (4) support promising young investigators with an interest in this topic area.

Pre-Meeting Patient Symposium and Opening Keynote

A pre-meeting Vitiligo and Melanoma Patient Symposium and Opening Keynote brought together vitiligo, melanoma, and xeroderma pigmentosum (XP) patients to learn from one another and share perspectives with clinicians and researchers attending the main scientific meeting. Through this inspiring event, we created a venue where patients and supporters could share their thoughts about their diseases, react to science, and have their questions answered by experts in the field. This special introduction created a sense of urgency and relevance for the scientific sessions that followed.

With this unique audience, Michael Shapiro (University of Utah) shared the remarkable story of how the pigmentation and physical characteristics of pigeons have been used to uncover important pigmentation genes, their functions, and utility as a model system for better understanding evolutionary genetics and diversity of color. Not only do some of the same genes that underlie color variation in birds also regulate pigment diversity and disease in humans, but also surprising molecular links emerged between color patterning in pigeons and vision defects in both pigeons and humans (Boer et al., 2017, Domyan et al., 2014, Vickrey et al., 2018).

Session 1: Animal Models

In a fascinating convergence of disciplines leading to transdisciplinary discussion, Karen Osborn (Smithsonian Institution) presented on the diversity of form and function in ocean creatures that live in the midwater "Twilight Zone," where light is so scarce that everything looks dark to the human eye (Bagge et al., 2016). Deep-sea fish, such as viperfish, are "super black," absorbing >99.9% of light to make them all but invisible. Using sophisticated microscopy, Osborn and colleagues revealed the secret to being super black was not only black pigment but also the arrangement of pigment granules into complex organized structures that trapped virtually all light.

Genetically engineered mouse models and/or specialized cell lines have enabled investigation of various aspects of melanoma and vitiligo pathogenesis and treatment. Helen Michael (National Cancer Institute) presented her work in the Glenn Merlino lab on the use of DNA sequencing of UV-induced melanomas in hepatocyte growth factor transgenic mice to identify a series of genes that drive the pathogenesis of these melanocytic lesions. Lively discussion followed on the potential influence of the dermis in this melanoma model.

Catherine van Raamsdonk (University of British Columbia) presented data on a novel mouse model for uveal melanoma, leptomeningeal melanoma, and blue nevus-like melanoma. In the mouse, mutant GNAQ, when expressed in the melanocytic lineage leads to marked proliferation of melanocytes in the uveal tract, leptomeninges and dermal melanocytic neoplasms recapitulating the distribution of tumor with Gq pathway mutations in the human.

Pivoting to a vitiligo model, Zhussipbek Mukhatayev (Northwestern University) described an innovative approach to vitiligo treatment based on regulatory T cells targeted (through chimeric antigen receptor technology) to a molecule that is upregulated in vitiligo skin. Preliminary evidence suggested that these cells act as immunosuppressive engines,

decreasing the expression of signature cytokines and representing a promising approach for suppression of vitiligo.

Session 2: Human Model Systems

Hensin Tsao (Harvard Medical School), Margaret Tucker (National Cancer Institute), and Kenneth Kraemer (National Cancer Institute) described over forty years of research into melanoma and XP genetics and its direct impact on patients. The spectrum of familial melanoma has been expanded to include familial atypical mole and melanoma (FAMM) syndrome and the BAP1 tumor syndrome. Sequencing of large cohorts identified association with mutations in *CDKN2A*, *CDK4* and *EBF3*. Detailed study of XP patients revealed a 10,000-fold increase in non-melanoma skin cancer (NMSC) and a 2,000-fold increase in melanoma in patients under 20 years; comparison of NMSC and melanoma in these patients showed differential anatomic site distributions and genetic mutational associations relative to the general population, suggesting differential mechanisms of carcinogenesis.

Understanding the basic biology of DNA damage repair and the phenotype of patients with genetic repair syndromes has opened multiple avenues for cancer therapy with the goal of improving chemotherapy for cases where targeted therapy and immunotherapy are unavailable. Sarah Arron (University of California, San Francisco) discussed multiple compounds in clinical development targeting ATM, CHK1/2, and nucleotide excision repair, which regulate the cell cycle and allow repair of DNA damage.

A clinician-driven panel discussion addressed recent developments in sunscreen-based prevention of skin cancer. Panelist John DiGiovanna (National Cancer Institute) discussed sunscreens causing death of coral reefs, while Douglas Brash (Yale University) noted development of biodegradable bioadhesive nanoparticle sunscreens.

Poster Session Young Investigator Talks

Supporting young investigators fulfills a primary mission of both the Montagna Symposium on the Biology of Skin and the PanAmerican Society for Pigment Cell Research (PASPCR). Young investigators, in dedicated short-talk sessions, explored mouse models of basic melanocyte biology, improvement of treatment options for melanoma, and clarification of the order and identity of mutations acquired during melanomagenesis from phenotypically normal cell(s) to metastatic status.

Two of these presentations highlighted results from the use of CRISPR technology. Corinne Rauck (University of Cincinnati) showed that excision of the adhesion protein CEACAM1 decreased tumor growth upon transplantation into syngeneic and immunodeficient mice. This suggests potential for targeting of CEACAM1 with other immune checkpoint antigens, including PD-1, PD-L1, and CTLA-4, in advanced melanoma. Isoforms of MITF are mutated in familial melanoma and Waardenburg syndrome, and Jessica Flesher (University of California, Irvine) pursued studies in mice selectively lacking isoforms Mitf-A and -F. On the one hand, *Mitf-M-null* mice lacked melanocytes in hair follicles and choroid but had a normal retinal pigment epithelium, while on the other hand, skin and eyes of the *Mitf-A-null* mice developed normally, indicating a functional redundancy between MITF isoforms.

Noel Turner (Yale University) used a congenic mouse melanoma cell model (Meeth et al., 2016) to discover that immune checkpoint inhibitors impede growth of the melanoma cells treated with UV-B (BrafV600E, Pten−/−, Cdkn2a−/− cells, YUMMER1.7), compared to the untreated parental tumors (YUMM1.7). This was IFNγR-dependent, correlating efficacy with the increased somatic mutations and immunogenic neoepitopes that are considered hallmarks of human melanoma vulnerability to immune checkpoint inhibitors.

Session 3: Stem Cells & Development

A focus of this session was development and disease progression in zebrafish models. David Parichy (University of Virginia) presented his group's work on single cell RNA-sequencing to identify transcriptomic signatures in post-embryonic neural crest-derived cells in zebrafish. Two different classes of pigment cells exhibited distinct transcriptomic responses to thyroid hormone in pigment cell development, suggesting different modes of lineage establishment, which provides insight into endocrine factor roles in post-embryonic development of vertebrate pigmentation. E. Elizabeth Patton (University of Edinburgh) discussed MITF activity in melanoma progression in zebrafish, identifying a new target for 5-nitrofurans, which selectively targets melanoma subpopulations that are enriched for ALDH1 activity and have tumor initiating potential. Morgan Sturgeon (University of Iowa) showed that loss of magnesium in *trpm7* zebrafish mutants via magnesium-exporter slc41a1 is at least partly responsible for the cell death of melanocytes.

Two presenters addressed pigment cell quiescence and pigment loss. Melissa Harris (University of Alabama at Birmingham) described exploitation of Quantitative Trait Locus (QTL) mapping to find genetic modifiers that contribute to resistance to melanocyte stem cell differentiation, a cellular phenotype associated with melanocyte stem cell aging and gray hair. Interestingly, Harris and colleagues also uncovered a role for PD-L1, which is involved in immune privilege, quiescence, and retention in aged melanocyte stem cells. Emi Nishimura (Tokyo Medical and Dental University) discussed melanocyte stem cells and their roles in hair graying and development of acral melanoma, pointing out that the tyrosinase promoter in transgenic mice yields mainly "dermal" melanocytes in mice versus melanocyte lineage cells analogous to melanocyte stem cells within human epidermis.

Vijayasaradhi Setaluri (University of Wisconsin-Madison) added notable disease relevance to the session by discussing the plasticity of melanoma cells, revealing their limited ability to generate an induced pluripotent-like state (iPSC) and that this capacity diminished during progression from primary to metastatic stage. Importantly, iPSC derived from melanomas, independent of the clinical stage and histological type of lesions, failed to undergo melanocyte differentiation but produced neural-type cells that were less sensitive to MAPKi, associating with the drug resistant phenotype.

Session 4: Microenvironment & Immunology

The recent Nobel Prize in Medicine awarded for anti-CTLA-4 and anti-PD-1 checkpoint inhibition provided impetus for discussion about the cutaneous microenvironment and its impact on immune responses from vitiligo to melanoma. We were reminded by Rosalie

Luiten (University of Amsterdam) that vitiligo patients are less likely to develop melanoma, whereas melanoma patients are prone to developing vitiligo (Teulings et al., 2017). Thus, anti-melanocyte responses in vitiligo may present tractable therapeutic strategies in melanoma. Environmental phenolic agents (e.g., monobenzone) can interact with tyrosinase to generate cytotoxic quinones that induce contact vitiligo and subsequently elicit therapeutic immune responses in melanoma (Teulings et al., 2018).

As discussed by Arup Indra (Oregon State University), Jodi Johnson (Northwestern University), and Youwen Zhou (University of British Columbia) the epidermis is a dynamic microenvironment that supports melanocyte biology but also may drive transformation, in part by desmoglein-1 induced IL-6 and IL-8, as well as nuclear receptor signaling mediated by retinoid-X-receptors in the surrounding keratinocytes (Chagani et al., 2017). Additionally, while the contribution of keratinocytes to depigmentation in skin has unfolded for some time, there is an emerging role for other cell types, such as Schwann cells, in this process.

Caroline Le Poole (Northwestern University) addressed the roles of T cell receptors (TCR) in pigmentation and melanoma treatment response. Interestingly, cytotoxic T cells (CTLs), the active agents of depigmentation and melanoma control, are tuned by antigen expression (Eby et al., 2018). Exposed to low antigen concentrations, TCRs can dictate an IL-17-like cytokine pattern, switching to IFNγ at higher concentrations. The IL-17 phenotype is quite conducive to anti-tumor responses and relies in part on TCR affinity. By contrast, Mayumi Fujita (University of Colorado) pointed out that inflammation can negatively impact tumor regression when it involves IL-1 secretion and autocrine stimulation by tumors cells (Zhai et al., 2017).

Independent of intrinsic T cell phenotype, CTLs must be retained in tumors, behavior that may be at least partially dependent on PD-1/PD-L1 signaling, as addressed in recent publications and in unpublished data presented by Niroshana Anandasabapathy (Weill Cornell Medical College), Ryan Lane (Oregon Health & Science University), and Amanda Lund (Oregon Health & Science University). Tissue resident T cells that are retained in skin in a quiescent state are PD-1 high and activate protective immunity as a function of interaction with dendritic cells (DC). Furthermore, PD-L1 expressed by lymphatic vessels contributes to T cell accumulation such that loss of IFNγR on lymphatic vessels improves tumor control (Lane et al., 2018). This is just one of several surprising roles that IFNγ plays in stratifying melanoma patients (Nirschl et al., 2017). Furthermore, T cells that are not retained by tumors exit tissue via lymphatic vessels and may interact with immunosuppressive molecules presented by this endothelium. Thus, besides affecting T cell activity through DC populations, limiting the departure of CTLs by manipulating surface and homing molecule expression by lymphatic vessels offers exciting new therapeutic strategies to impact tumor growth.

Session 5: Genetics, Early Detection & Prevention

Cellular and molecular features that result from genetic changes can be applied to prevention and early detection of human disease. Illustrating how the field is poised to understand the

convergence of multiple regulatory pathways and capitalizing on systems biology approaches and rapidly evolving computational biology tools, presentations in this session highlighted new discoveries in vitiligo genetics, microRNA biomarkers, and novel genetic alterations for mucosal melanoma.

Richard Spritz (University of Colorado School of Medicine) summarized data that not only demonstrated the genetic relationship between vitiligo and other autoimmune conditions but also highlighted particular genetic features of vitiligo predisposition that are known to protect against melanoma. Robert Judson Torres (University of California, San Francisco) identified a panel of microRNAs that help distinguish melanomas from nevi. He applied machine learning to develop a microRNA analysis that may lead to a new class of melanoma biomarkers. Through the investigation of a powerful set of mucosal melanomas, Iwei Yeh (University of California, San Francisco) demonstrated that SPRED1, a member of the Sprouty family of proteins that is associated with Legius syndrome, is frequently inactivated by mutations and/or deletions in mucosal melanoma. SPRED1 loss leads to RAS activation downstream of KIT. *SPRED1* mutations often co-occurred with *KIT* mutations and may explain why the effect of KIT inhibitors in patients with *KIT* mutant mucosal melanoma is not as pronounced. This suggests that simultaneous targeting of the pathway at the level of KIT and MEK may lead to more pronounced clinical responses in patients.

An overall highlight of the meeting was its transdisciplinary focus, including Karen Osborn's presentation on super black fish and a presentation by Roger Hanlon (Marine Biology Lab/Brown University), a cephalopod expert. Hanlon amazed all with videos of cuttlefish and octopus that demonstrated the versatility of pigmentation systems for camouflage, inspiring ideas about possible medical or "body art" applications of optical systems and artificial skin mimicking structural properties to that of cephalopods.

Session 6: Signal Transduction

In a transdisciplinary session keynote, Ze'ev Ronai (Sanford Burnham Prebys Medical Research Institute) presented work on the ubiquitin ligase RNF5 in regulation of gut microbiota and anti-tumor immunity. Mice lacking RNF5 were more resistant to developing melanoma, dependent on their gut microbiome. Bacterial strains were mapped and shown to be capable of eliciting anti-tumor immunity and inhibiting tumor growth, involving altered unfolded protein response (UPR) in intestinal epithelial cells and affecting antigen presentation and antimicrobial peptide expression (Li et al., 2019).

John D'Orazio (University of Kentucky) and Zalfa Abdel-Malek (University of Cincinnati) elaborated on nucleotide excision repair, the major genome maintenance pathway by which melanocytes rid their DNA of mutagenic UV photodamage. D'Orazio described cAMP signaling regulation of nucleotide excision repair, suggesting that the kinase ATR phosphorylates the key repair factor xeroderma pigmentosum A (XPA) protein and that this phosphorylation is dependent on deacetylation of XPA on three lysine residues by the sirtuin 1 deacetylase (Jarrett et al., 2018). Abdel-Malek showed that melanocytic nucleotide excision repair is regulated not only by melanocortin-MC1R interactions but by endothelin and neuregulin signaling pathways as well (Hernando et al., 2018).

Keiran Smalley (Moffitt Cancer Center) and Todd Ridky (University of Pennsylvania) presented novel perspectives informing treatment of melanoma with targeted therapy. Smalley described new data that identified the role of histone deacetylase 8 in the adaptation of melanoma cells to targeted therapy. HDAC8 rewired the signaling network of melanoma cells to a resistant state that was mediated through enhanced AP-1 mediated gene transcription and increased receptor tyrosine kinase signaling. In *in vivo* studies, Smalley's group demonstrated that this HDAC mediated resistance program could be overcome through use of pan-HDAC inhibitors and that this was associated with more durable anti-tumor responses to the BRAF inhibitor vemurafenib. Ridky presented compelling data from his group showing that estrogen binds to GPER, a melanocyte cell surface G-protein coupled receptor, and signals through the cAMP pathway to enhance melanocyte pigment production and differentiation. Importantly, estrogen-GPER interactions promote melanization even in the absence of MC1R, suggesting an alternate route for UV protection—and potential clinical application—in fair-skinned UV-sensitive MC1R-defective individuals. Ridky also shared data that showed that estrogen-GPER signaling decreased the capacity of melanoma cells to induce immune checkpoint by downregulating surface expression of PD-1 (Natale et al., 2018, Smalley, 2018).

Session 7: Photochemistry & Toxicology of Pigment Cells

The distinctive ability to synthesize melanin significantly impacts the biophysical and chemical properties of melanocytes. Gregory Payne (University of Maryland) discussed the complexity of melanin polymers, which has hampered investigation of melanin structure and biochemistry. A novel approach to address this problem is to exploit melanin's ability to be both an anti- and pro-oxidant. The Payne group has developed a device that probes the electrochemical response of melanin by applying voltage and measuring output current. This also allows for investigation of agents that alter the electrochemical properties of melanin, as well as showing that pheomelanin has more oxidative potential than eumelanin, that melanin repeatedly donates and accepts electrons allowing for free radical scavenging, and that melanin interactions can modulate the pharmacological activity of certain drugs.

Jason Belitsky (Oberlin College) returned to the meeting's focus on supporting young investigators and encouraging them to explore careers skin-related research. Belitsky discussed the discovery of small-molecule catalysts that promote eumelanin production. The assay development and screening were undertaken as part of a course-based research experience for students at Oberlin, highlighting a unique opportunity to study melanin while teaching chemistry to undergraduates.

Neuromelanins are found in autolysosomes that accumulate in the aging brain, most famously in the substantia nigra. Luigi Zecca (Institute of Biomedical Technologies – National Research Council of Italy) presented his work on neuromelanin levels, which depend on cytosolic catecholamine concentration and can be protective or toxic, and their suspected role in the etiology of Parkinson's disease. Neuromelanin-containing organelles also contain major histocompatibility complex class I proteins that can present antigens; as a result, CD8+ T-cells will target neurons – an autoimmune mechanism of cell death in Parkinson's. Intriguingly, it may be possible to exploit the chemical nature of neuromelanin

to diagnose Parkinson's using magnetic resonance imaging. This topic stimulated speculation upon as yet unfathomed parallels for melanin protection versus toxicity in organs other than skin.

A point/counterpoint discussion moderated by Pamela Cassidy (Oregon Health & Science University) addressed whether antioxidants were "good or bad" as part of cancer prevention strategies. Particular concerns among discussants were that the effects of antioxidant dietary supplements have not been investigated in large, controlled clinical studies and that the current environment of care discourages both patients disclosing supplement use to providers and providers openly discussing it with patients.

Conclusion

Gestalt, defined as something made of many parts and yet more than or different from the sum of these parts, aptly describes this meeting, a confluence of two organizations, over 40 outstanding lectures, and 164 participants (Figure 1). It was choreographed in a way that brought intellectual diversity to the forefront, from the "opposite" fields of vitiligo and melanoma, to the spectrum of career levels represented on the program, to the inclusion of transdisciplinary presentations throughout. Certainly, the breadth of topics, activities, and participants (patients, physicians, and scientists) created an event much more than the sum of its parts.

Society for Investigative Dermatology Eugene M. Farber Travel Awards for Young Investigators

Robert-Marlo Bautista (University of Kentucky), Rachel Belote (University of California, San Francisco), Evan Carpenter (Oregon State University), Yeon Sook Choi (Harvard Medical School), Eric Domyan (Utah Valley University), Mark Evans (University of California, Irvine), Donald Koroma (Brown University), Olga Lavinda (New York University), Zhussipbek Mukhatayev (Northwestern University), Nabanita Mukherjee (University of Colorado School of Medicine), Corinne Rauck (University of Cincinnati), Maria Steele (Oregon Health & Science University); Montagna Symposium on the Biology of Skin Director's Award: Zoya Anderson (University of Alabama at Birmingham); **PanAmerican Society for Pigment Cell Research Travel Awards:** Fabian V. Filipp (University of California, Merced), Jessica Flesher (University of California, Irvine), Shirley Fong (Chapman University School of Pharmacy), Shobhan Gaddameedhi (Washington State University), Alec K. Gramann (University of Massachusetts Medical School), Chelsey Kline (Oregon Health & Science University), Stephen P.G. Moore (Boston University School of Medicine), Jenny Mae Sampson (University of Colorado School of Medicine), Lauren Saunders (University of Washington), Hunter Shain (University of California, San Francisco), Noel Turner (Yale School of Medicine); **Japanese Society for Investigative Dermatology Travel Award for Young Investigators:** Takeshi Yamauchi (Tohoku University Graduate School of Medicine); **National Psoriasis Foundation Travel Grant:** Jennifer Chung (University of Connecticut)

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Figure 1.
Group photo (courtesy of Christina Topham)