

PASPCR

September 2004
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Newsletter



Introduction...

by **Bill Oetting**

The XIIth Annual Meeting of the PASPCR, held in Newport Beach, was another great annual meeting! Frank Meyskens, Alistair Cochran and Roger Bowers did a fabulous job of providing an excellent venue for the meeting, as well as looking to our comfort in between the talks. We should also thank Joyce Merchant for all of the 'behind the scenes' work that she did to make our annual meeting such a great success.

There were many excellent talks and a good deal of discussion, both within the lecture rooms and in the hallways. A report of the meeting begins on page 8 of this newsletter. The PASPCR web site also contains the meeting report, as well as several pictures of the meeting. The next scientific gathering for the PASPCR will be the 19th International Pigment Cell Conference, hosted by Vince Hearing in Reston VA. This also promises to be a highly informative meeting. Look to the PASPCR Newsletter for up-to-date information on the meeting (page 5 of this issue), or go to the IPCC web site at ipcc.info.

The *PASPCR Newsletter* is published quarterly and is intended to serve as a means of communication for the members of our Society. You are invited to contribute articles, or other information you feel will be of interest to members of the PASPCR. If you attend a scientific meeting and have heard results which you think will be of interest to the membership of the PASPCR, please write a few paragraphs summarizing what was presented and

share it with us. Any information on upcoming meetings of interest will be added to the "Calendar of Events". This is your newsletter, and we depend upon you to help us make sure it best serves the Society's needs. Contributions and comments can be sent to me, preferably by E-mail, to bill@lenti.med.umn.edu.

The PASPCR Web Site is the major, up-to-date source of current information for the PASPCR membership and for individuals who are interested in the PASPCR. If there is additional information that you would like to see on the Web site, or you would like to include information of past PASPCR activities, please let me know and I will include them.

Don't Forget to Vote

PASPCR candidates for 2005
can be found on pages 4-5.

The PASPCR Web Site can be found at:

<http://www.paspcr.org>

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Richard A. King
past-President PASPCR

Calendar of Events:

Nov 13-16, 2004 Second International Melanoma Research Congress, to be held in Phoenix, Arizona, USA
Contact: Dr. Menashe Bar-Eli
E-mail: mbareli@mdanderson.org.
Web: <http://www.ulb.ac.be/medecine/loce/espctr/pub/smr.htm>

Nov 27-28, 2004 The 18th Annual Meeting of the Japanese Society for Pigment Cell Research, to be held in Kumamoto City, Japan.
Contact: Dr. Toshiro Kageshita
E-mail: toshiro@kaiju.medic.kumamoto-u.ac.jp

Sept 18-22, 2005 XIVth International Pigment Cell Conference (IPCC), to be held near Washington DC, USA.
Contact: Dr. Vince. Hearing
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2006 XIIIth Meeting of the ESPCR
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If you know of future meetings that you feel would be of interest to the PASPCR membership, please let us know.

The *PASPCR Newsletter* is published quarterly by the PanAmerican Society for Pigment Cell Research. All views are those of the authors. For further information or to submit articles, please contact members of the Publications Committee.

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Corporate Sponsors by *Raymond E. Boissy*

The PASPCR would like to acknowledge and thank our Corporate Sponsors; the list below reflects contributions over the past 2 years. Financial gifts from these sponsors have allowed our Society to increase benefits to the membership far out of proportion to the actual dues collected from members. Monies contributed by these sponsors have been used over the years to support various PASPCR functions including our Young Investigator Award program, meeting travel stipends, annual meeting expenses and this Newsletter.

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Congratulations to all PASPCR award recipients.

Below are lists of recipients of the awards presented during the XIIth Annual Meeting of the PASPCR.

Recipients of PASPCR travel stipend awards

Graduate Students:

Roman Garcia	Florida International Univ.
Jennifer Hauser	University of Cincinnati
Avner Ittah	Florida International Univ.
Becky Lockhart	University of Arkansas
Dilshika Wijesekera	University of Arkansas

Postdoctoral Fellows:

Esther Guzman	Henry Ford
Ana Luisa Kadekaro	University of Cincinnati
Yan Liu	Duke University
Mingke Yu	Univ. Southern California

Recipients of the PASPCR Young Investigator Award

Roman J. Garcia, Graduate Student, Florida International University

For his talk:

“Endothelin 3 causes hyperpigmentation in an inducible mouse model”

Ana Luisa Kadekaro, Postdoctoral Fellow, University of Cincinnati

For her talk:

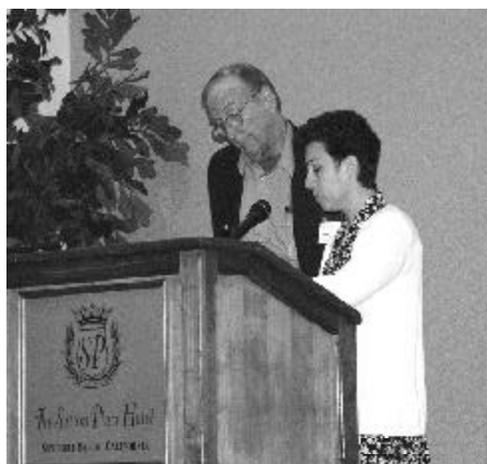
“Implications of the survival effects of MSH and endothelin-1 on the repair of UV-induced DNA damage and genomic stability of human melanocytes”

Marjan Huizing, Junior Faculty, NIGRI-NIH

For her talk:

“The cell biology of Hermansky-Pudlak Syndrome”

Recipient of the Aaron Lerner Lectureship



John Pawelek is presented the Aaron Lerner Lectureship award by PASPCR president Zalfa Abdel-Malek. The Lectureship is Sponsored by The Johnson & Johnson Consumer Companies, Inc.

From the President

Dear fellow members of the PASPCR

I hope all of you had a pleasant summer and are starting a new work season with full vigor and renewed energy. It was wonderful seeing you in Newport Beach in June, and it was refreshing to witness the great success of our annual conference. I send many thanks to Frank Meyskens and his program and organizational committee who put together a superb scientific program. Our PASPCR meetings have always been a success, and this is due mostly to the enthusiastic participation of our members. PASPCR is **you**, and its success is a reflection of your commitment and support of the society. This year, we continued with our most cherished tradition, giving Young Investigator's Awards. The awardees were Marjan Huizing, junior faculty member at NHGRI, Ana Luisa Kadekaro, postdoctoral fellow, Department of Dermatology, University of Cincinnati, and Roman Garcia, graduate student, Department of Biological Sciences, Florida International University. Congratulations to our awardees!

I am looking forward to the IPCC in September 2005 that is organized by Vincent Hearing and his program committee. The scientific program is already in place, and undoubtedly, it will be a memorable conference with outstanding invited speakers. I hope all our members plan to attend this very important event.

On behalf of PASPCR, I would like to express our thanks to Vincent Hearing for the tremendous effort he put in his role as Editor of Pigment Cell Research. Vince has brought the impact factor of PCR from less than 1 to 2.919. What an achievement!!

I would like to take this opportunity to officially announce the inception of a new sister society, the Asian Society for pigment Cell Research (ASPCR). The first scientific conference for ASPCR will be held in the first week of February 2005 in New Delhi. Professor Prasad Kumarasinghe from Sri Lanka is the first President, and Dr. Davinder Parsad is the Secretary for ASPCR. We welcome ASPCR members to the growing family of pigment cell researchers, and wish them success.

I end by wishing you continued success, and more commitment to strengthening our society.

Sincerely,

Zalfa Abdel-Malek, Ph.D.
PASPCR President

PASPCR election

Dear PASPCR Members:

Ballots with anonymous envelopes will be set out by mail to you on 10/20/2004. Please send in the ballots with your votes as soon as possible. Remember, vote for one individual for president and up to three individuals for council membership.

Sincerely,

Ray Boissy, Secretary/Treasurer

PRESIDENT-ELECT (choose 1)

Frank Meyskens

My laboratory based research for the last 7-8 years can be categorized as "What is the role of redox in the etiology, pathogenesis and treatment of human melanoma" and is summarized in three recently published reviews. Our studies have led to a new take on the etiology of melanoma and have also provided a practical and conceptual framework for development of a new class of agents (lipophilic chelators) for the treatment of melanoma. We have also described the role of NFkB and AP-1 in this process. Most recently we have begun to develop a therapeutic strategy based on the structural and functional characteristics of AP-1 and its modulation by Apurinic endonuclease/redox effector factor using molecular modeling techniques. Resveratrol, a polyphenolic antioxidant, found in red wine appears to be a good candidate for further development. Eventually this basic information will be utilized to inform new platforms for the prevention and treatment of human melanoma.

Miri Seiberg

My research interests are centered on keratinocyte-melanocyte interactions, melanosome transfer, the role of keratinocytes in the regulation of skin pigmentation, mechanistic understanding of ethnic skin pigmentary responses, post inflammatory hyper-pigmentation, modulation of skin color in healthy skin and in pigmentary diseases, and signaling pathways that affect human skin pigmentation. I am currently a member of the PASPCR council.

COUNCIL (choose 3)

Esteban Dell'Angelica

Work in my laboratory is focused on the products of genes implicated in the pathogenesis of Hermansky-

Continued next page

Pudlak syndrome (HPS), as these gene products are required for the normal biogenesis of melanosomes (and of other specialized organelles such as platelet dense granules). Specifically, we are studying the biochemical and functional properties of those HPS gene products that display no homology to any protein of known function. We and others have found that these "novel HPS proteins" are subunits of at least three distinct, stable protein complexes (the "BLOCs"). Through the characterization of one of these BLOCs we have recently identified previously unknown pigmentation genes. Understanding the molecular function of these protein complexes is expected to provide important new insights into how melanosomes are formed.

Marjan Huizing

My laboratory studies Hermansky-Pudlak syndrome and related disorders of hypopigmentation and prolonged bleeding (Chediak-Higashi syndrome, Gray Platelet syndrome, Griscelli syndrome). The patient's cells allow for identification of intracellular membrane trafficking pathways, novel protein interactions, and functions of vesicular transport genes, thereby increasing understanding of lysosome related organelle biogenesis.

Lidia Kos

Lidia Kos's laboratory works on melanocyte development. We are particularly interested in the role various signaling pathways (endothelin, neuregulin, kit ligand, wnts) play during this process and how they interact with each other. We are currently focusing on the effects of over-expression of endothelin 3 in vivo. Apart from its developmental effects, this project has led us to study a possible role for the endothelin signaling pathway in regulating pigment switching along with agouti and the melanocortin receptor. We are also investigating whether the endothelin pathway is involved in melanogenesis.

William Oetting

My laboratory is at the University of Minnesota. My interests include the analysis of tyrosinase and P gene mutations associated with oculocutaneous albinism. I am currently identifying cryptic mutations associated with OCA1. These are mutations located outside the coding region and the proximal promoter. Potential locations for these mutations are distal promoter regions and intronic enhancers. I am also the editor of the PASPCR Newsletter and Webmaster for the PASPCR.

Bill Pavan

My developmental genetics laboratory focuses on the mechanisms that regulate mammalian development and the alterations in these processes that result in human

disease. Our research uses a combination of molecular embryology, mouse genetics, transgenesis and microarray technologies to elucidate the etiology of neural crest development and disease. We have focusing on the transcriptional hierarchies involved in Waardenburg syndrome.

Giselle Thibaudeau

I am currently an Associate Professor in the Department of Biological Sciences at Mississippi State University (MSU). My research interests focus on embryonic cellular processes such as cell migration and cell differentiation. I use the amphibian embryonic neural-crest cell population, and more specifically the neural crest-derived pigment cell population as a model system to ask questions about cell decision-making processes. My lab is currently involved in studies aimed at identifying cell-cell (melanophore-xanthophore) interactions that ultimately lead to pigment pattern formation in the larval salamander. I am also an Associate Faculty at the Center for Science, Mathematics, and Technology at MSU and am very interested in involving undergraduate students in research, not just in my own research laboratory, but also across campus, across disciplines, and at other institutions. I believe that undergraduate involvement in the research enterprise is mutually beneficial for the student and the research university.

From the 19th International Pigment Cell Conference -

***** WWW.IPCC.INFO *****

The 19th IPCC is just about 1 year away and active planning of the scientific and social program by the Local Organizing and International Scientific Program Committees continues at a fast pace. We have selected 6 Outstanding Keynote Speakers who will present lectures at various times during the course of the IPCC (Prof. Elizabeth Blackburn, Dr. Francis Collins, Dr. Jennifer Lippincott-Schwartz, Prof. Shin-ichi Nishikawa, Prof. Jonathan Rees and Prof. Robert Weinberg). Add to that stellar list the names of Prof. Dorothy Bennett (who will present the IFPCS Presidential lecture) and Prof. Greg S. Barsh (who will present the Aaron B. Lerner lecture) as well as the Seiji lecturer (yet to be determined). Those speakers alone could constitute an outstanding Conference but we aren't finished yet. Each of the 13 Plenary Symposia will also have 2 outstanding Plenary Lecturers who are currently being selected, and whose names will probably be posted in the Scientific Program on the web site (www.ipcc.info) by the time you read this.

Continued next page

(19th IPCC continued)

Each of those Plenary Symposia will also feature 3 or 4 oral presentations selected by the co-chairs of the various sessions from the abstracts submitted. In addition, there will be 14 Concurrent Sessions, each also featuring 8 oral presentations selected by the co-chairs from the abstracts submitted. A planned Poster Session combined with a wine & cheese session should prove lively as will Sunrise Sessions by experts in the field who will provide background each day for those not expert in those topics.

The IPCC Conference site, the Hyatt Regency Hotel in Reston, Virginia, is a magnificent conference facility with quick (10 min) and reasonable (free) access to Dulles International Airport. It is located on a pedestrian mall with plenty of shops and restaurants for diversion and culinary choices.

We have not ignored the Social aspects of the meeting and planning is underway for an Opening Cocktail reception (Sunday, Sept 18th), a Wine & Cheese poster session (Tuesday, Sept 20th), a Tour and Conference banquet (Wednesday, Sept 21st) and a farewell drink (Thursday, Sept 22nd). Friday (Sept 23rd) will feature a number of Satellite Sessions to be arranged by various groups and anyone wanting to host one of those should contact the Organizer as soon as possible. Preference will be given to IFPCS special interest groups and already we are scheduling Satellite sessions on Melanoma, Vitiligo, Photobiology and a Genetics Workshop. Plan to bring along an accompanying person; we are arranging an activity each day for them, and their registration fees will cover those activities along with the other social functions mentioned above.

We are soliciting funds from societies, government institutions and corporate sponsors to make this meeting as affordable as possible. Travel stipends will be available to students and junior faculty that are members of one of the regional pigment cell societies. However, pay attention to the deadlines below as fees and hotel expenses will increase significantly as the meeting approaches.

IMPORTANT DATES:

- **January 1, 2005** - web site (www.ipcc.info) becomes active for abstract submission, early registration and hotel reservations
- **April 1, 2005** -deadline for abstract submission
- **July 1, 2005** - deadline for early registration (prices then increase by \$100)
- **Aug 1, 2005** - deadline for hotel reservation discount (prices ~double)
- **Sept 1, 2005** - deadline for normal registration (prices then increase again by \$100)

Research in the PASPCR Gisela F. Erf

Understanding Factors and Mechanisms Involved in the Development of Autoimmune Vitiligo in Smyth Line Chickens

The mutant Smyth line (SL) chicken developed by Dr. J. Robert Smyth, Jr. at the University of Massachusetts, Amherst, MA, is an important animal model for autoimmune vitiligo. The incidence of vitiligo in this line ranges from 70 to 95% and visible signs of pigment loss in the feathers are evident when the chickens are between 8 and 20 weeks of age. Previous studies by J. Robert Smyth, Jr. and co-workers describe the presence of a competent pigment system at hatch. Prior to visible signs of vitiligo, the earliest abnormality detected within SL melanocytes are irregularly shaped melanosomes containing pigmented membrane extension, hyperactive melanization, and selective autophagocytosis of melanosomes. These aberrant processes precede the degeneration of SL melanocytes, but are not sufficient to cause vitiligo without a functioning immune system. They do, however, appear to be involved in provoking an immune response resulting in autoimmune destruction of melanocytes. Our research has further defined the immune system involvement in SL vitiligo: 1) immunohistochemistry and cell population analyses conducted throughout the development of vitiligo pointed strongly to an important role of cell-mediated immune activity in the destruction of melanocytes; 2) *in vivo* studies demonstrated the presence of feather melanocyte-specific cell-mediated immunity in SL chickens with vitiligo; 3) *in situ* studies provided evidence that melanocytes in SL vitiligo die by apoptosis, a process which appeared to be initiated by cytotoxic T cells; and 4) Northern and Western plots demonstration interferon gamma production in feathers during active vitiligo. Additionally, our research uncovered a strong association between administration of live turkey herpesvirus (HVT) vaccine at hatch and the expression of vitiligo in vitiligo-susceptible SL chickens. Hence, the expression of SL vitiligo requires an environmental component (e.g., HVT, which translocates to the feather) in addition to a genetic and immune system component, a phenomenon typically observed in autoimmune disorders.

Considering the accessibility of the target tissue (the feather), the ability of the target tissue to regenerate, and the predictability of the development of SL vitiligo, this animal model offers unique opportunities to study the etiopathology of autoimmune vitiligo. Moreover,
(continued next page)

there are two MHC-matched ($B^{l01/101}$) lines of chickens that serve as controls. These are the parental Brown line (BL) of chickens, which has a < 2% incidence of vitiligo, and the Light Brown Leghorn chickens, which are vitiligo-resistant. Together, the SL and control lines of chickens allow for various comparisons between different phenotypes. Using these lines of chickens, concurrent efforts in our laboratory focus on further defining the local melanocyte environment prior to and throughout the development of vitiligo with regard to 1) aspects of anti-melanocyte cell-mediated immune activity, including cytokine profiles; 2) assessments of oxidative stress and antioxidant capacity; and 3) defining the nature (latent and/or productive) of HVT infection and associated anti-HVT immune activity. Additionally, studies using cultured feather- and embryo-derived melanocytes are underway to examine the melanocyte defect. Lastly, we are also currently examining the incidence and severity of associated autoimmune diseases such as autoimmune thyroiditis observed in SL and BL chickens.

C57BL/10 Mice

Maintained by Dr. Tomohiso Hirobe

B10 mice offer the pigment cell community an alternative research model that complements C57BL/6J. B10 mice possess more epidermal melanoblasts and melanocytes than C57BL/6J mice, and these cells grow very well in culture. A colony of B10 mice has been established to compare congenic cell lines of mice carrying pigment cell mutants.

Primary culture without serum standard conditions, no TPA, no Bovine serum or extracts.

<u>Genotype</u>	<u>Epidermal Melanoblasts/cytes</u>	<u>Proliferative Rate</u>
e/e	small number	prolif & dif slow
slaty	normal for B10	prolif & dif slow
c/c	normal for B10	low prolif & dif
b/b	normal for B10	dif a little slow, prolif nor
agouti	normal	norm prolif & dif

note: pheomelanin synthesis induced by L tyrosine, also pheomelanin and 5-SCD increased in medium

<u>Genotype</u>	<u>Epidermal Melanoblasts/cytes</u>	<u>Proliferative Rate</u>
dilute	normal	normal both (distribution of melanin abnormal)
pinkeyed dilution	very small number blasts/cytes	prolif very slow and dif

note: Differentiation and proliferation stimulated by L-tyrosine. 2 to 2.5 fold increase in melanin content, eumelanin and pheomelanin and those found in culture medium are extremely increased.

W-sash	keratinocyte is normal no blasts and cytes	
B10	normal	Normal

note: Effect of ultraviolet irradiation can be studied using B10 hairless mice because they have so many pigment cells in the skin, compared with most other mice. However, the stock is no longer available.

B10 is a very good model for studying the effect of X-ray, gamma ray, heavy ions, because B10 is very sensitive to irradiation. Radiation affects the dendrogenesis of mouse hair melanocytes. Many abnormal hair follicles that possess round melanocytes devoid of dendrites are observed. Only 0.25 of gamma rays is sufficient for obtaining a statistical difference in melanoblasts and melanocytes. The appearance of ventral white spots following irradiation is very frequent in B10 mice and very low in C3H/He mice, and is also low in C57BL/6J.

In C3H/He the number of epidermal melanocytes is smaller than in C57BL/6J, but the number of undifferentiated melanoblasts is much larger than B10 and/or B6. So in culture C3H melanoblasts grow more quickly than those of B10 and numerous melanoblasts can be obtained, but differentiation is very limited and it is hard to obtain differentiated melanocytes. Frequency of abnormal hair follicles in and white spotting in C3H is very low compared with B10.

Lynn Lamoreux

Report on the 11th Annual Meeting of the PASPCR

**Newport Beach, CA
June 24-27, 2004**

Session I - The Genetics of Pigment Cell Diseases

by *William Oetting*

Margaret Tucker, MD of the National Cancer Institute gave an invited lecture on the "The Epidemiology of Melanoma". Melanoma is rapidly increasing in incidence. Many risk factors have been well described with sun exposure being the greatest risk. In this study, investigators created medical histories of research subjects (individuals diagnosed with invasive melanoma) and determined the level of UVB flux they have received. Melanoma cases were found to have a higher UV exposure compared to controls. It is interesting to note that there is more UV exposure for people who tan well and it was found that skin type is closely related to UV exposure. Though a dark tan decreases melanoma risk, individuals usually have increased UV exposure resulting in increased melanoma risk. Public health implications for these results were discussed.

Dysplastic nevi are a major risk factor for melanoma. Risk increased when family members were diagnosed with melanoma. For familial melanoma, CDK4 and CDKN2A mutations are major risk genes. CDKN2A mutations are associated with 20% of familial cases. Screening for melanoma is controversial. Two step screening process should be used. First, determine skin type, # moles on back, freckling/solar exposure on back, sunburn history and pregnancy. 2nd screen, diagnosis of nevi. Summary: 1) Melanoma is a complex heterogenous disease. 2) Major susceptibility genes contribute little to population risk and at present, mutation screening is not warranted. 3) A readily identifiable phenotype can predict melanoma risk. 4) Risk assessment tools will be need to test in clinical settings. As for sunscreen use, there is no increase risk, and may be protective. Tanning parlors though increase melanoma risk.

William Oetting (University of Minnesota) talked about "The R402Q Mutation of the Tyrosinase Gene: Lack of Association with Oculocutaneous Albinism Type 1 (OCA1)". Previous reports had associated the glutamine allele at codon 402 with autosomal recessive ocular albinism (AROC) when co-inherited with a null activity allele on the homologous chromosome. Family members that had one null activity and the glutamine

allele on the homologous chromosome were identified and clinically evaluated. Results showed the glutamine allele is not associated with any form of albinism.

Ray Boissy (University of Cincinnati) showed that "Tyrosinase is Aberrantly Trafficked in Melanocytes of Hermansky Pudlak Syndrome-Type 3". There are 7 different genes associated with Hermansky Pudlak Syndrome (HPS). HPS3 is the mildest form of the seven types so far recognized. There is less hypopigmentation and little or no pulmonary disease. Analysis of biopsies from both HPS1 and HPS3 exhibit high level of endogenous tyrosinase activity. Functional tyrosinase activity is muted in HPS3, but more for HPS1. There is also reduced melanin production. The cellular location of tyrosinase for HPS3 exhibits diffuse staining and less distinct throughout the cytoplasm, unlike wild type in which tyrosinase staining appears granulated. WT tyrosinase and TRP1 co-localized. TRP1 and tyrosinase in individuals with HPS3 do not co-localize to the same extent. TRP1 is also diffuse. TRP2, LAMP1 and 3 also exhibit diffuse localization where and other melanocyte proteins (HPS1, adaptin 3, RAB27, transferrin, c-kit) have normal cellular distribution. At the EM level, melanosomes are less developed. Melanosome morphology is normal, with fewer mature melanosomes. It appears that some tyrosinase-positive, 50-nm, vesicles are misdirected and extend throughout the cell body and dendrites. Therefore, specific melanocyte enzymes are retained in trafficking vesicles that appear inefficiently targeted to the melanosome

Daniel Pinkel (University of California, San Francisco) gave an invited lecture on "BRAF and Melanocytic Diseases". Dr. Pinkel began by stating that there are genomic alterations in melanoma and that in cancer all genomes are unstable. UV is thought to be a major predisposing factor to melanoma. Using comparative genomic hybridization (CGH), the copy number (stability) of different genes associated with cancer was determined in several skin biopsies that had different degrees of sun exposure. BRAF mutations with no copy number increase were found in skin with no chronic sun damage (CSD). BRAF mutations are a possible driver of chromosome 7 gain in melanoma. Mutations in BRAF were also associated with a loss of chromosome 10 including PTEN. Melanomas on

glabrous skin (non-hair bearing) exhibited a higher frequency amplification of cyclin D1. CGH also showed chromosome loss or gain of several other chromosomes as well. It is suggested that the mutational mechanism for melanoma will be different in different anatomic sites and is most likely due to different levels of sun exposure. More detailed comparisons are necessary to identify potential candidate genes in cases with no detectable mutations in the MAP kinase pathway.

Marjan Huizing (NIH) spoke on "The cell Biology of Hermansky Pudlak Syndrome". Hermansky Pudlak syndrome (HPS) is an autosomal recessive genetic disorder which includes albinism, absence of dense bodies, ceroid deposition, pulmonary fibrosis (PF), and colitis. Seven human genes had been associated with HPS. HPS1 and 4 are most the severe, having PF which can be life threatening. The other types of HPS are less severe, usually not having PF. Of 112 patients analyzed, 20-30 have an unknown subtype. Determining the subtype is important for proper prognosis. At this point, fibroblasts are used for screening HPS subtypes. Fibroblasts were immunostained for a number of proteins to determine the biology of the different HPS types. Fixed fibroblasts were initially stained for LAMP3 using F-actin as a control. HPS1 and HPS4 were found to be less dendritic than the other HPS types, including HPS3, 5, and 6. HPS3 was found to be normal and HPS5 and 6 exhibited a slight defect. HPS5 can be diagnosed using this technique as seen by altered LAMP3 staining in fibroblasts. In the case of mutations within pearl, mocha, and HPS2, AP3 complex tyrosinase does not reach melanosome. Current analysis can distinguish HPS1 and HPS4 but not HPS3, HPS5 and HPS6.

Amanda Heilp-Wooley (NIH) spoke on "Localization and Clathrin Binding of the Hermansky Pudlak syndrome type 3 Protein". HPS3 is a relatively mild subtype of HPS with no pulmonary fibrosis. The murine locus for HPS3 is *cocoa*. This is a member of the BLOC2 complex along with HPS5 and 6. HPS3 contains a Clathrin binding motif, LLDFE, indicating a possible interaction between HPS3 and clathrin. Data given in the talk showed that HPS3 protein has a functional clathrin-binding domain and is important for proper trafficking of endosomal and lysosomal vesicles in both fibroblasts and melanocytes

Avner Ittah (Florida International University) spoke on "Early Over and Mis-Expression of Endothelin Receptor B Causes Coat Color Spotting"

Dopachrome Tautomerase (DCT) is the earliest temporal marker for melanocyte development. It is also known that endothelin 3 (*edn3*) regulates the expression of many melanocyte genes. The *edn3* gene was expressed in transgenic mice using the nestin gene enhancer. This results in the over expression of *edn3* during stages E 8.5 to 10.5 throughout the entire neurotube. Nes-Ednr mis- and over expression does not affect neuronal fate. It did produce some hypopigmentation as spotting defects. This phenotype was augmented when the transgene was placed on a piebald lethal (*ednrB* null) background. The hypopigmentation is possibly a result of sequestering of *edn3*. Over expression of EDN3 rescues the Nes-EdnrB phenotype

Ana Luisa Kaderkaro (University of Cincinnati) spoke on the "Implications of the Survival Effects of α -MSH and Endothelin-1 on the Repair of UV-Induced DNA Damage and Genomic Stability of Human Melanocytes." α -Melanocyte stimulating hormone (α -MSH) and endothelin 1 (*Edn1*) are important for melanocyte survival. ET1 and α -MSH after irradiation with UV will protect albino melanocytes. ET1 and α -MSH cause the phosphorylation of several proteins that effect cell survival. Rate of repair of cyclobutane nucleotide dimers (CPD) UV damage is increased by functional MC1R. α -MSH allows for the restoration of genomic stability of human melanocytes and loss of function mutations in MC1R reduce the DNA repair capacity of melanocytes, increasing the possibility of transformation.

Douglas C. Wallace (University of California-Irvine) gave an invited lecture on "The Mitochondrial Role in Aging and Cancer". Cells contain from 100-1000 mitochondria. All mitochondria proteins are necessary for oxidative phosphorylation (OxPhos). With time there is an accumulation of mutations providing an aging clock for disease. This is different than observed with a Mendelian disorder. As individuals age, their mitochondria accumulate mutations resulting in the production of oxygen radicals. This inhibition of mitochondria, due to mutations, results in an increase of electrons and an increase in reactive oxygen species (ROS). The production of ROS will eventually contribute to cancer and aging. When mitochondria are not working well, with an increase in ROS, the cell will go through apoptosis. There is also an association between prostate cancer and changes in mtRNA. This has been shown by observing changes in mitochondrial complex I (COI) transcripts. Prostate cancer frequency

increases with COI mutations. African Americans have ancient COI variants that are associated with increases in prostate cancer. About 25% of these ancient polymorphisms are adaptive and allowed populations to move into colder climates. Some of these variants are also associated with longevity, and predisposition to Parkinson and Alzheimer Disease.

Session II- Mechanisms of Melanocyte Proliferation and Differentiation

by Francois Rouzaud

The second session of the conference was held on Friday, June 25th and focused on the mechanisms of melanocyte proliferation and differentiation.

Ruth Halaban (Yale University) presented a 20 min invited lecture about novel pathways involved in the transformation of melanocytes to melanoma cells assessed by the microarray technique. She presented evidence that several groups of genes including those belonging to the receptor activity (like the insulin growth factor or FGFR1) were up-regulated in melanoma. The lecture described then several pathways that are modified in melanoma. Among them, NOTCH signaling has been shown to determine proliferation, differentiation, and, more recently, apoptosis in several mammalian cell types, and TWIST, a transcription factor essential for tumor metastasis which is described as a potential prognostic marker. The interferon pathway was also shown to be down-regulated as well as the genes coding for Ras-members small GTP-binding proteins or growth suppressors like Necdin (neurally differentiated embryonal carcinoma-cell derived factor), one of four known protein-coding genes that are deficient in people with Prader-Willi syndrome (PWS). The data presented is used as a basis for further evaluation of the genes for which the expression is modified in melanoma as pathways leading to malignant transformation, prognostic markers and/or as drug targets.

The second invited lecture of the day was then given by **Ann Richmond** (VA Medical Center) about NFkB that is constitutively activated in melanoma and therefore offers a potential target for therapy. The work presented is part of a larger goal to establish therapies for a number of chronic inflammatory conditions and cancers, including malignant melanoma. The inhibition of NFkB activity by IKK inhibitor BMS-345541 or PS-341, a 26S proteasome inhibitor lead the authors to test these drugs in a nude mouse xenograft model for ability

to inhibit the growth of human melanoma tumors. Evidence was presented that the nuclear translocation of NFkB was hampered and that the hyper-proliferation of melanoma cells was stopped. BMS-345541 was capable of inducing melanoma apoptosis through down-regulation of IKK activity and suppression of NFkB-dependent transcription in melanoma. The BMS-345541 inhibition of NFkB dependent transcription blocked the over-expression of the chemokine CXCL1, a secreted factor that induces IKK activation in melanoma through an autocrine mechanism. Treatment by proteasome inhibitor significantly reduced the growth of melanoma cells in vitro and showed reduced tumor growth in the nude mouse model. Taken together, the results presented suggest that NFkB can be considered as a target for melanoma therapy.

Then, the session moved on with a series of competitive lectures. The first one was given by **James Fryer** (University of Minnesota) who presented his study on the 5' distal enhancer of the tyrosinase gene. The project presented was based on the fact that about 15% of OCA1 alleles do not show any mutation in the coding sequence of the tyr gene, suggesting that regulatory regions have to be investigated in order to find novel mutations responsible for an inactivation of tyrosinase. The speaker presented sequences located in 5' and which are shown to be critical for full activation of reporter genes. Proceeding with sequential deletions in the 5' region, reporter genes activity is tested in order to identify regulatory sequences and therefore regulatory elements in the non-coding part of the human tyrosinase gene in an effort to better understand the mechanisms of OCA1.

The following lecture presented by **Francois Rouzaud** (NIH) focused on the patterns of expression of two isoforms of MC1R, namely MC1R317 and MC1R350 with respect to their amino-acid lengths, in human melanocytes and skin of various pigmentation and ethnic origin upon stimulation by MSH and UVR. MC1R350 is a novel isoform that contains an additional 33 amino-acid sequence in its C-ter, including 5 Cys residues. Both isoforms expression was studied at the mRNA and protein levels, and evidence was presented that MC1R317 expression correlates well with the total melanin content whilst MC1R350 doesn't. Measurements after stimulation by MSH or UVR showed that if MC1R317 increased its expression, the response of MC1R350 was more heterogeneous, opening avenues to further investigations in order to fully analyze the expression of the MC1R isoforms to

better understand the role of MC1R350 in pigmentation and melanoma susceptibility and its interactions with MC1R317.

Bill Pavan (NIH) presented a lecture about the promotion of melanocytes expansion from the neural crest through the stimulation of the WNT signaling pathway. The model used is a transgenic mouse that expresses the TVA cell surface receptor, thus rendering the cells susceptible to infection with avian RCAS viruses. The system allows for precise spatio-temporal introduction of genes into selected cell types, making it an ideal system for studying the roles of genes expression in neural crest derived cells during development. The fate of neural crest derived cells, originally mostly smooth muscle cells could be biased to melanocytes by inducing the canonical WNT signaling pathway through intrinsic over-expression of WNT3a or by treatment with soluble WNT3a. WNT1 was shown to act in a distinct mode of action to expand melanocytes by paracrine signaling on melanoblast precursors.

Yuji Yamaguchi (NIH) reported that the topographic regulation of melanocyte differentiation is differentially regulated via mesenchymal-epithelial interactions by fibroblasts derived from palmoplantar and nonpalmoplantar skin. Evidence was presented that the density of melanocytes in skin on the palms and soles is five times lower than that found in other sites of the body in adult humans. Co-culture with palmoplantar fibroblasts significantly decreased melanocyte function, as measured by effects on proliferation and on the production of melanosomal proteins and melanin. Palmoplantar fibroblasts showed high expression levels of DKK1 (an inhibitor of the canonical wnt signaling pathway), whereas nonpalmoplantar fibroblasts showed higher expression levels of DKK3. Transfection studies revealed that DKK1 could indeed decrease melanocyte function, probably through the inactivation of MITF, which can be suppressed by the decreased expression of beta-catenin. Thus, the results presented provide a basis to explain why the palms and soles are generally hypopigmented and why melanocytes stop migrating in palmoplantar areas during human embryogenesis.

The session was then ended by two invited speakers, the first one being **Estela Medrano** (Baylor College of Medicine) giving a lecture about the epigenetic regulation of senescence in human melanocytes. Epigenetics defines all meiotically and mitotically heritable changes in gene expression that are not coded

in the DNA sequence itself, and that arise during development, cellular proliferation and in the environment. Epigenetic modifications consist of DNA methylation, histone post-transcriptional modifications including methylation, acetylation and phosphorylation, and ATP-dependent, structural modifications of chromatin. Epigenetic silencing is almost universally associated with histone deacetylation, which is catalyzed by at least three classes of HDACs in human cells. The work presented focused on HDAC1 which expression is increased in senescent NHM, resulting in the transcriptional silencing of the cyclin E gene. Evidence was presented that increased HDAC1 activity coincides with increased levels of trimethylated Lys9 of Histone H3, a critical modification in the regulation of epigenetic transitions in chromatin. Increased HDAC activity appears to be causally related to cellular senescence, as overexpression of a dominant negative p300 histone acetyltransferase (p300DN1572-1903), or treatment with Lys-CoA, a specific chemical inhibitor of p300 results in irreversible growth arrest and senescence of normal human melanocytes. Taken together, the results presented suggest that targeting HDAC activity and DNA methylation could offer great promises, as hypoacetylation of histones leads to cellular senescence in NHMs, and that cellular senescence functions to suppress tumor formation.

The final presentation of the session was the Aaron B. Lerner award lecture given by **John Pawelek** (Yale University School of Medicine). The talk titled "Melanoma pigmentation and progression: some things new under the sun" focused on melanosomes packaging differences between NHM and melanoma cells. Melanosomes are the membrane delimited organelles in which the synthesis and storage of pigment in melanocytes and other pigmented cell types are accomplished. In a survey of pathology specimens of more than 500 primary and metastatic melanomas, and at least some melanoma cell lines, melanosomes were frequently packaged as coarse melanin, autophagic vesicles containing multiple melanosomes and previously described in invasive human melanomas. Those melanoma cells produce more melanin than NHM and are responsible for hypermelanotic areas of primary cutaneous melanomas. The work presented analyzed cell lines producing coarse melanin for beta1,6-branched oligosaccharides, gp100/pm1-17 (a melanosomal structural component) and CD63 (a late endosome/lysosome component associated with melanoma and certain other human cancers). Coarse melanin granules co-localized with stains for beta1,6-branched

oligosaccharides, gp100/pmel 17, and CD63. It was also reported that amelanotic melanomas often show similar coarse melanin vesicles positive for the same markers, therefore indicating that melanosomal packaging and trafficking cannot readily be extrapolated between normal and malignant melanocytes. It was mentioned that elevated expression of beta1,6-branched N-glycans, concurrent with the production of coarse melanin is a significant risk factor. Thus, understanding the molecular genetic mechanisms linking altered glycosylation with pigmentation, coarse vesicles, and metastatic progression is of considerable interest.

Session III, Properties of Melanin and Melanosomes by Pat Farmer

The session started off with a presentation by **Esteban Dell'Angelica** from UCLA on the family of BLOC proteins involved in the biogenesis of lysosomes. These proteins were identified in the autosomal recessive disorder Hermansky-Pudlak Syndrome, or HPS, which cause albinism from disruption of the melanosome formation. Working in murine HPS models, they have identified several HPS proteins connected to the phenotype and compared them with the better known family of similar proteins from yeast. Various combinations of these proteins form stable protein complexes termed the "Biogenesis of Lysosome-related Organelles Complexes" BLOC-1, -2 and -3. The implication is that these protein complexes, formed from pools of various HPS proteins in the cytosol, ultimately control suborganelle biogenesis and membrane fusion, and by extension the pigmentation.

The second speaker, **John Simon** from Duke University, described recent work on the structure and metal-binding properties of melanin particles isolated from *Sepia officinalis*. His group has previously used AFM and SEM imaging to study the structural properties of melanin particles from *Sepia*, and developed very nice ways of handling and removing the protein coating by enzymatic digestion. An interesting result was that EDTA treatment of such melanin particles removes a large majority of the metals ions adsorbed within such particles. Using ICP, they could then study the loading of various metal ions such as Fe and Zn into these particles. By looking at sequential competitive loadings of the same samples, they suggested that Ca and Mg ions exchange with the same binding sites and that Fe bound to different sites. Most recently, they have used photo-emission spectroscopy to measure the apparent

oxidation potentials of melanin samples; their initial data suggest that pheomelanin is substantially more easily oxidized than eumelanin. Questions asked included the inherent role of metal ions in melanin aggregation, and possible redox-cycling by pheomelanin in vivo.

Pat Farmer (University of California – Irvine) spoke next, first giving a broad overview of the metal-induced pro-oxidant response of melanins that generates ROS like superoxide and hydroxyl radicals. Using this method as an assay, several metal ions were investigated first with synthetic melanin, and then against melanoma in culture. Of these, Cu(II) is dominant, but In(III) also showed surprising anti-melanoma activity in vitro. The metal-sensitivity of melanoma was first described by Borovansky, and suggested to be due to exposed melanin within this cancer. Farmer's group have shown that Cu and Zn dithiocarbamate complexes have high toxicity to melanoma that is enhanced under oxygen. The toxicity of disulfiram, a dithiocarbamate derivative widely used for anti-alcohol abuse treatment, is also tied to the intracellular uptake of Cu. A new x-ray fluorescence technique was used to image the intracellular Cu ion distributions associated with DSF treatment.

Tad Sarna, from the Jagiellonian University, described his recent studies on the antioxidant and photoprotective properties of iridial melanins from human and bovine eyes. The key question addressed was how melanins photoprotective abilities change with age, as measured by photoreactivity and antioxidant properties. Human samples were pooled by age and color, as well as bovine and human; the eu- and pheomelanin ratio determined by the Ito method and correlated by EPR spectra, but only small differences seen. Largest differences were observed for the photoconsumption of oxygen, with human melanin more photoreactive than bovine, and importantly, samples from older patients more reactive than younger. This difference was enhanced in the presence of ascorbate, thus the gist of the work suggests that the anti-oxidant ability of iris melanin decreases with age.

Frank Meyskens, UC Irvine, presented his theory on the missing attributable risk in the pathogenesis of melanoma- that a chemical insult, from heavy metals or redox-active agents, may be a causative factor in melanoma carcinogenesis, engendering a pro-oxidant response from the catecholic melanin species that induce oxidative stress and mutation. Melanogenesis is slow, the product of multiple mutations over the

lifetime of a melanocyte, assumed to be due to multiple oxidative injuries. Epidemiologically, a 1.5 to 4.0 fold increased risk is seen in the electronics and chemical industries, where such exposure might occur. Pawlek asked specifically what the role of the metal might be, as a promoter of ROS solely, as it affects growth pathways such as angiogenesis or turn on responses of various transcriptional factors. Wickes noted his earlier hypothesis that inhibition of melanogenesis might be the key to metastasizing melanoma, as inhibition of the pathway decreases mutagenesis and prevents immunosuppression.

Gertrude Costin from the NIH spoke on the effect of mutations of dopachrome tautomerase, Dct, on the eu-/pheomelanin ratios and enzymatic activity in murine models. Samples of DCT-mutant melanocytes were obtained from Slaty and Slaty-lite mice, the Slaty contains a mutation in the Zn-binding site, Slaty-lite in a membrane-binding domain. The membrane-binding mutation had a greater effect on Dct and tyrosinase activity. Dct activity apparently helps determine the preference for either the eu- or pheo-melanin pathways.

Julio Valencia from the Hearing lab at NCI described his work in understanding the trafficking of Pmel17, a melanosomal membrane protein, and its control by various clathrin adaptor-proteins (AP complexes). By fractionating purified murine melanosome samples, and then using mass spectrometry immunoblotting, they looked at colocalization of Pmel17, tyrosinase and the AP complexes. Early melanosomes had AP1 and 2, but not Pmel17 or AP3 and 4. Their results suggest specific roles for different AP complexes as possible carriers of Pmel17 and tyrosinase to melanosomes.

Toshihiko Hoashi, also from the Hearing lab, spoke on the analysis of melanosomal proteins by RNAi, a new approach to using siRNA to downregulate gene expression; in addition they transfected genes back into knockout cells to rescue the phenotypes. Using this methodology, he found that the MART1 protein is important in trafficking of proteins to target organelles.

Mary Hendrix, Northwestern Children's Research Institute, spoke of the "Plasticity of Human Melanoma", using a proteomics approach to discern the importance of microenvironments on the phenotype of melanoma cells. They isolated different subpopulations of cells from tumor samples, and analyzed gene and protein expression, and histopathology. The most aggressive

cell populations generated vascular systems in vitro culture, and also expressed stem cell markers (e.g. matrix metalloproteinase activity, endothelial adhesion, and variety of overexpressed genes). This suggests a stem cell origin for tumor components- potentially a new target for treatment and prevention. There were several questions regarding the extracellular effect on epigenetic differences between primary and metastatic tumors.

Miri Seiberg, from Johnson & Johnson, finished the long session with a case study overview of the workings of translational research in industry- from target identification, discovery research, clinical development and regulatory review. The story starts with the discovery of the Protease-Activated Receptor-2 (PAR-2) expressed in keratinocytes, a phagocytic receptor that is tied to skin color. Certain soybean products contain proteins that inhibit PAR-2, can be extracted from non-denatured soy, but heating or denaturation kills these inhibitors. Identification of these proteins led to further research and insight into the mechanism of action; but ultimately, the products that have made their way to market utilize natural soy extracts. These have an amazing array of uses, from lightening skin color, enhancing skin elasticity, delaying hair growth, and even inhibiting carcinogenesis.

Session IV. Newer Animal Models of Pigmentary Abnormalities and Melanoma *by Richard Swank*

Zalfa Abdel-Malek (Univ. of Cincinnati), the current PASPCR president, delivered the President's Talk, highlighting several years' research in her laboratory on the role of paracrine factors in UV signaling in human melanocytes. Zalfa, who is motivated by the importance of cutaneous pigmentation in photoprotection, introduced the talk with an appropriate cautionary note on a possible increase in UVC exposure due to environmental degradation. Both autocrine and paracrine factors including endothelin-1, alpha MSH and ACTH mediate the responses of human melanocytes to UV. This research group demonstrated that the melanogenic response of human melanocytes to UV involves the activation of the cAMP pathway. More recently they found that endothelin and alpha MSH inhibit apoptosis of human melanocytes after UV exposure. Melanocytes irradiated with UV mount an immediate response to ensure their survival and genomic stability and a latent response including increased melanin synthesis to protect from further UV exposure.

Michael Pickart (Univ. of Minnesota) reported on the exciting genetic and developmental studies potential of the zebrafish, a very new animal model for the study of pigmentary abnormalities. As one example, morpholinos were used for the targeted knock-down of tyrosinase expression, an experiment which demonstrated the conserved nature of this gene in pigment development. Thirteen percent, or 21 of 157 genes studied, were found to affect zebrafish melanophores, demonstrating the potential of this system for the discovery of novel genes regulating pigmentation during development. Nearly all genes implicated in vertebrate pigmentation are found in zebrafish, confirming the value of this system in the study of conserved genes involved in vertebrate pigmentation.

Francis Noonan (George Washington Univ. Medical Center) presented data on a new mouse model of UV-induced melanoma. These mice are transgenic for hepatocyte growth factor/scatter factor (HGF/SF) driven by the metallothionein promoter, retain high numbers of extra-follicular melanocytes throughout life and develop spontaneous dermal melanomas upon aging. This is a promising model that strongly recapitulates human disease in etiology, histopathology and molecular pathogenesis. Melanomas appear at 6-9 months with a high incidence only in animals receiving neonatal UV irradiation. About 20% of UV melanomas showed metastases to multiple organs. The neonatally irradiated HGF/SF model thus allows assessment of environmental risk factors and the mechanism of induction and progression of UV-induced melanoma. Dr. Noonan's data indicate that, in contrast to predictions from the *Xiphophorus* fish model, UVB rather than UVA is sufficient for melanoma initiation in this model.

Mingke Yu (Univ. Southern California) studied the contribution of melanin to patterns on the feather vane of the Barred Plymouth Rock and Silver Laced Cochin chickens. He showed that tyrosinase activity is turned on before any visible melanin formation during melanoblast differentiation, persisted through the peak of melanin synthesis and gradually disappeared with the completion of feather development. Tyrosinase activity is dynamically regulated with a pulse-like on/off pattern that accounts for the feather pigment pattern.

Sreenivasulu Chintala (Roswell Park Cancer Institute) reported on the subtle gray (sut) mouse, which is a model for a mild form of Hermansky-Pudlak

Syndrome and affects pheomelanin pigment production. To more clearly visualize the effects of the mutation on pigmentation, the sut gene was incorporated into the yellow semidominant background which is yellow due to overexpression of the agouti locus. A marked decrease in yellow pigment phenotype, with no effect on eumelanin, was observed on this background, a result confirmed by chemical analysis of eumelanin and pheomelanin in mutant hair. It appears that the sut gene causes reduction of pheomelanin pigmentation rather than a replacement of pheomelanin with eumelanin as is the case in MSH receptor related mutants such as mahogany and mahoganyoid.

Roman Garcia (Florida International Univ.) showed that endothelin3, a 21 amino acid polypeptide, is crucial to the normal development of melanocytes. He utilized a tetracycline inducible endothelin3 gain-of-function transgenic mouse model to target endothelin3 to keratinocytes of the skin. Such transgenic mice have areas of pigment in foot pads, external genitalia, ears and other areas not normally pigmented in control mice. These findings suggest that endothelin3 is not acting as a migratory factor similar to Steel factor.

Jennifer Hauser (Univ. of Cincinnati) investigated the induction and repair of UV-induced DNA damage in cultured human melanocytes with different melanin content and either functional or non-functional melanocortin 1 receptors. Induction of damage photoproducts was inversely related to constitutive melanin content in neonatal as well as adult human melanocytes. Two loss-of-function mutations in the MC1R gene had lack of repair up to 36 hours after UV irradiation. These results confirm the photoprotective effect of melanin and suggest the significance of the melanocortin receptor in restoring genomic stability through regulating DNA repair. They also offer an explanation for the association of loss of function mutations in the melanocortin receptor gene with increased risk for melanoma.

Manickam Sugumaran (Univ. Massachusetts) utilized a bioinformatics analysis coupled with molecular biological studies on *Drosophila* mutants to analyze the function of unannotated genes associated with the melanogenic and sclerotinogenic pathway. The Flybase website was searched for mutant fly stocks that were described as "body color defective". In the Freckled (Frd) stock, a 11 base pair deletion was identified in the coding domain of a prophenoloxidase. For the tyr-1 stock a point mutation was identified in the catalytic domain

of a trypsin protease likely involved in activation of prophenoloxidase. For black, an upstream deletion was identified in aspartate decarboxylase, which is necessary for the biosynthesis of the insect sclera.

Eugene Gerner (Arizona Cancer Center) reviewed the functions of the naturally occurring cations spermidine, spermine and putrescine, which are essential for normal growth and development of mammals. In mammals ornithine decarboxylase (ODC), the first enzyme in polyamine synthesis, is a target of c-myc, a transcriptional regulator of survival and apoptotic responses of several cell and tissue types. In humans with familial adenomatous polyposis aberrant expression of ODC appears to be at least partially responsible for intestinal cancers. The expression of other genes involved in polyamine metabolism is influenced by oncogenes and common nonsteroidal anti-inflammatory drugs. Aspirin reduces the risk of adenoma recurrence in humans with the appropriate ODC genotype by up to 90%. The polyamines mediate cell phenotypes, at least in part, by affecting patterns of gene expression. For example, a novel amino acid, termed hypusine, in the putative eukaryotic translation initiation factor 5A is formed by modification of a lysine residue and spermidine. This modification in turn regulates features of RNA processing. Altogether, unique features of polyamine metabolism are attractive targets for treatment of cancer.

Session V - Non-Malignant Abnormalities of Pigment Cells *by Vincent Hearing*

This session comprised a series of invited lectures and competitive lectures on topics ranging from developmental biology to genetics to pigmentary disorders (vitiligo and HPS) and responses to UV.

Martin Garcia-Castro began the Session by presenting an Invited lecture that was an overview of that group's work on the avian system. Neural crest cells are an active stem cell population which can migrate and give rise to the peripheral nervous system, endocrine cells, melanocytes, etc. He focused his presentation on the role of Pax7, which is important in determining the fate of neural crest cells, as is Pax3. Pax3 has been shown to be involved in various forms of Waardenburg Syndrome but so far Pax7 has not been similarly associated with an inherited pigmentary disease. Pax7 works through the Wnt signaling pathway, and regulation of Wnt function is sufficient to induce the specification

and development of neural crest cells. Pax7 regulates Sox10 expression (as does Pax3). Noggin, a BMP inhibitor, completely blocks the development of neural crest cells. They used morpholino antisense inhibition as an approach to study these processes.

Murray Brilliant then summarized in another Invited lecture what is known about the genetics of albinism and the pigmentation of skin, hair and eyes. He reviewed the various types of OCA (1 through 4) and their mechanisms of dysfunction in the context of genes known to cause them (Tyr, Tyrp1, P and MATP). In a study that will eventually involve 1,000 subjects, 800 individuals have been characterized so far. They have detected 52 polymorphisms in 16 different genes that are associated with variations in skin, hair and/or eye pigmentation. MATP, ASIP and P genes are 3 primary genes involved in determining skin color (assessed by reflectance) and these account for 66% of the cases (obviously other genes are also functional at this level). Hair color is determined by MATP and P primarily (for the amount of melanin), and that accounts for 75% of the variants in the amount of melanin in human hair. The ratio of eumelanin to pheomelanin in hair is primarily (68%) determined by MC1R and ASIP. Eye color is not so clearly defined.

Those Invited lectures were then followed by 5 Competitive lectures selected from submitted abstracts. **Dilshika Wijesekera** discussed the role of oxidative stress in the loss of melanocytes in chickens (70% of Smyth line [SL] chickens develop progressive vitiligo). Their study suggests that autoimmunity plays an active role in the process but that initiation of the depigmentation probably results from some type of environmental factor, perhaps oxidative stress and the generation of reactive oxygen species (ROS). They examined the antioxidant capacity and markers of oxidative stress in the blood and regenerating feathers of SL chickens, and determined levels of lipid peroxidation and lipid soluble antioxidants using HPLC and other assay methods. There were higher levels of lipid peroxidation and lower levels of antioxidants in vitiliginous chickens compared to normal, non-vitiliginous chickens.

Becky Lockhart then continued this theme of research from the Erf laboratory, i.e. studying vitiligo in SL chickens as a model for human vitiligo. She discussed the hypothesis that an imbalance of stress leads to the induction of vitiligo and they monitored the generation of ROS in cells cultured from chicken feather bulbs.

GSH was increased in SL chickens although not at a statistically significant level. ROS activity in melanocytes was not different, but in intact feathers, ROS levels were higher in SL chickens compared with Light Brown Leghorn (LBL) controls. Melanocytes derived from SL chick embryos were inherently sensitive to lipid peroxidation, and that, combined with the higher levels of ROS, may contribute to the death of those melanocytes.

Vince Hearing then discussed his laboratory's collaborative research project on the effects of UV on human skin of varying racial/ethnic types. This study examined 110 normal human subjects which were placed in 11 different groups (10 subjects each). Each subject was irradiated with 1 MED UVA+UVB and shave biopsies of skin were taken before, immediately after, 1 day after and 1 week after the UV exposure. The DNA damage levels show the important role of melanin in reducing photodamage to underlying cells and those data were published a year ago in FASEB J. This talk reported the further analysis of those sections with respect to melanocyte density, expression of various melanocyte specific proteins, and the distribution of melanin. The density of melanocytes in Caucasian (C), Asian (A) and African-American (B) skin was virtually identical and was not changed within 1 week of UV exposure. Constitutive MITF levels were similar in all skin types, as were the expression of TYR, TYRP1, DCT, GP100 and MART-1, although the melanin content reflected visible levels of constitutive pigmentation. MITF levels increased at 1 day and 7 days after UV exposure, as did levels of TYR and GP100; the other melanosomal markers were only minimally affected within this time frame. The most dramatic change was the redistribution of existing melanin in the skin, and the relative amount in the basal layer was reduced by 15-20% after 1 week, while that in the middle layer of the skin was increased by a comparable amount, thus leading to the increased 'tan' of the skin visible by eye.

Eugene Elmore then reported on the development of an assay for determining prevention of human melanoma (or agents that can act in that fashion). They found that E-cadherin and N-cadherin are excellent markers for melanoma-genesis since their expression patterns are radically different in normal versus transformed melanocytes. They also used HLA-DR and Annexin V as suitable markers. Expression of E-cadherin is dramatically decreased following UVB irradiation and was the most sensitive marker tested

for radial growth phase (RGM), vertical growth phase (VGM) and metastatic (MM) melanomas. Cells were cultured for several days in the presence of agents to be tested, were then removed from them for 1 day during which time the cells were exposed to UVB, and then were further cultured in the presence of the agents until testing. They found that RGM melanoma cells were the most responsive to such preventive agents and that E-cadherin may be the most sensitive marker to assess. They found that DFMO was more active than 4-HPR, which was more potent than nimesulfide, 9-cis-RA and then polyphenon E in turn (several other agents tested were inactive).

Raymond Boissy then discussed the etiology of vitiligo, which contains genetic, immune and stress components. He discussed how TYRP1 may be involved in the susceptibility to cytotoxicity to phenolic derivatives (especially 4-tert-butylphenol, 4TBP) which is commonly involved in contact sensitivity. They examined whether melanocytes from vitiligo-susceptible individuals are genetically disposed towards inefficient survival when faced with various types of stress / trauma. They found that when vitiligo-susceptible melanocytes were stressed, they underwent apoptosis which triggered an immune response, which could then lead to further melanocyte destruction by the immune system. They found a good correlation between stress induced by 4TBP and apoptosis, and this was accompanied by decreased expression/function of MITF. Addition of catalase could abrogate the cytotoxic effects of 4TBP. Their hypothesis is that melanocytes from vitiligo-susceptible individuals are not resistant to various forms of stress and that this leads to the progressive loss of melanocytes in vitiliginous skin.

Jo Lambert ended the session by reporting on the function of Rab27B in Griscelli syndrome (GS). They had previously found that some patients with GS did not reveal mutations in any of the 3 genes linked to that disease (Rab27A, myosin VA and melanophilin). Interestingly, in one GS patient with normal skin pigmentation, the deletion of Rab27A function was associated with impaired, but not complete loss, of melanosome distribution in melanocytes. They suspected that Rab27B, which shares 71% homology with Rab27A and has similar functional characteristics, was able to at least in part substitute for Rab27A. They used confocal immunohistochemistry and yeast 2 hybrid screening to show that Rab27B can indeed form a complex with melanophilin and co-localizes with melanosomes. PCR analyses showed that expression

of Rab27B was up-regulated in this GS patient and was thus able to reduce the effects of Rab27A deletion.

Session VI - Advances in Understanding the Biology of Melanoma and its Consequences
by *Alistair J Cochran and James Grichnik*

David S. Hoon, PhD. Of the John Wayne Cancer Institute presented a talk titled "*Clinical Utility of Serum and Tissue Molecular Markers as Prognostic Factors of Malignant Cutaneous Melanoma.*" His efforts have focused on the detection of metastatic melanoma cells within sentinel nodes or circulating in the blood. Recent efforts have not only demonstrated the utility of PCR based approaches to upstage sentinel nodes not identified as positive through routine and immunohistologic methods but also to give further prognostic information on the basis of the number of markers expressed. Free circulating tumor DNA was also noted to be useful as a potential predictor of treatment response.

Alistair J. Cochran, M.D. of the University of California Los Angeles presented a talk titled "*Update on the Sentinel Node Procedure.*" His efforts have focused on optimizing the sentinel node evaluation to guide prognostic and therapeutic decisions. Knowledge of the nodal architecture allows for efficient pathological evaluation. The area of tumor (as a percentage of the node) and dendritic cell area and density all are predictors of melanoma risk. Conventional pathologic approaches may in the future be supplemented by the techniques of molecular pathology. The sentinel node procedure is the best source of accurate prognostic information for patients with early stage melanoma. Information on the effect of this procedure on survival awaits outcome analysis of ongoing and recently completed clinical trials.

Susan McNulty, Ph.D. of the University of California Irvine presented a talk titled "*Effects of CK2 Inhibition in Melanoma.*" Her efforts have been focused on inhibition of CK2 with apigenin. While NFkB complexes containing p50-dimers alone or complexed with RelA and cRel can be identified in controls, apigenin results in a single major band containing RelA and RelB but not p50. Therefore inhibition of CK2 may lead to a shift in NFkB DNA interactions due to the formation of alternate dimer pairs which may affect the mitotic checkpoint in cells. The apigenin treatment also resulted in increased apoptosis in the setting of decreased survivin protein and mRNA.

Hiroyoski Inoue, M.D. of Sapporo Medical University (Hokkaido, Japan) presented a talk titled "*Gene Analysis of Melanocortin 1 Receptor of Japanese Malignant Melanoma.*" His efforts have been focused on melanocortin 1 receptor polymorphisms and have shown that in contrast to the 30 MC1R polymorphisms detected in the Caucasian subjects only 4 were identified in the Japanese. One mutation was found at high frequency in the Japanese population compared to the Caucasian population (Arg163Gln) but this was not related to melanoma risk. A second mutation, Val92Met was correlated with a 2.3 fold increased frequency in melanoma patients compared to controls.

John P. Fruehauf, M.D., Ph.D. of the University of California (Irvine) presented a talk titled "*Dysregulation of Angiogenesis Promotes Melanoma Progression: A Potential Target for Chemoprevention.*" His efforts have focused on the role of angiogenesis in the progression of neoplasia. Dysplastic nevi were found to have increased expression of VEGF compared to banal nevi but did not have the increase in vessel counts seen in melanoma. Hypothetically this was due to retention of angiogenesis suppressor signals in the dysplastic nevi that were lost in melanomas. Thus it was suggested that angiogenesis inhibitors might be able to prevent transition to the malignant phenotype.

Rong-Rong Huang M.D. of the University of California Los Angeles presented a paper entitled "*MHC-Class II molecules expression by dendritic cells correlates with activated OPD4+ T cells in sentinel and non-sentinel lymph nodes from melanoma patients*". This reports an evaluation of the immunobiology of the regional nodes in melanoma patients. Using single and cocktail triple immunohistochemical staining they evaluated 18 sets of tumor free sentinel (SN) and non-sentinel nodes (NSN) for the frequency of antigen-presenting dendritic leukocytes (DL) expressing MHC-class II molecules and the frequency of DC-associated OPD4+ activated T cells. The area occupied by MHC-class II + DL and their density is significantly reduced in SN relative to NSN as is the density of OPD4+ T cells. These findings support the view that SN are immune down-regulated. Significant variation in these indices between the quadrants of SN, variation that exceeds that seen in NSN, supports the view that SN are influenced by extra nodal (tumor) cell products that are delivered via the

afferent lymphatic. Tumor-related nodal immune modulation may facilitate the establishment of metastatic melanoma in the SN.

James Grichnik M.D., Ph.D. of Duke University Medical Center delivered his paper

“*Side population analysis for the identification of melanoma “tumor stem cells”*” He reported studies of the possibility of identifying melanoma “tumor stem cells” that are likely to be critical for tumor maintenance and spread. Using flow cytometry they examined melanoma cultures for the presence of “side population” cells, cells that have a high capacity to exclude Hoechst 33342 dye and that are reported to be enriched for stem cells. They identified three sub-regions within the cultures, including an area of small melanoma cells that efficiently effluxed the dye. Relative to the other sub-components of the cultures studied, the cells from this area were notable for their enhanced ability to expand in culture. The authors believe that this subpopulation of cultured melanoma cells is rich in tumor stem cells with the critical ability maintain melanoma growth and facilitate the development of metastases.

Dahzi Cen M.D. of the University of California, Irvine presented a talk entitled “*Disulfiram facilitates intracellular copper transport that causes oxidative stress and cell death in human melanoma cells*”. This described one facet of the ongoing, innovative and timely efforts at UCLA to develop alternative therapies for chemoresistant melanomas. Melanoma cell lines from different stages of the disease are damaged by the redox-modulating agent disulfiram (DSF). The effects of DSF are enhanced in the presence of induced

enhanced intracytoplasmic copper (and are almost completely abolished in the presence of a copper chelator. The cytolytic effect of ionizing radiation is substantially increased in the presence of DSF. These novel approaches to drug-induced apoptosis of melanoma cells offer useful investigative avenues to the development of more effective alternatives to currently ineffective chemotherapy in the management of malignant melanoma.

Sun Yang Ph.D. of the University of California, Irvine delivered a paper “*Resveratrol induces AP-1 inhibition, altered AP-1 composition and increased expression of specific Jun and Fos family proteins in human melanoma cells*”. This paper reported a detailed enquiry into the pharmacological effects of Resveratrol, a compound with known therapeutic effectiveness on various animal tumors, on human melanoma. Resveratrol inhibited anchorage-independent growth of human melanoma *in vitro*, altered melanoma cell morphology and upregulated cell surface expression of MHC class I antigen and Fas. Expression and function of AP-1, Fra-1 and Fra-2 were altered while c-jun was not affected. Supershift assays revealed alterations in AP-1 composition after treatment. Overexpression studies showed reduced AP-1 transcription activity and TPA-induced transcriptional transactivation and increased MHC class I. H₂O₂ reversed inhibition of colony formation in the presence of complex intracellular effects. Restoration of AP-1 transcription signaling and reduced intracellular ROS are proposed as key to the phenotypic alterations associated with Resveratrol.

Positions - Wanted and Available

Postings for **Positions Available** will be open to all individuals and institutions so long as the position is related to pigment cell research. Postings for **Positions Wanted** will be open only to members of the PanAmerican Society for Pigment Cell Research or its sister societies (JSPCR and ESPCR). Send postings to Bill Oetting at bill@lenti.med.umn.edu. Please provide an expiration date for any submitted postings. Final decisions will be made by the Publications Committee of the PASPCR.

Postdoctoral position

A postdoctoral position available in the laboratory of Dr. Andrew Aplin in the Center for Cell Biology and Cancer Research at Albany Medical College, NY. Research will focus on the critical signaling proteins involved in anchorage-dependent cell growth of melanocytes and that may be aberrantly regulated in melanoma cells. Further details and recent publications can be obtained at <http://www.amc.edu/academic/research/CBCResearcher.cfm?ID=170>

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Candidates with a recent PhD or MD/PhD with a strong background in molecular and cellular biology are encouraged to apply. Excellent financial compensation and benefits are provided. Please submit a resume and the names of references to:

Andrew E. Aplin, Ph.D.
Center for Cell Biology & Cancer Research
Albany Medical College,
47 New Scotland Avenue
Albany, NY 12208
Email: aplina@mail.amc.edu

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Department of Dermatology Chair

The University of California, Irvine, College of Medicine seeks candidates for the position of Chair, Department of Dermatology. The candidate must be an accomplished investigator, clinician and teacher, eligible for appointment at the level of associate professor or professor, with leadership skills appropriate for a major university department. Send CV, plus names and addresses of at least three references to:

Frank L. Meyskens, Jr., M.D.
Chair, Dermatology Search Committee
c/o Kit Scott
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Dean's Office
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A Postdoctoral Position is available to study the role of UV radiation in the development of primary melanoma. The project will use transgenic and

pigment cell mutant mice and cell cultures to study molecular mechanisms of melanoma initiation and progression. A strong background in pigment cell biology, cellular mechanisms of toxicology, carcinogenesis, or molecular biology is desired. Send curriculum vitae, names of 3 references, and a brief summary of research interests to:

Faith M. Strickland, Ph.D.
Dermatology Research 4D49
Henry Ford Hospital
One Ford Place
Detroit, MI 48202
E-mail: FSTRICK1@hfhs.org
Phone: 313-874-3385
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Postdoctoral Research Associate

Fox Chase Cancer Center.
Two NIH-funded postdoctoral positions are available to work on the development of neural crest-derived melanocytes and enteric neurons in mice. We are interested in the signals required for proper migration and differentiation of these lineages during mouse embryogenesis and use various genetic manipulation techniques and existing mutants for our studies. Fox Chase Cancer offers competitive salaries to its postdocs and was recently named one of the best places to work for Postdocs (<http://www.fccc.edu/news/2003/Best-Places-for-Postdocs-02-20-2003.html>). Candidates with a recent PhD or MD/PhD with strong background in molecular biology, genetics or developmental biology are encouraged to apply. Please submit CV, and names of 3 references to:

Dr. Myung K. Shin
Program in Cellular and Developmental
Biology
Fox Chase Cancer Center
Philadelphia, PA 19111, USA
Email: MK_Shin@fccc.edu

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The Bibliography published in this issue covers the period June, 2004 through August, 2004. If you notice a paper that was not detected by this search that should be included, please send it to us and we will include it in the next issue. By its very nature, assignment of a reference to a particular category is arbitrary and we urge you to read through all categories to make sure you don't miss any pertinent to your field.

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