PASPCR Newsletter

September 2006
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Introduction...
by Bill Oetting

The PASPCR Membership contact list has been updated once again. The updated version can be viewed at the PASPCR Web Site (http://paspcr.med.umn.edu/members.htm). Please check your contact information, especially your email address, to make sure that it is correct. If you notice any errors, please send your corrections to me at bill@lenti.med.umn.edu.

I hope tha you had a great time at the PASPCR annual meeting. The meeting report for the 13th Annual Meeting of the PanAmerican Society for Pigment Cell Research can be seen in this issue as well as in the PASPCR website (on the PASPCR Information Page). Also, check out the PASPCR Commentary Page. New articles are being added each month. If you missed an issue, you can find past commentaries there as well.

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 add them.

The IFPCS web site can now be reached by using the domain name **ifpcs.org**. The domain name **ipcc.info** will take you to the IPCC web site, providing you the most up to date information on the International Pigment Cell Conference which will be held on May 7 - 12, 2008 in Sapporo, Japan.

The PASPCR Web Site can be found at:

http://www.paspcr.org

In this Issue . . . . .

The PanAmerican Society for Pigment Cell Ressarch

C/O Dr. Raymond E. Boissy
Department of Dermatology
University of Cincinnati
231 Bethesda Avenue
Cincinnati, OH 45267-0592

Officers:

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Richard Spritz
Giselle Thibaudeau

IFPCS Represenative:

Zalfa Abdel-Malek,
President, IFPCS
Past-President, PASPCR

Calendar of Events:

2006 20th Annual Meeting of the Japanese Society for Pigment Cell Research (JSPCR) will be held on November 25 and 26, 2006 in Matsumoto City, Japan
Contact: Prof. Toshiaki Saita

2007 XIVth Meeting of the PASPCR
Chicago, Illinois
Contact: Caroline Le Poole
E-mail: ilepool@lumc.edu

2007 The 21th Annual Meeting of the Japanese Society for Pigment Cell Research (JSPCR) will be held on December 8 and 9, 2007 in Toyoake City, Japan
Contact: Prof. Kazumasa Wakamatsu

2007 2nd Conference of the Asian Society for Pigment Cell Research (ASPCR). July 6-8, Singapore
Contact: Mrs Alice Chew
E-mail: training@nsc.gov.sg

2007 XIVth Meeting of the ESPCR, September , Bari, Italy
Contact: Prof. Rosa Cicero
E-mail: r.cicero@biolgene.uniba.it

2008 XXth International Pigment Cell Conference and Vth International Melanoma Research Congress
Contact: Kowichi Jimbow
E-mail: Go to web page for contact information
www.ipcc.info

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.

Publications Committee:

William S. Oetting, Ph.D.
Editor
University of Minnesota
Department of Medicine- Genetics
MMC 485
420 Delaware St. SE
Minneapolis, MN 55455
(612) 624-1139
bill@lenti.med.umn.edu

Manickam Sugumaran, Ph.D.
Univ of Massachusetts at Boston
Department of Biology
100 Marrissey Boulevard
Boston, MA 02125
(617) 287-6600
manickam.sugumaran@umb.edu

Richard T. Swank, Ph.D.
Roswell Park Cancer Institute
Department of Molecular & Cell Biology
Elm and Carlton Streets
Buffalo, NY 14263
(716) 845-3429
richard.swank@roswellpark.edu

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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New Members
by Raymond E. Boissy

The PASPCR woud like to welcome these new members to the Society:

Tamara Handerson
Old Lyme, CT

Younghwan Song
Pukyong National University
Pusan, South Korea

Rossitza Lazova
Yale University
New Haven, CT

Mitchell Denning
Loyola University
Maywood, IL

Bryan Plumlee
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Manpreet Randhawa
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Michal Zmijewski
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Memphis, TN

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Cheri Millikin
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Keith Cheng
Pennsylvania State University College of Medicine
Hershey, PA

Valerie Trapp
University of California-Irvine
Orange, CA

Jesse Leverett
Alticor Inc
Ada, MI

New Members (continued)

Ivana de la Serna
Medical University of Ohio
Toledo, OH

Russell Wyborski
AVON
Suffern, NY

Jesse Leverett
Aticor Inc.
Ada, MI

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Medical University of Ohio
Toledo, OH

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Duke University
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Linda Eastham
Marshall University School of Medicine
Huntington, WV

Victor Canfield
Penn State College of Medicine
Hershey, PA

Pamela Cassidy
University of Utah
Salt Lake City, UT

Maria Landi
National Cancer Institute
Bethesda, MD

George Eakins
Mississippi State University
Mississippi State, MS

Welcome to the PASPCR!

PASPCR Awards

The following awards were presented at the 13th Annual Meeting of the PanAmerican Society for Pigment Cell Research.

The Aaron B. Lerner Award and Lectureship was presented to Zalfa Abdel-Malek. Zalfa spoke on "Being in the "Red", the Price of MC1R variants".

The Young Investigator Awardees were:

Junior Faculty (tie): John D'Orazio (Univ. Kentucky)
Ana Kadekaro (Univ Cincinnati)

Post Doc Fellow: Michal Zmijewski (Univ Tennessee)

Graduate Student: Melissa Harris (UC-Davis)

Roger Bowers was awarded **Honorary Membership** to the PASPCR.

Congratulations!

Zalfa Abdel-Malek
The Aaron B. Lerner Award and Lectureship

Pigment Cell Research Now available online back to Vol. 1, 1987

by Pernille Hammelsø
Journal Publishing Manager

In early 2006, Blackwell decided to digitize Pigment Cell Research as part of our legacy program. Over the last couple of years we have had an increasing number of requests from the pigment cell community to make the journal accessible online back to Volume 1, and also, libraries want to be able to provide seamless electronic access to the complete run of a journal, rather than having some of it available electronically and the rest in print.

The electronic version of Pigment Cell Research from 1987 to 1999 is available with XML based abstracts and references and a PDF of the body of the article. Due to ASCII format of the whole article, all papers are fully searchable though.

Thanks to the Editor-in-Chiefs of Pigment Cell Research over the years, who have carefully kept a an almost complete archive of the journal back to Volume 1, combined with our own archive, we have fairly easy been able to reconstruct a complete collection of Pigment Cell Research – including supplements.

We hope the archive will be welcomed and widely used by the whole community.

To access this archive, go to the Pigment Cell Research web page at:
www.blackwell-synergy.com/loi/pcr

PIGMENT CELL
Research

MINUTES OF THE COUNCIL OF THE
PANAMERICAN SOCIETY OF PIGMENT CELL RESEARCH
Thursday, October 7, 2006
Plaza Board Room – Kingsgate Marriott Conference Hotel
Cincinnati, OH (13th PASPCR Conference)
9:00 – 11:00 AM EST

1. John Pawelek, President, opened the meeting.
2. In attendance: John Pawelek, Zalfa Abdel-Malek, Frank Meyskens, Raymond Boissy, Murray Brilliant, James Grichnik, Sancy Leachman, William Pavan, and Richard Spritz. (also present as guest was Caroline Le Poole as host of the 2007 PASPCR meeting). A quorum existed.
3. The minutes of the 2/06 council meeting and the current Treasurer's Report was presented, discussed and approved.
4. Boissy reported on membership. Current membership for 2006 is 108, down from 116 of last year. Discussion of improving membership ensued. It was decided that a new membership form be compiled that emphasizes the benefits of being a PASPCR member. This new membership form will be compiled by Leachman and Abdel-Malek.
5. Abdel-Malek discussed the 13th PASPCR meeting in Cincinnati. There were 124 registrants for the meeting. Motion was made and approved to offer reduced registration fees to meeting participants who wished to become PASPCR members.
6. Le Poole presented plans for the 14th PASPCR meeting in downtown Chicago on Sept 13-16, 2007. The title of the meeting will be "Pigmentation & Diversity". The organizing committee is recruiting sponsors. A R13 grant has been submitted to NIH. The meeting site will be the Knickerbocker Hotel. The website will be launched on October 15th and CME credits will be available. It was recommended after discussions that Corporate Sponsors for the

(Continued next page)

(PASPCR Minutes continued from page 5)

meeting be provided with one free registration to the meeting and that invited keynote speakers be given an honorarium plus free membership to PASPCR.

7. Pawelek discussed the "Commentary" and the successful recruitment of authors. Meyskens will assume the responsibility for the commentary when becoming president in 2008. It was suggested to consider international authors for the commentary for which Abdel-Malek will present this idea to the IFPSC council meeting next month.
8. The Society for Melanoma Research is looking for a journal and has begun discussion with Pigment Cell Research. The Pros and Cons of this were discussed extensively.
9. Pertaining to the PASPCR 2007 election for new Council Members, the Nomination Committee will be chaired by President Elect Meyskens with James Grichnik as the Council member plus 3 members at large to be determined.
10. A Membership Committee was established consisting of Leachman and Abdel-Malek and a Funding Committee was established consisting of Le Poole, Setaluri, and Boissy.
11. Richard King was unanimously elected as Emeritus Member.
12. The PASPCR Newsletter Editor, Oetting, will be retiring the position at the end of next year. Discussion of a replacement ensued and an announcement recruiting volunteers was recommended.
13. Determining a site for the 15th PASPCR meeting in 2009 was discussed. It was suggested that a site in the Rocky Mountains be considered. Leachman proposed thinking about it.
14. Meeting was adjourned.

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.

MEDICAL ONCOLOGY AND HEMATOLOGY
UNIVERSITY OF CALIFORNIA, IRVINE

Two new positions in medical oncology and hematology are available at the Assistant/Associate/ Full Health Sciences (Clinical) Professor level (rank dependent on qualifications) in the Department of Medicine, Division of Hematology/Oncology at the University of California, Irvine, site of an NCI designated comprehensive cancer center. Applicants must have MD or MD/PhD and be BE/BC in Medical Oncology. These positions are for Academic Clinicians who, in addition to patient care activities, are interested in participating in established clinical trials and teaching. Time and resources to assist in the development and execution of novel translational research and develop investigator-initiated trials will be made available. One position is for an individual with interest in melanoma and the other for an individual with interest in pancreatic and hepatobiliary cancers.

UCI is an equal opportunity employer committed to excellence through diversity. Send curriculum vitae with names and telephone numbers of three references and a statement of your academic goals to:

Randall F. Holcombe, M.D.
Chief, Division of Hematology/Oncology
Associate Director, Chao Family Comprehensive Cancer Center
c/o Krista Hollinger, Divisional MSO
101 The City Drive
Bldg 56, RT 81, ZOT 4061
Orange, CA 92868
Tel: 714-456-5153
Email: kholling@uci.edu

Report on the 13th Annual Meeting of the PASPCR

Cincinnati, OH
September 7-10, 2006

Symposium I – Genetic Regulation and Developmental Aspects of Pigmentation
Report by Lidia Kos

In his keynote presentation **Dr. Daniel Nebert** gave a general overview of the various molecular approaches that have been used to assess interindividual susceptibility to environmental toxicants and cancer. He concluded that we have not yet reached the point where these assessments are reliable and that new technologies and insights will be required if a complete picture of genotype-phenotype association studies are to be achieved. **Dr. Murray Brilliant** presented a comprehensive study of the genes and polymorphisms that account for variations in hair, eye and skin color. He concluded that a small number of polymorphisms in a few genes are actually responsible for pigmentation variations. He highlighted the relevance of genes that code for pumps that move molecules in and out of melanosomes. One of these genes, SLC24A5, was the focus of the talk presented by **Dr. Victor Canfield**. SLC24A5, is a putative sodium-calcium exchanger, that is mutated in the zebrafish golden mutant. In humans, allelic variants of these genes show associations with particular geographical locations and skin pigmentation tones. SLC24A5 is most likely localized to the melanosomal membrane overlapping with PMEL 17. **Dr. Richard Spritz** presented results from his studies that have aimed at identifying genes involved in vitiligo. His group has mapped a susceptibility locus to chromosome 17p and has found a gene that might be associated with various autoimmune and anti-inflammatory disorders. This gene is not expressed in melanocytes but in certain immune cells and causes reduced apoptosis of monocytes. In her keynote address, **Dr. Polly Matzinger** gave a very exciting new interpretation of how the immune system works. She proposed that the "self-non-self" dogma cannot explain various immune responses. She believes that immune system cells respond to "alarm signals" produced by damaged cells and the responses generated are tissue specific.

Dr. Heinz Arnheiter discussed the regulation of mitf in the retinal pigment epithelium (RPE). His group has found that of all nine mitf promoters, the D-promoter is the one with highest expression in the RPE. Although D knock out mice do not show any eye phenotype, crosses with chx10 heterozygous lead to microphtalmia. The abnormal eye phenotype of chx10 homozygous mutants is, however, rescued in the D knock out background indicating that chx10, most likely, negatively regulates mitf in the RPE by binding to the D promoter. **Roman Garcia** described the phenotype of an inducible transgenic mouse in which endothelin 3 is expressed under the control of the keratin 5 promoter. These mice develop highly pigmented skin due to the presence of melanocytes and abundant melanin in the dermis. The expression of the transgene is required around embryonic day 11.5 and onwards for the generation and maintenance of the hyperpigmentation phenotype indicating that endotehlin 3 is required for the survival of dermal melanocytes and might be involved in cases of dermal melanocytosis such as blue nevi. **Melissa Harris** showed that in the avian system neural crest cells destined to become melanocytes and take the dorsolateral migratory pathway depend on endothelin receptor b2 for the early migration from the neural tube and kit for the later movement of these cells into the epidermis. This is somewhat in contrast to what has been proposed for the mouse, in which the very early migratory steps seem to be independent of endothelin receptor b and dependent on kit signaling.

Symposium II – Stress Signaling and Survival Pathways in Melanocytes
Report by Richard Niles

This session was led by an outstanding key note presentation by **Al Fornace** from the Harvard School of Public Health, discussing the role of Gadd45a in various signaling pathways following UV radiation. Gadd45 directly binds a number of signaling molecules, including p38MAPK and beta-catenin. There is accumulating evidence that Gadd45a is dysregulated in human melanoma cell lines. Gadd45a activation in dermal keratinocytes leads to activation of p38 with subsequent induction of growth arrest and apoptotic genes. In skin

Gadd45a is required for p53-mediated sunburn response. In Gadd45a -/- mice chronic UV exposure leads to an increase number of skin tumors. Wip-1 is frequently amplified in cancer and can allow cells to bypass the normal checkpoint role of Gadd45a/p53. A combination of Wnt and Wip1 overexpression in transgenic mice can induce breast cancer.

The invited presenter for this Symposium was **Ruth Halaban** from Yale. Her recent work is concerned with epigenetic changes in chromatin and gene expression in melanocytic lesions. The lab performed gene expression profiles in melanoma cell lines treated with low dose 5-aza-cytidine for two days. About 190 genes changed their expression. One group of genes that was reactivated encoded matrix and remodeling proteins such as collagens and MMPs. One gene, Rab 33A was explored in more detail. Expression of Rab 33A was decreased in melanoma, expressed in normal nevi, and downregulated in congenital nevi. Treatment of melanoma cells with 5-aza-cytidine reactivates the expression of this gene.

The second keynote speaker of this Symposium was **Eric Knudsen** from the University of Cincinnati. His work is focused on Rb, which is a high frequency target in melanoma. He found that CDK4/6 inhibitors restores Rb function and if Rb is not expressed then a constitutively active (lacks phosphorylation sites) Rb can restore the function of this important molecule. Typically, Rb inactivation occurs through loss of p16ink4a. However differential knockout studies suggest that these tumor suppressors control the cell cycle by different mechanisms. Knockout of Rb in the liver has no effect on organ size, but cells have giant nuclei. The liver of knockout mice are more susceptible to carcinogens and cells become hyperploid. These results suggest that Rb is also involved in maintaining genome integrity.

The Symposium ended with three oral presentations selected from submitted abstracts. **K.C. Park** from Seoul National University described how heat treatments decreased melanin synthesis by inactivating protein phosphatase 2A . Heat treatment also decreased amounts of MITF thus contributing to decreased melanin synthesis.

R Sarangarajan from Massachusetts College of Pharmacy discussed how BHT and BHA affects melanocytic cell function. Both of these compounds did not affect the viability, tyrosinase expression or melanin content of SKmel23 or SKmel19 cells. These compounds also did not increase the toxicity of 4-TBP in these two cell lines.

A-L Kadekaro from the University of Cincinnati used DNA microarrays to investigate the pathways involved in the ability of alpha – MSH to counter act the effects of UV radiation on human melanocytes. Her results showed that 1226 genes were altered by UV in cells with functional MC1R compared to 808 genes in non-functional MC1R cells. In melanocyte relevant genes, 7/8 reduced in expression by UV were increased by alpha-MSH. The microarray data for selected genes was validated by Northern or Western blot analysis.

Symposium III – Sensing the Environment: Cellular Interactions
Report by Prashiela Manga

Keynote speaker **Steve Boyce**, presented a clear success story in his group's ability to generate skin tissue in the form of cultured skin substitutes (CSS), which could be used in the treatment of severe burns. The CSS is formed using cultured autologous human keratinocytes and fibroblasts seeded onto collagen-based sponges, which can be layered over burn areas and will be integrated to recompose the skin. However, incorporating melanocytes into this model remains challenging resulting in differential pigmentation between the patient's unaffected and regenerated skin. Incorporation of melanocytes into this model would not only improve the outcome for burn patients, but would also provide a useful tool for in vitro and in vivo studies of melanocyte and cellular interactions in the skin.

Flavia Brito next presented an intriguing finding of melanocytes in the valvuloseptal apparatus of the heart. The origin of these melanocytes was traced in transgenic mice that express LacZ under the control of a dopachrome tautomerase promoter. Cardiac melanoblats that will eventually populate the heart tissue at first migrate with the melanoblasts that will popu-

late the skin, however at E11.5, some cells begin to migrate towards the heart, which is reached by E12.5 and where the numbers increase slightly. While the precise function of the melanocytes at this location remain unclear, the melanocytes retain their ability to respond to chemokines such as endothelin and stem cell factor.

Jun Fan discussed the role of the tetraspanin family member CD9 in melanoma progression, invasion, and metastasis. CD9 was seen to be down-regulated in melanoma cells as compared to normal melanocytes. Treatment of WM9 and B16F1 melanoma cells with retinoic acid caused a decrease in CD9 expression. Altered expression in B16F1 cells caused morphological changes, changed the distribution patterns of cell in culture dishes and altered the potential for invasion. It was however noted that proliferation rates were not changed.

Akira Hachiya presented an alternative methodology for the generation of human skin substitutes (HSSs), which could allow for incorporation of melanocytes. The skin substitute was generated on the backs of SCID mice by seeding an incision with cultured, human foreskin derived keratinocytes and melanocytes. After three months, a stratified epthilelium was seen. By mixing cells from different racial groups, this model was used to characterize the contribution of melanocytes and keratinocytes in determining pigmentation. Changing the source of keratinocytes from light to dark skin derived was found to increase the amount of pigment generated by melanocytes. Melanosomes were also found as single entities as well as clustered in membranes following transfer to keratinocytes. These data suggest a major role for the keratinocyte in determining constitutive pigmentation.

Invited speaker **Glynis Scott** addressed the role of secretory phospholipases as mediators of melanocyte dendricity and melanosome transfer. Phospholipases are required for production of arachidonic acid and lysophospholipids such as lysophosphatidylcholine (LPC). Human melanocytes express phospholipase A2 receptor (PLA2R) and two G-protein coupled receptors for lysophosphatidylcholine (G2A and GPR119). sPLA2-X, a phosopholipase expressed in keratinocytes and induced by UV exposure, increased both tyrosinase activity and melanocyte dendricity. The effects of sPLA2-X were found to be mediated by LPC and not arachidonic acid. LPC treatment activated protein kinase Cz. These data provide an additional mechanism for paracrine regulation of melanocytes by keratinocytes.

John D'Orazio discussed the induction of eumelanin synthesis in mice that lack functional melanocortin 1 receptor (mc1r) expression using topical application of forskolin. Melanocytes from these mice are unable to respond to melanocyte stimulating hormone due to the lack of the receptor. In humans, reduced activity is a risk factor for melanoma. Forskolin bypasses the receptor by inducing production of cyclic AMP and thus stimulating melanogenesis. Pheomelanotic mice were found to produce eumelanin following topical application of forskolin, which protected the mouse skin against UV-induced damage. While forskolin itself may not be useful as a topical treatment in humans due to its effect on multiple pathways, the group is pursuing the use of other molecules with similar properties.

Kazu Wakamatsu reported on the contribution of melanin content to iris color. Eumelanin (EM) and pheomelanin (PM) content of cultured iridal and choroidal melanocytes from eyes of various colors were determined. EM was found to increase as the eyes darkened, while there was little variation in the amount of PM in cells from different eye colors. Thus eye color is determined both by total melanin content as well as the amount of eumelanin.

Manikum Sugumaran discussed the parallels between eumelanin synthesis and sclerotinogenesis. Both processes rely on catalysis by phenol oxidases, in the case of sclerotin production however, there is oxidation of dehydro-N-acetyldopamine, which is produced from the tautomeric quinone methide imine amide and is required for the cross-linking of the insect cuticle during sclerotization.

James Grichnik presented evidence of the usefulness of dermoscopy in characterizing nevi. Nevi progress through growth, maturation, and regression phases, thus attempts to categorize them has proved

difficult. Careful classification of these nevi may provide further clues as to the risk of progression to melanoma.

Symposium IV – Photobiology, Melanocyte Transformation, Melanoma
Report by Suzie Chen

Dr. Maria Teresa Landi was the keynote speaker for the first part of this symposium. Dr. Landi showed a strong correlation between variants in melanocortin-1 receptor (MC1R) and risk for development of cutaneous melanoma. There are over 70 MC1R variants reported to date, carriers with multiple MC1R variants have been shown to be high risk for melanoma even when the skin type is adjusted. In addition, the thickness of the lesions, the number of primary melanomas and the onset age of development of melanoma all have been associated with MC1R variants. Some variants of MC1R exhibit loss of function, when these individuals are exposed to environmental insults including UV, an induction of reactive oxygen species may lead to genomic instability and mutations in BRAF. Combination of MC1R variants and mutated BRAF play important roles in melanoma development.

Dr. Sancy Leachman presented her studies on hereditary melanoma. Dr. Leachman being in Utah has a unique resource for the studies of hereditary melanoma. There is a Utah Population Database Genealogy Record, which is linked to Utah Cancer Registry and Birth/Death Record. Hereditary Melanoma accounts for about 10% of human melanomas. Three high penetrance melanoma predisposition gene products have been identified. Two of the gene products are encoded by cyclin-dependent kinase inhibitor 2A (CDK2A) with an alternative splice give rise to two distinct proteins, p16 and p19. The third one is cyclin-dependent kinase 4 (CDK4). These three proteins account for about 20-40% of familial melanomas while the remaining 60-80% carry predisposition gene(s) that have not been identified. Presumably, some of these low-penetrance susceptibility genes interact with other modifiers (genetic or environmental) leading to melanoma development. One such candidate is MC1R variants, as shown by an increase in melanoma susceptibility.

Three short selected oral presentations followed Dr. Leachman's talk.

Dr. Pawelek reported that the co-localization of melanoma cells with melanophages is frequently detected in hyperpigmented region of cutaneous malignant melanoma. Furthermore, both cell types were shown to express beta 1,6-branched oligosaccharides. Further analyses with archival human melanoma tissue samples and tissue microarray, they showed the presence of melanophages in hyperpigmented, LPHA lectin-positive area. In primary melanoma, association of melanophages with LPHA-positive tumors showed improved outcome, but no correlation was found with metastatic melanoma.

Dr. Jamal and colleagues performed immunohistochemical screening of expression of endothelin-1 in various stages of progression of human melanoma from melanocytic nevi to melanoma in situ and finally to invasive melanoma. While low levels of endothelin-1 stain can be detected in surrounding dermal cells but none was detected in melanocytic cells in nevi or melanoma in situ. In contrast, in invasive melanoma, in addition to uncovering a higher percentage of dermal cells with endothelin-1 expression a portion of melanoma cells also displayed positive endothelin-1 staining. Taken together, these results suggest possible role of endothelin-1 in melanoma progression.

Dr. Yang from Dr. Meyskens's group showed specific mutations in mitochondria DNA by DNA sequencing in two out of three human melanoma cell lines in comparison to human mitochondria DNA database. Growth of cells in low concentration of ethidium bromide will selectively deplete mitochondria DNA. When human primary melanocytes and melanoma cells were subjected to such growth conditions, the melanoma cells exhibited apoptosis and higher levels of reactive oxygen species. In contrast, primary human melanocytes only showed marginal levels of apoptotic cells. These results implicate the possibility of using mitochondria as a target for therapy.

Dr. Ronai gave the second keynote lecture for this symposium. The transcriptional factor ATF2 is known to function in human melanoma cells by enhancing the resistance to apoptosis through dimerization with c-Jun

and activation of a variety of target genes some of which are involved in anti-apoptotic activities. Subfragments of ATF2 were made in length of 10-50 amino acids, when these subfragments were applied to in vivo mouse model with xenografts of human melanoma cells, one particular peptide was shown to be active in the inhibition of tumor cells growth. Screening of a library with 3000 natural compounds for suppression of proliferation of human melanoma cells, Dr. Ronai and colleagues identified one to be active and specific in inducing apoptotic response in human melanoma cells. A second unexpected activity of ATF2 was identified. Two serine residues at the C-terminal domain of ATF2 were identified to be a substrate for ATM kinase. When cells are exposed to environmental insults such as irradiation, activation of ATF2 by ATM occurs. Activated ATF2 with phosphorylation at these two serine residues is then translocated to DNA damage foci and recruitment of several factors including Rad50, Nbs1 and histone acetylase TIP60. TIP60 activates ATM via acetylation. ATF2 apparently contributes to its own activity via its participation in DNA damage. Dr. Ronai also showed that autoregulation of c-Jun in human melanoma cells, this is mediated through the constitutive stimulation of ERK by external stimuli (cytokines, growth factors), stimulated ERK phosphorylates CREB and GSK3. Phospho-CREB activated its target c-Jun. Phosphorylation of GSK renders it inactive resulting in stabilization of c-Jun which in turn activates RACK1 and subsequent JNK activation. Activated JNK activates c-Jun and creating an autoregulated loop.

Dr. Chen presented studies on the oncogenic activity of a neuronal G-protein-coupled –seven-transmembrane-domain receptor, metabotropic glutamate receptor 1 (Grm1) in melanocytes. Using a transgenic mouse models they identified the aberrant expression of Grm1 in melanocytes in vivo was sufficient to generate spontaneous melanoma. Introduction of Grm1 into MelanA cells resulted in several stable clones exhibiting partial transformed phenotypes as defined by the lost of TPA requirement, increase in cell proliferation rate but very limited growth in anchorage-independent conditions. Surprisingly, when these stable Grm1 cells (106 per site) were injected into immuno-deficient mice, very robust tumors formed within 10-12 days. These results suggest the in vivo favorable microenvironment promoting the growth of these Grm1-cells. Condition media from mixtures of keratinocytes :fibroblasts:melanocytes did not support the growth of these stable Grm1-clones in culture condition. The identities of these in vivo growth-promoting factors are not known. Several inducible siGrm1 clones were isolated and the dependency on Grm1 expression for cell proliferation was demonstrated by addition of doxycycline in the growth media. Taken together, these studies strongly suggest an oncogenic role of Grm1 in melanocytes.

Three selected oral presentations were made. **Dr. Fruehauf** presented the first one.
Dr. Fruehauf showed several promising compounds with pro-apoptotic activities when applied to human melanoma cells. The mode of action of these compounds is mediated by depletion of scavengers of reactive oxygen species such as glutathione or Cu/Zn superoxide dismutase. It is well known that enhanced level of reactive oxygen species in human melanoma cells is one of the consequences of distorted structure of melanosomes. Cell growth assays, measurements for levels of glutathione and superoxide dismutase were used to test possible synergistic effects of compounds with activities of depletion of reactive oxygen species. A synergistic effect was detected with two of these compounds.

Dr. Pawelek showed previously when macrophages are fused with melanoma cells with low metastatic potential, the resulting hybrids have an increase in melanin content and metastatic potentials. This was found to be correlated with an upregulation of the enzyme glucosyltransferase GnT-V and the production of beta 1,6-branched oligosaccharides. GnT-III is a known competitive inhibitor of GnT-V , GnT-III was used to investigate the role of GnT-V in an increase in the levels of melanin and an increase in metastatic potential in melanoma. Transfection of GnT-III into macrophages fused with mouse melanoma hybrid cells resulted in hybrids with a decrease in melanin production, tyrosinase activity and cell motility as measured by in vitro migration assays. These results strongly suggest a direct role of the enzyme, GnT-V in melanogenesis and tumor progression.

Dr. Medrano showed the dual activities of SKI. It is known that SKI transforms melanocytes, however, SKI can also functions as a tumor suppressor. TGFb fosters metastatic potential of melanoma however, in culture, TGFb has inhibitory activity. Normally, SKI functions as a potent repressor of TGFb pathway, however, the interaction between SKI and TGFb in melanoma is not well understood. Using a gel filtration chromatography and co-immunoprecipitation, they showed that SKI is associated with Smads, mSin3, HDAC1 and other proteins in the presences of TGFb. rthermore, they also showed that in siSKI cells the reduced ability to grow in vivo correlated with a decrease in the levels of zonula occluden1. As shown previously by M. Herlyn and colleagues that one of the consequences of decreasing zonula occluden1 is suppression in invasion.

Symposium V – Regulation of Pigmentation, Growth Factors, Hormones
Report by Francois Rouzaud.

Dr. Tobin from Bradford University, England, gave a Keynote Presentation on the neuro-endocrine regulation of human follicular melanocyte biology. The lecturer went through the increase of knowledge of skin function that happened during the past few years, and particularly a large amount of data emerging from the relatively new subject of Cutaneous Neuroendocrinology. This field positions the skin as a major sensor of the periphery, a capability that is integral to the maintenance of mammalian homeostasis and which needs to intersect with the skin's major support systems e.g. blood, innervation, muscle, immune, psycho-emotion, UV-sensing, as well as the (neuro) endocrine system. Locally-produced melanocortins have been reported to play a significant role in skin homeostasis, particularly by helping to neutralize noxious stimuli. The cutaneous pigmentary system in particular is an important stress response element of the skin's stimulus-sensing apparatus (e.g. to UVR). Corticotrophin releasing hormone (CRH) and proopiomelanocortin (POMC) peptides in particular respond to such stimuli in part by helping to regulate pigmentation in the epidermis and hair follicle. These distinct (but open) cutaneous pigmentary units are organized into symmetrical functional units composed of CRH and the melanocortin POMC peptides (e.g., a-melanocyte stimulating hormone, adrenocorticotropic hormone, and also the opiate b-endorphin). New findings have led to the concept of 'self-similarity' of melanocortin systems based on their expression both at the local (skin) and systemic (CNS) levels, where the only apparent difference appears to be one of scale. This lecture explored this concept and described how the components of the CRH/POMC systems may help regulate the human hair follicle pigmentary unit.

Dr. Tom Hornyak, from the Dermatology Branch of the NCI at NIH then gave an Invited Presentation on the Mechanisms of hypo- and hyperpigmentation and the lessons learned from mouse models of Waardenburg syndrome and neurofibromatosis. Waardenburg syndrome Type 2a (WS2a)/Tietz syndrome and Type I neurofibromatosis (NF1) are disorders of hypopigmentation and hyperpigmentation, respectively. Both WS2a and Tietz syndrome are caused by mutations in MITF and feature a combination of hypopigmentation and congenital deafness. WS2a patients have localized hypopigmentation whereas Tietz syndrome patients exhibit generalized hypopigmentation. NF1 results from mutations in the gene NF1, encoding the protein neurofibromin. NF1 patients exhibit cutaneous hyperpigmented patches of different size. The authors utilized the MitfMi-wh/+ mouse, which exhibits both coat colour dilution and white spotting, as a model of human Waardenburg and Tietz syndromes. MitfMi-wh/+ mice exhibit a profound hearing deficit. This was associated with loss of melanocytes from the cochlea, but not from the majority of the coat, of affected animals during early postnatal life. A combination of stem cell factor (SCF)/Kit ligand and endothelin-1 rescued MitfMi-wh/+ melanocytes in organotypic stria vascularis cultures. To investigate the pigmentary properties of Nf1-deficient melanocytes, the authors resorted to using the Nf1 +/) mouse. Nf1 +/) mice modified the phenotype of both Kit and Mitf mutant mice, indicating a genetic interaction between these alleles. Furthermore, primary Nf1 +/) melanocytes showed a distinct expression pattern of melanogenic proteins and altered responsiveness to signaling pathway perturbations that can be caused by changes in the cutaneous environment. Hence, the results of each of these studies, though designed to

investigate opposing pigmentary changes, point to the importance of the local environment for determining the survival and differentiation state of sets of melanocytes with mutational perturbations.

We then switched to 4 consecutive selected oral presentations, the first of which was given by **Dr. Akiyama** from Keio University in Tokyo, Japan, about the high expression of endothelin 3 detected by in situ hybridization in Silky chicken embryos . Dr Akiyama reported the results obtained by her group on the effects of endothelins (ETs)-endothelin receptor B2 (EDNRB2) in hyper pigmentation in internal organs in Silky chicken. Cultured melanocytes from neural crest revealed prominent proliferation and differentiation depending on synthetic mouse type endothelins (ETs). Northern blot disclosed that these melanocytes expressed endothelin receptor B2 (EDNRB2) and fibroblast like cells isolated from internal organs expressed endothelin 3. Furthermore, the authors cloned the chicken ET3 and identified only one amino acid substitution with that of human/mouse type. Then, using the cloned sequence and other primers they determined the expression doses of several genes by the quantitative RT-PCR method during embryogenesis and obtained high dose expression of ET3 and EDNRB2 in stage 18. In situ hybridization was carried out to disclose the localization of ET3 in early embryos (stage 18). The expression was specifically observed in integumental layer in trunk region and mesodermal area of foregut in both Silky and Barred Plymouth Rock (BPR) similarly but the expression dose in internal organs of Silky was clearly higher than that of BPR. From the unquestionable negative reaction with sense codon, the results were thought to be reliable. This high dose expression was in accordance with the previous quantitative RT-PCR. These results imply that the produced high dose ET3 enters into aorta and circulates to whole body. Such internal environment in Silky is seemed to permit the prominent proliferation and survival of melanocytes and to work for hyper pigmentation finally.

Manpreet Randhawa, from the group of Dr. Ancha Baranova at George Mason University gave the next presentation. As a new member of the PASPCR, Manpreet told us about extra-melanocytic melanin and the possibility of the melanin biosynthesis in human and murine adipocytes. Melanocortins are critical both for energy balance and also for regulation of the hair and skin pigmentation. Previous findings from the same group revealed statistically significant overexpression of melanogenesis related genes in visceral fat of obese individuals, including TYRP1, TYRP2, RAB27A and Melan-A. For tyrosinase itself these differences were confirmed by Real-Time PCR experiments. These findings prompted the authors to speculate that adipocytes may be able to perform melanin biosynthesis. Immunohistochemical stainings of human fat tissue slices confirmed expression of TYR, MITF, MART1, GP100, and alpha-MSH in human visceral adipose tissue. Antibodies against MART1, MSH and TYR showed specific patterns of expression in the periphery of adipocytes. To study whether the expression of the genes involved in the melanogenesis in adipocytes can be regulated by alpha-MSH, the authors performed Real-Time PCR and L-DOPA assays on mRNA and protein extracts of alpha-MSH treated murine 3T3-L1 cells. The alpha-MSH dependent increases of TYR mRNA levels were registered in 2-day and 4-day differentiated cells, but not in preadipocytes. Increases in expression were characterized by 2- peak pattern, with maximum at 2 and 24 h after exposure. In preadipocytes, exposure to alpha-MSH leads to the gradual decrease in the TYR mRNA. A gradual decrease in the rate of Ldopa oxidation was observed spectrophotometrically at wavelength of 475 nm in both preadipocytes and differentiated adipocytes. These collective findings indicate the complexity of the possible regulation of the melanin synthesis pathway in adipocytes.

Francois Rouzaud gave the 3rd Selected Oral Presentation about preliminary data obtained in Dr. Hearing's lab at NIH on the residual function of the truncated Mc1r encoded by the murine recessive yellow allele. The murine melanocortin 1-receptor (Mc1r) has been extensively studied as a major determinant of mouse coat pigmentation before and after it was cloned more than a decade ago. The recessive yellow Mc1r mutation (e) results from a single nucleotide deletion in the gene monoexon that induces a frameshift and the synthesis of a truncated receptor bearing only four transmembrane domains. Animals homozygous for that allele display a yellow hair color, mainly due to

what has been reported in non-melanocytic cellular models as a non-functional Mc1r unable to bind MSH and to activate tyrosinase through cAMP increase. However, a few reports on several species have indicated that the truncated receptor could retain some partial function. The authors have established immortalized murine C57BL/6J e/e epidermal melanocytes in culture and characterized their responses to stimulation by their physiological agonist and antagonist, MSH and ASP respectively. They show that tyrosinase activity is increased by MSH, and even more by ASP, leading to a slight cAMP-independent increase in phaeomelanin but not in eumelanin synthesis. This process is examined in the light of the potential role of glycosylation patterns on tyrosinase activity. Immunofluorescence and Electron Microscopy analysis verify that the changes in melanin synthesis correlate with an expected modification of melanosomal maturation and arrangement without interfering with the normal distribution of tyrosinase, Tyrp1 and Dct. The sum of the results show that the mutant Mc1r expressed in e/e melanocytes retains the ability to bind its physiological ligands but its response is distinct from the wildtype receptor.

The last presentation before the coffee break was given by **Dr. Andzej Slominski** from the University of Tennessee, Memphis, on the CRH signaling system in melanocytes. Besides triggering HPA axis activation, CRH, together with related peptides urocortin I-III participates in behavioral, autonomic, endocrine, reproductive, cardiovascular, gastro-intestinal and metabolic functions. CRH also has local immunomodulatory (predominantly proinflammatory) effects, differing from its central immunosuppressive activity (through the HPA axis). CRH, CRH receptors, POMC and corticosteroidogenic activities are also expressed in human skin, mostly in epidermal melanocytes, regulated by ultraviolet radiation. Epidermal melanocytes predominantly express the CRH-R1a isoform, and ligand activation increases intracellular cAMP, IP3, or Ca2+ levels. Cellular functions affected by activation of CRH-R1 are dependent on nutritional status and include inhibition of proliferation in the presence of growth factors, anti-apoptotic effect (when cells are starved) and inhibition of NF-KB activity (immunoinhibitory effect). CRH is also a component of a local structure organized similarly to the HPA axis. In normal epidermal melanocytes CRH stimulates POMC gene expression and production of ACTH; effects abolished by the CRH-R1 antagonist. CRH and ACTH enhance melanocyte production of cortisol and corticosterone, which is abolished by POMC gene silencing or by antalarmine. These actions absent in cultured keratinocytes are specific for cells of neural crest origin, melanocytes. Thus, epidermal melanocytes have a CRH-led stress response system homolog to that operating at the central level. In addition, locally produced CRH and CRH-related peptides act as pleiotropic cytokines whose function and activity are dependent on cell type and location.

At 4:30 PM, **Dr. Vijay Setaluri** from the University of Wisconsin, Madison, gave an invited presentation entitled “On the road to the melanosome: TYRed and TRPed by the traffic.” The lecturer started by going through a decade of research on melanosomal proteins trafficking and the controversies and debates encountered. While different groups set out to understand how normal melanocytes orchestrate the congregation of Tyr and TRPs to assemble a functional melanosome, it is the study of abnormal melanocytes that unraveled novel pathways and players involved in this process. It is now known that the ER, the starting point of the journey, itself can control the outflow of melanosomal proteins via its quality control mechanisms. New clues are emerging on how interaction of cytosolic proteins with TRP1 cytoplasmic tails influence its exit from the ER. Beyond the ER, the concept of origin of premelanosomal vesicles from the smooth ER is undergoing a revision with a suggestion that not all melanosomal traffic follows a similar path. How melanocytes accomplish the feat of sorting Tyr and TRPs at the TGN and in the endosomes still remain a mystery. However, it has become clear that despite a striking relationship to lysosome, a ubiquitously present organelle, melanosomes are indeed distinct entities. In the final leg of the journey to the melanosome, Tyr and TRPs appear to be guided by a hierarchy of adaptors (APs) and large blocks of protein complexes (BLOCs). The lecture was a fine overview of past and new advances in melanosomal research towards the understanding of melanosomal proteins trafficking.

We ended the session with the last 2 Selected Oral

Presentations, the first one given by **S. Chawla** from the University of Cincinnati about the mechanism of Toxicity and Tyrosinase Inhibition of deoxyArbutin and Second Generation Derivatives. Therapeutic treatment of skin pigmentary disorders such as melasma, solar lentigo, and post-inflammatory hyperpigmentation is currently challenging and seldom successful. The authors have therefore investigated the effect of deoxyArbutin (dA) and second-generation derivatives (i.e. deoxyFuran, thio-dA, and fluoro-dA) on melanocyte viability and function with the aim of developing safer and more effective modulators of skin pigmentation. The dA and its second generation derivatives, at their respective non-toxic concentration inhibited both tyrosine hydroxylase and DOPAoxidase activities of tyrosinase in cultured normal human melanocytes, that subsequently down-regulated melanin synthesis that was reversible 5 days after the treatment was stopped. Line weaver-Burke plot analysis revealed that these compounds had higher competitive inhibitor potency against tyrosinase as compared to hydroquinone. With higher concentrations of dA and its derivatives, viability of melanocytes was compromised due to an inhibition of cell proliferation as opposed to the initiation of apoptosis that was induced by hydroquinone. This cytostatic effect may be due to redox imbalance within the melanocyte. A minimal amount of Reactive Oxygen Species (ROS) was generated upon treatment with dA and derivatives, in contrast to the dramatic amount of ROS induced by hydroquinone. This increase in ROS up-regulated the endogenous antioxidant (catalase) in treated melanocytes. Supplementation with exogenous antioxidants conferred further protection on cells treated with hydroquinone, but not dA and derivatives. Thus dA and second generation derivatives demonstrate great potential for therapeutic use in hyperpigmentation because they are effective tyrosinase inhibitors and less toxic relative to hydroquinone.

The Symposium was closed by the lecture of **R. Kuliawat** from the Albert Einstein College of Medicine on Dominant White Expression Hinders the Formation of HMB-45 Positive Fibrils. Melanosomes are lysosome related organelles, which produce and store melanin. As melanosomes mature, the first morphological characteristic is the appearance of intralumenal fibrillar striations. Subsequently, melanin is synthesized and deposited along these fibrillar structures. Pmel, an integral membrane protein and an important component of the melanosomal matrix, is post-translationally cleaved to produce a soluble luminal domain, which is incorporated into these fibrils. By analogy to amyloid, the luminal domain of Pmel becomes insoluble in Triton X100 and this insoluble fraction is specifically recognized by the monoclonal antibody HMB-45. In addition, as previous studies have shown, melanoma cells which fail to express Pmel or process it into an HMB-45 recognizable form, do not form Stage II melanosomes and do not store melanin. To further characterize the role of the striations in melanin storage, the authors tested fibril formation of Pmel in the absence or presence of the product of the Dominant white locus, Mmp115. They show that Mmp115, which inhibits the expression of eumelanin in vivo, decreases the fraction of HMB-45-positive Pmel. Surprisingly, Mmp115 is also largely detergent insoluble in Triton extraction assays. Size exclusion chromatography on FPLC columns confirms that both proteins expressed separately or together elute as large polymers. Based on immunofluorescence and sucrose gradient analysis, Mmp115 and Pmel co-localize. The authors presume that this co-localization occurs in multivesicular bodies (MVBs) because immunoEM has previously shown Pmel to be associated with MVB intraluminal vesicles (ILVs). Co-immunoprecipitation experiments show that Mmp115 and Pmel interact. The lumenal domain of Pmel interacts with raft lipids but the HMB-45 positive form of Pmel, and Mmp115 expressed alone, do not. Importantly, expression of Pmel is necessary to relocate Mmp115 to the raft fraction. Since biochemical analysis of ILVs has shown them to be sphingolipid rich, these results suggest that intracellular localization of Mmp115 is influenced by Pmel. However, this difference in Mmp115 distribution in the presence of Pmel is associated with a loss of HMB-45-positive fibrils. The authors conclude that the loss of the pigmented phenotype caused by Mmp115 cannot be readily attributed to prevention of Pmel mediated fibril formation. Rather, loss of the HMB-45 positive epitope in the presence of Mmp115, suggests that the presence of Mmp115 alters Pmel conformation in a manner that decreases net melanin deposition.

Symposium VI: Pigmentary Disorders
Report by Marjan Huizing

Jerry Kaplan; *"Regulation of organelle size: studies on the function of Chediak-Higashi/Beige protein."* Chediak-Higashi syndrome (CHS) is a human disorder of decreased pigmentation (eyes, hair and skin) and immunodeficiency that can in some cases lead to a lethal hemophagocytic syndrome/accelerated phase and adult onset neurologic dysfuntion. CHS is caused by mutations in the *CHS/LYST/beige* gene, also found mutated in other mammals: the *beige* mouse, a killerwhale, and the blue mink. *CHS* deficient cells have giant lysosomes and transfection/overexpression of CHS in normal cells leads to an access of lysosomes, but with a normal size. Complementation studies (normal and CHS deficient cells) suggested that the giant lysosomes in CHS result from decreased membrane fission, instead of increased membrane fusion. The CHS protein might recruit molecular motors to move lysosomes or related organelles and CHS might also function in sensing lysosomal size. The *CHS* gene is low expressed in every cell type, and the translated protein is large and of unknown function, but contains a few motifs: HEAT, BEACH, and WD40. Combined WD40+BEACH domains are found in some other proteins: neurobeachin, FAN and CDC4/LBA. A yeast-2-hybrid screen identified LIP5 as a CHS interactor. LIP5 functions in removal of the ESCORT complex from multiple vesicular body membranes. LIP5 deficiency results in more multiple vesicular body formation, but the size of lysosomes remains normal.

Marjan Huizing; *"Hermansky-Pudlak syndrome and related disorders."* Clinical features of patients with defects in the biogenesis of lysosome-related organelles can include hypopigmentation (melanosome biogenesis defect), prolonged bleeding times and easy bruising (platelet delta and/or alpha granule defects), frequent infections (cytotoxic T-cell lytic granule defect), pulmonary fibrosis, or colitis. Human disorders of lysosome-related organelles include Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome, Griscelli syndrome, and other yet to identify disorders represented by a growing group of unclassified patients (no gene defects identified). Identifying the gene defect and disorder in each patient is not only important for the patients (anticipation of symptoms and/or treatment options) but also for studying the cell-biological aspects of normal lysosome-related organelle biogenesis (by using the patients' cells). For example, cells of patients and mouse models of Griscelli syndrome have helped identify a complex of Rab27A, Myosin 5A and melanophilin assisting lysosome-related organelles to transfer from microtubuli to the actin meshwork in the periphery of the cell. And cells from patients with HPS type 2, have helped identify the function of adaptor complex 3 (AP3) in the sorting and transport of lysosome -and related organelle- destined proteins/membranes. Other disorders of lysosome-related organelles might assist in the future in elucidating some still obscure mechanisms in this biogenesis pathway.

Wendy Westbroek; "*Chediak Higashi syndrome: A genotype-phenotype correlation.*" A genotype-phenotype correlation was demonstrated in 2 patients with Chediak-Higashi syndrome. Patient CHS4 had two severe, truncating mutations in the *CHS/LYST* gene (nonsense and a frame-shift mutation), while patient CHS6 had two less severe mutations (a frame shift and a missense mutation). CHS4 suffered from severe, early childhood onset of the syndrome, including severe infections, while CHS6 had a milder adult onset form. Fibroblasts and melanocytes of CHS4 had dramatically enlarged lysosomes/melanosomes, localized to the peri-nuclear area while CHS6 had moderately enlarged lysosomes which were mostly normal localized. These findings were confirmed by electron microscopy (routine and DOPA stained) on patients' and normal melanocytes. The missense mutation in CHS6; N3376S is located in the conserved BEACH domain of the LYST protein and might assist in future functional studies of LYST.

Amanda Helip-Wooley; *"Improper trafficking of melanocyte-specific proteins in Hermansky-Pudlak syndrome type-5."* Hermansky-Pudlak syndrome is a disorder of defective lysosome-related organelle biogenesis, resulting in albinism and prolonged bleeding. HPS type 5 is caused by mutations in the HPS5 protein, which is a component the protein complex BLOC-2 (biogenesis of lysosome-related organelles 2). The function of HPS5 is unknown and it lacks homology to other known proteins or functional domains. Cultured

melanocytes from HPS-5 patients were studied by immuno-fluorescence and (immuno-)EM. These cells contained predominantly early stage melanosomes and many small DOPA-positive vesicles throughout the cells. The melanogenic proteins tyrosinase and TYRP1/ TYRP2 had a reduced abundance and abnormal localization in HPS5 deficient cells. These studies suggest a role for HPS5 in trafficking a subset of proteins that are required for melanosome maturation.

Pei-Win Chiang, *"Hermansky-Pudlak syndrome BLOC-3 interacting protein."* The Hermansky-Pudlak syndrome proteins HPS1 and HPS4 are components of BLOC-3, of unknown function. Interaction studies revealed a new BLOC-3 component/ interactor, which functions in the regulation of the rac-GTPase pathway in melanocytes. This novel interactor had a predominantly cytosolic localization, co-localized with HPS1 and HPS4, fractionated in the same sucrose-gradient fraction, and down-regulation of this gene by siRNA resulted in an HPS-like cellular phenotype. More work needs to be done, but this protein might be a novel candidate for causing Hermansky-Pudlak syndrome and might function as a negative regulator of rac GTPase.

Prashiela Manga; *"±-MSH sensitizes melanocytes to chemical induced oxidative stress."* Vitiligo results from epidermal melanocyte death likely due to an environmental challenge. 4-TBP is an environmental toxin known to trigger vitiligo. This effect can be exacerbated by the melanocyte-stimulating hormone (±-MSH) through formation of reactive oxygen species. Melanocytes deficient in TYRP1 or the P-gene proved to be less sensitive to 4-TBP. And HSP70 and mortalin expression increased 4-TBP sensitivity. The fact that ±-MSH regulates melanosomal expression of TYRP1, P, mortalin and HSP70, indicates that ±-MSH induced expression of these genes increases 4-TBP toxicity. Therefore, the regulation of alpha-MSH is an important factor in the etiology of vitiligo and the related disorder leucoderma.

Pedro Oyarbide-Valencia; *"HSP70 accelerates depigmentation in a mouse model for autoimmune vitiligo.*" Hypopigmentation/vitiligo was induced in mice by 'gene gun' cDNA vaccination (of TRP2 or gp100, in combination with or without HSP70 cDNA). Mice vaccinated with a combination of HSP70 and TRP2 or gp100 depigmented faster than mice vaccinated with TRP2 or gp100 alone. Immunostaining of depigmented areas showed loss of follicular TRP2 as well as reduced epithelial and perifollicular CD3e. These findings suggest an involvement of HSP70 in the development of autoimmune vitiligo.

Gisela Erf, *"Smyth line chicken autoimmune vitiligo model revisited."* The mutant Smith line (SL) of chicken is an established model for vitiligo, which recapitulates clinical and biological aspects of the human disease. Since melanocytes are localized in the feather, they are easy accessable and regeneration of feathers allows for non-invasive repeated access to a target area/lesion in the same chicken. Basic research on other human disorders (autoimmune thyroiditis, alopecia areata and uvetitis) have also taken advantage of these avian features. Now the chicken genome is completely sequenced, avian models can provide unique contributions for general pigment cell research, and also for multi-factiorial disorders like vitiligo.

Bryan Plumlee; *"Differential cytokine expression in feathers from vitiliginous Smyth line chicken."* The role of cell-mediated immunity in the Smyth line chicken (a model for autoimmune vitiligo) was studied by cytokine expression in the feathers prior to onset and during the disease. IFN-gamma RNA levels increased with appearance of vitiligo. Since IFN-gamma is released during an inflammatory, cell-mediated T helper-1 (Th1) immune response, these findings support a role of a Th1-dominated, cell-mediated immune response in the loss of melanocytes in Smith-Line vitiligo.

Cecele Denman; *"Vitiligo: the patient's point of view."* A vitiligo questionnaire on the etiology and treatment of the disease was answered by 200 patients. The tallied results revealed an unexpected gender bias (more females affected). Physical or emotional stress (33%) hereditary factors (26%), autoimmunity (3%; surpringly low) and infections or antibiotic treatment (3%; surprisingly high) were the main reasons patients pointed as the primary cause of their disease. Vitiligo treatment was sought mainly by patients with a recent onset of the disease.

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