PASPCR Newsletter

Volume 9 Number 3 **September, 2001**

Introduction . . .

The **PASPCR** ***Newsletter*** is published quarterly and is intended to serve as a means of communication for the members of our Society. As such, we invite our membership to actively contribute to it. If you attend a scientific meeting and 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 up-coming meetings of interest will also be included. We also want to note any change of affiliation or address that you may have had to help us keep our membership list up-to-date. 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 Bill Oetting, preferably by Email, to bill@lenti.med.umn.edu.

The PASPCR web page has a new address – **www.paspcr.org**. This new web address should make it easier to remember where the PASPCR web page is in the Internet Universe, as well as stabilize the address for the future. The PASPCR Web Site has had four different web addresses to date (see http://www.cbc.umn.edu/paspcr/webhist.htm). By obtaining this address, it will be assured that the URL to the PASPCR Web site will remain the same, even in the event that the web site is moved to a different server.

The **PASPCR Web** page is the major, up-to-date source of current information for the PASPCR membership. The PASPCR Web page contains information about the PASPCR including the goals, ByLaws and Rules of the Society, future meetings, past issues of the PASPCR *Newsletter* as well as links to other related sites including the InterPig DataBase, the International Federation of Pigment Cell Societies (IFPCS) and the regional Pigment Cell Societies from Europe and Japan. In addition, an updated PASPCR membership directory is available on the PASPCR Web page; please notify us if you wish any or all of your information to be modified or deleted on that site. The PASPCR home page also includes positions available and positions wanted. Postings for **Positions Available** are open to all individuals so long as the position is related to pigment cell research. Postings for **Positions Wanted** will be open only to members of the PASPCR or its sister societies (JSPCR and ESPCR). Please provide an expiration data for any submitted postings. If there is additional information that you wish to have added to this web page, please let us know. Send any comments and/or suggestions to the PASPCR WebMaster, Bill Oetting at bill@lenti.med.umn.edu.

IN THIS ISSUE . . . . .

PanAmerican Society for Pigment Cell Research

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Calendar of Events :

Sept 27 - 29, 2001 10th Annual Meeting of the European Society for Pigment Cell Research, to be held in Rome, Italy
Contact: Meeting Secretariat, Triumph P.R. S.r.l. Via Proba Petronia 3 00136 ROME - ITALY
Phone ++39.06.399631
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Dec 1-2, 2001 15th Japanese Society for Pigment Cell Research Meeting (JSPCR) Sendai, Japan,
Contact: Prof. S. Shibahara
E-Mail : shibahar@mail.cc.tohoku.ac.jp

Sept 9 - 13, 2002 The XVIIIth International Pigment Cell Conference, to be held in The Hague, Holland.
Contact: Dr. Stan Pavel, President ESPCR, University Hospital Leiden, Dept of Dermatology, PO Box 9600, NL - 2300 RC LEIDEN
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Sept 3-7, 2003 XIth Annual Meeting of the PanAmerican Society for Pigment Cell Research, to be held in Wood's Hole, MA.

Welcome to New Members

by James J Nordlund

We welcome the following new member to the **PASPCR** . . .

Sheila M. Schmutz, Ph.D.
University of Saskatchewan
Department of Animal Science

Deborah T. Spaulding
University of Oklahoma Health Sciences Center
Department of Biochemistry and Molecular Biology

Richard A. Spritz, M.D.
University of Colorado Health Sciences Center
Human Medical Genetics Program

If anyone is interested in joining our Society or wishes to sponsor a member, application forms can be obtained from Dr. James J. Nordlund at the PASPCR Secretary/Treasurer's office.

Corporate Sponsors

by James J Nordlund

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.

GOLD Corporate Patrons	***SILVER Corporate Patrons***
Procter and Gamble Co	Avon Products, Inc
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Mouse News

by Lynn Lamoreux

We are very pleased to announce that the congenic colony of mouse pigment mutants that is housed at Texas A&M University has been temporarily funded for three primary purposes:

1. To use these congenic mutants to make congenic pigment cell lines as appropriate;
2. To cryopreserve these important stocks so they will not again be threatened with extinction; and
3. To make them available to the community of pigment cell researchers and to the many scientists in other fields who share interest in our mutants.

This funding was obtained (in alphabetical order) by:
Dr. Dorothy Bennett, Professor, St. George Hospital Medical School Dr. Rick Ermel, Associate Professor, Texas A&M University Dr. M. Lynn Lamoreux, Visiting Research Scientist, Texas A&M University Dr. Jim Womack, NAS, Professor, Texas A&M University

Mouse News continued:

This colony emphasizes loci that drive the major functions of the pigment system, as follows:

1. Cell survival - the white-spotting loci are broadly represented. We hold a number of alleles at the MITF locus.
2. Melanogenesis - the loci that function in melanogenesis and are implicated in albinism, including tyr, trp-1, trp-2
3. Pheomelanin/eumelanin - representative alleles at the agouti locus, the Mcr1 locus, and modifying loci.
4. And varous other mutant pigment loci.

Alleles are held congenic with the inbred strain, C57BL/6J. Thus it is possible to make mice that contain one mutant or multiple mutant loci, all expressed within a controlled, uniform genetic background. This fact makes our stocks readily available to study the functions of individual gene loci, or to study the ways in which pigment loci (or their products/functions) INTERACT with each other and with their environment within the organism. Some alleles are also available on another inbred strain where they are expressed differently (in terms of mouse phenotype).

If you want to discuss these mutant mice or cell lines please contact Lynn Lamoreux (mllamoreux@hotmail.com) or Dot Bennett (dbennett@sghms.ac.uk).

From the Editor - *Pigment Cell Research*

***Vince Hearing**, Editor*

Announcement - Anyone interested in obtaining a limited number of back issues of the journal ***Pigment Cell Research***, please take note. The former Editors of the journal, Profs. Joseph Bagnara and Jiro Matsumoto, have forwarded all their extra copies of past issues of ***Pigment Cell Research*** to the current Editorial Office. Anyone who is missing a back issue or two of the journal from their collection can contact the office to request those. Not all back issues are available and they will be provided when available on a first-come, first-served basis. Contact the Editorial Office by Email (editor@pigment.org) and state the issue(s) needed; be sure to provide your full shipping address.

Notice from the Organizers of the 17th IPCC in Nagoya

IPCC-Nagoya Organizers are purchasing a limited number of **extra copies of the IPCC Supplement** to sell to those who are interested. These issues will cost 5,000 yen (about $50), and if you would like to reserve and order a copy, please contact Dr. Kazumasa Wakamatsu at kwaka@fujita-hu.ac.jp, and he will send you the information you need.

And now for the rest of the story.

In this issue, there is no **'rest of the story'**. This section will return for the December issue. If you wish to know how a particular line of investigation got started, or know of a story that would be interesting to readers of the PASPCR Newsletter, please email me at bill@lenti.med.umn.edu, and I will try to get **the rest of the story**.

Reports on the Xth Annual Meeting of the PASCPR
June 14-17, 2001
Minneapolis, Minnesota

Symposium I: Comparative Biology and Evolution
By Nels Granholm

It was the express purpose of the Organizing Committee of the 10th Annual PASPCR conference to present provocative symposia in order to place the concepts of pigment cell biology into a broader context. Symposium I – Comparative Biology and Evolution advanced that goal.

Three symposium and four platform speakers provided an overview and current state of the art on how demographic, evolutionary, and genetic factors may have altered the sequence and/or incidence of polymorphisms within the human MC1R gene (Makova, Rees), the value of genetic analysis of skin and hair color in humans as evidence for the modus operandi of evolution in humans (Shriver), and current updates on the overall reliability of various methods to measure response to UV radiation in human skin (Tadokora), contributions of P gene and MC1R gene mutations in the etiology of OCA2 (Schmidt), absence of human agouti gene polymorphisms in previously identified MC1R variants (van Daal), and roles of various stimulatory agents (IBMX, bafilomycin) on the dynamics of tyrosinase synthesis and/or activation in human melanocytes as mediated by hydrogen exchanger/transporter mechanisms within melanosomes (Spaulding).

MC1R, one of a five-member family of G protein-coupled seven-repeat transmembrane receptor encoding genes, is indeed an intriguing gene, since it plays a central role in skin color variation in humans. To date, MCIR is about the only gene known that can provide at least a partial explanation for phenotypic variation in human pigmentation. GenBank comparisons, including nucleotide change estimates of synonymous (no change in the amino acid) and non-synonymous (changes in nucleotides leading to a different amino acid) substitutions, indicate that MC1R has evolved at a faster rate than other members of the melanocortin receptor family.

Point mutations that affect the functionality of proteins are generally disfavored by natural selection; one would assume that amino sequences of such critically important proteins would remain constant over time within and between species, like histones perhaps or like the amino acids at active sites of specific enzymes. However, point mutations affecting amino acids of proteins not as essential for protein function are not disfavored and may become fixed in species ancestors by random genetic drift. And some mutations may be favored by selection and are thus rapidly fixed in a species. If the rate of change of DNA or amino acids is constant or linear over time (a kind of molecular clock), then we can make assumptions about when groups or species diverged from one another based on the numbers of substitutions. Contributions by Drs. Makova, Rees, and Shriver helped us to gain a practical application and understanding of these and related principles as applied to evolutionary changes in gene (MC1R) sequences.

Much of the data on MC1R dealt with the role of selection on MC1R nucleotide differences (polymorphisms) between African, Asian, and European populations. Jon Rees looked particularly at the ORF of MC1R whereas Dr. Makova characterized 6.6 kb of the MC1R upstream of the ORF. So, what does this tell us about the polymorphisms of MC1R? We have data on polymorphisms of the expressed sequences of MC1R as well as 6.6 kb of DNA "upstream" of the ORF.

Dr Makova drew the following conclusions: 1. The average nucleotide diversity (polymorphism) in the 6.6 kb upstream regions of human MC1R, exceptionally high when compared to other comparable gene sequences, may be due to high mutation rate, high recombination rate, and/or presence of Alu repeats, 2. As opposed to the coding region of MC1R, the promoter region is highly polymorphic in Africans when compared to Asians and Europeans, and this pattern is consistent with a population expansion in Africans, 3. Exhaustive analyses of patters of polymorphisms in 54 Asians, Africans, and Europeans suggest possible purifying selection acting within the middle and portions of the 5' subregions, diversifying selection in some sites, and possible relaxation of functional constraints, and 4. Dr. Makova also identified sites potentially important for MC1R promoter function.

Following Dr. Makova's analysis of the non-coding region of MC1R, Dr. Jon Rees summarized the current status of the MC1R coding region in his presentation, "The Importance of being Red". Sequence analysis of MC1R can enable us to determine the extent to which MC1R controls human pigmentation. It is of interest to know the number of MC1R functional variants, how those variants regulate phenotype, and in an evolutionary sense, what can MC1R tell us about evolution of pigmentation and about human evolution in general. Dr. Rees outlined a number of common sequence variants (codons 151, 160, 294, and 142) that account for about 80% of northern Europeans with red hair. MC1R also has an effect on cutaneous phenotypes, especially in response to

UV irradiation; Dr. Rees reported a dosage effect of UV between wildtype, heterozygote, and compound heterozygote genotypes of MC1R. Experiments designed to relate MC1R genotype to precise pigmentation patterns in hair (balance of eu- and phaeomelanin) and skin response to UV allow Dr. Rees and coworkers to further our understanding of the relationship between MC1R sequence diversity and the actual physiology of the mutated receptors.

Dr. Mark Shriver outlined his recent work on the identification of genes contributing to pigmentation phenotypes in humans. As contrasted from the analysis of other complex multifactorial human disorders (e.g., obesity, diabetes, hypertension), Dr. Shriver believes that mammalian pigmentation genes may offer a more compelling experimental model to assess complex genetic interaction in the understanding of human pathology etiologies. For example many of the known pigmentation genes in mice and other mammals possess homologous sequences in humans that are responsible for human pathologies (e.g., albinism and Waardenberg Syndrome) that regulate in part the wide variation in human pigmentary phenotypes. By adopting methods like Mapping by Admixture Linkage Disequilibrium (MALD) to identify genes for polygenic traits, Dr. Shriver outlined current studies designed to detect and map pigmentation genes for skin color, hair color, eye color, and UV responsiveness.

Slide Session I: Pigmentation
By Nels Granholm

Dr. Tadokora and others presented data on the ability of normal human skin of various racial/ethnic groups to respond to UV exposure as determined by DNA damage/repair and melanin content as well as melanin synthesis. Their results suggest that both skin sensitivity as well as racial/ethnic origin are important determinants in response to UV and may be of value in predicting the risk of skin cancers.

An unusually pigmented human subject predicted to be a compound mutant at both P and MC1R loci (OCA2 plus unusual red hair) was discussed by Schmidt and others. Sequence analysis revealed a compound heterozygote for the P gene (N489D/W679C) and heterozygous at MC1R (R160W). This is the first published identification of a human OCA-like phenotype associated with red hair; the particular type of OCA for this subject should be distinguished from OCA3 (rufous/red OCA) due to the unique compound genotype.

Because of the existence of red-haired human phenotypes possessing wildtype MC1R sequences, additional loci besides MC1R may be directly involved in hair color. The agouti locus is a likely candidate due to its prominent role in coat color genetics of mice and other mammals. Drs. van Daal and Voisey undertook a study to analyze the entire agouti gene in humans (various racial/ethnic groups) for the presence of polymorphisms. Interestingly, following exhaustive analyses of agouti (ASP) sequences of subjects previously identified as positive for unusual MC1R variations, no polymorphisms were detected. Thus loci other than ASP and MC1Rmost likely participate in hair color in humans.

Tyrosinase activity in human melanosomes may be regulated in part by melanosomal pH. Data presented by Spaulding and others support a potentiating effect of IBMX and bafilomycin on the activation of preexisting tyrosinase rather than de novo tyrosinase synthesis. Regarding the mechanism, these authors also presented data suggesting that cAMP-elevating drugs like IBMX may be functioning in part via a hydrogen exchanger/transported within melanosomes.

To summarize, analysis of MC1R is not only interesting in and of itself but also as a model for human evolution. Characterizations of MC1R DNA and various expressed mutant proteins provide valuable data on generation of pigmentation phenotypes, UV susceptibility, as well as physiologically significant ligand-receptor interactions at MC1R as well as other members of the melanocortin family. Secondly, as a determinant of human skin and hair color, MC1R may be a major model gene, along with a number of others, for the analysis of human evolution. Thanks to all speakers of this session for provocative discussions.

Symposium II: New Approaches to the Pigment Cell
By Jean Bolognia

Using Gene Expression Patterns to Characterize Biological Diversity
Charles P. Perou, PhD, UNC

- cluster analyses of cDNA microarrays were utilized as a means to investigate the biological diversity of breast cancers that is noted clinically and histologically
- a common reference was developed in order to have baseline signal intensity; 11 different cell lines, both benign and malignant, composed this common reference
- an examination of biopsy specimens from 40 patients with T3 (≥5cm) breast cancers (in 20 cases, samples pre- as well as post-treatment with adriamycin were available) demonstrated: (1) the individuality of each breast cancer and the maintenance of this individuality post chemotherapy; (2) clusters of proliferation genes that correlated with the mitotic rate and the PCNA- and Ki67-labelling of the tumors; and (3) confirmation of the estrogen-receptor (ER) and ERBB2 status of the carcinomas
- the microarray analyses led to unexpected results including identification of: (1) a subtype of ER-positive breast carcinomas that had a poor prognosis (ER-positive breast carcinomas generally have a good prognosis); and (2) breast carcinomas with few p53 mutations that had a good prognosis as compared to those with multiple p53 mutations that had a poor prognosis
- in the future, such prognostic information could be used prospectively to identify individuals who would require more intensive therapy

The Role of Stem Cells in the Development of the Retina
Thomas Reh, PhD, Univ Washington

- the optic vesicle gives rise to the neural retina, the pigmented epithelium, and the optic stalk and this process requires interaction with the surrounding tissues
- factors expressed in the microenvironment include FGF and sonic hedgehog, and FGF produced by the nearby surface ectoderm promotes the development of the neural retina; overexpression of FGF leads to two layers of neural retina and no pigmented epithelium (the normal situation is one layer of neural retina and one layer of pigmented epithelium)
- the mesenchyme of the head produces the signals required for the development of the pigmented epithelium such that removal of this mesenchyme leads to decreased expression of two genes associated with the development of the pigmented epithelium, *MITF* then *Wnt13*; at the same time, the mesenchyme inhibited the expression of genes associated with the development of the neural retina
- studies pointed to activin, a TGFß-related protein, as one of the factors produced by the mesenchyme of the head (which is a neural crest-derived tissue); in organ cultures, activin can substitute for the mesenchyme of the head
- development of the neural retina is viewed as a default pathway and in amphibians as well as chicken and mammalian embryos, the pigmented epithelium has the ability to regenerate the neural retina; FGF promotes this process of regeneration and activin inhibits it
- greater insight into the process of regeneration of the neural retina could lead to its application clinically

Modulation of Melanogenesis in vitro: Importance of Keratinocyte-Melanocyte Interactions
Rainer Schmidt, PhD, L'Oréal

- co-cultures of normal human keratinocytes (NHK) and normal human melanocytes (NHM) that contained a ratio of melanocytes:keratinocytes similar to the *in vivo* situation were made possible via a defined medium
- in the presence of fetal calf serum and high concentrations of calcium, interactions between the cultured keratinocytes and melanocytes were enhanced
- in co-cultures as well as raft organ cultures utilizing NHK, NHM and de-epithelialized dermis, the rate of melanin synthesis was assessed via 2-^{14}C thiouracil uptake
- irradiation of co-cultures with UVB or UVA resulted in a dose-dependent increase in melanin synthesis while UVB irradiation of NHM (without NHK) led to increased melanin production only in the setting of cytotoxicity
- the expected enhancement or inhibition of melanin synthesis was observed in the organ cultures following treatment with tyrosine, kojic acid, or UV irradiation plus sunscreens
- the baseline pigmentation of the organ cultures was dependent upon the skin type of the donor of the NHM and independent of the skin type of the donor of the NHK

Slide session II: Cell biology
By Jean Bolognia

The Pink-Eyed Dilution Protein Acts Early in Melanosome Biogenesis
P. Manga, K. Chen, S.J. Orlow, New York University SOM

- the potential functions of the transmembrane P protein include: (1) tyrosine transporter; (2) structural protein of the melanosome; (3) stabilization of the melanosomal complex; (4) regulation of melanosomal pH; and (5) localization of melanosomal proteins
- evidence was provided to support this fifth possible function of the P protein; e.g., in *p* null melanocytes: (1) a major portion of the tyrosinase is cleaved, released from its membrane location and excreted into the culture media; (2) a fraction of the tyrosinase is retained in the ER; and (3) the P protein co-localizes with endoplasmic reticulum (ER) markers
- treatment with bafilomycin induces pigmentation and an increase in tyrosinase activity (but not an increase in tyrosinase protein) in null *p* melanocytes; this is accompanied by a decrease in the retention of tyrosinase within the ER and a decrease in the excretion of tyrosinase
- proposed functions for the P protein include proper folding of the tyrosinase protein within the ER or pH regulation within the ER (in particular an increase in the pH of the ER)

Melanosome Mapping by Purification of Early Stage Melanosomes
T. Kushimoto, V. Basrur, J. Valencia, J. Matsunaga, W.D. Vieira, J. Muller, E. Appella, V.J. Hearing, NCI, NIH

- melanosomes from human melanoma cells were isolated via a sucrose-density gradient, subjected to free flow electrophoresis for further purification, and then examined for enzyme activities
- stage II melanosomes were found to have high levels of tyrosinase and Dct activity; they also contained the proteins MART1 and gp100 (as detected in association with the internal matrix of the melanosome by HMB45)
- stage I melanosomes were found to have high levels of Tyrp1 and gp100 protein (as detected on the exterior surface of the melanosome by a-PEP13)
- a model was presented where tyrosinase, Tyrp1 and Lamp 2 are transported to stage I melanosomes via early and late endosomes while gp100 is transported to stage I melanosomes directly from the smooth ER (see presentation by Michael Marks for different model)

Melanosome Transfer to Keratinocytes is Regulated by Surface Glycoproteins and Melanosome Distribution in Keratinocytes is Regulated by the Recipient Keratinocytes
R.E. Boissy, L. Minwalla, I.C. LePoole, R.R. Wickett: presented by R. Sarangarajan Univ of Cincinnati SOM

- the use of fluorescein-labelled melanosomes allowed the examination of melanosomes within keratinocytes in co-cultures of melanocytes and keratinocytes
- the addition of specific neoglycoproteins and lectins as well as mixtures of these glycoproteins inhibited the transfer of melanosomes (14-44% by FACS analysis and 67-93% by EM); those glycoproteins that bind galactose were more effective inhibitors than those that bind mannose
- in co-cultures of NHK and NHM from lightly pigmented skin and co-cultures of NHK and NHM from darkly pigmented skin, the expected clustering of melanosomes [61%] and single dispersion of melanosomes [78%] within keratinocytes, respectively, was observed
- in co-cultures of NHK from lightly pigmented skin and NHM from darkly pigmented skin clustering of melanosomes [66%] was observed while single dispersion [64%] was observed in co-cultures of NHK from darkly pigmented skin and NHM from lightly pigmented skin; i.e., the source of the keratinocytes determined the distribution pattern (see Rainer Schmidt abstract for comparison)

Induction of Melanogenesis and Cellular Signaling Pathways by Bicyclic Monoterpene Diols
D.A. Brown, J.W. Galvin, M.T. Canning, A.B. Brown, D.B. Yarosh, AGI Dermatics

- monoterpenes are natural plant products that have aroma and are used in products such as perfumes
- two synthesized bicyclic monoterpene diols (BMD) were shown to increase tyrosinase activity in co-cultures of NHK and NHM; in two mutation assays, neither compound was mutagenic and the 2,2-dimethyl-3-propanyldiol norbornane proved to be the more potent agent
- the BMD's induced nitric oxide (NO) synthesis and based upon studies utilizing inhibitors of various steps in the NO/cGMP/PKG pathway, were hypothesized to work via this signaling pathway
- in a pilot study, application of BMD-containing liposomes to human skin in combination with retinols enhanced pigmentation to a greater extent than retinols alone

Analysis of the Signaling Pathway and the DNA Damaging Effects of UVB on Human Melanocytes
E. Pereira, M.C. Scott, A.L. Kadekaro, R. Kavanagh, H.G. Shertzer, and Z.A. Abdel-Malek, Univ Cincinnati SOM
UVA Induces Oxidative Stress and Genotoxicity in Human Melanocytes
Z.A. Abdel-Malek, A.L. Kadekaro, M.C. Scott, E. Pereira, R. Kavanagh, H. Kanto, and H.G. Shertzer, Univ Cincinnati SOM

- *in vitro*, melanocytes isolated from darkly pigmented skin have a greater melanogenic response to UVB irradiation than do melanocytes isolated from lightly pigmented skin and a higher frequency of cyclobutane dimer formation
- UVB irradiation of NHM also results in an arrest in the G0-G1 phase of the cell cycle as well as a dose-dependent increase in the production of H_2O_2
- UVB irradiation induces apoptosis of NHM as evidenced by an increase in the levels of Bax and a decrease in Bcl2
- UVB irradiation induced the phosphorylation of the stress activated MAP kinases p38 and JNK/SAPK (independent of $p90^{rek}$)
- oxidative stress as well as photoproduct production were thought to be involved in the effects of UVB irradiation on NHM in culture
- UVA irradiation penetrates deeper into the dermis than UVB and is known to generate oxygen species; a single UVA irradiation can increase tyrosinase activity
- UVA in doses of 22 to 100 J/cm^2 resulted in a dose-dependent inhibition of growth with arrest of cells at the G1-S boundary; cytotoxicity was observed at doses >58J/cm^2
- UVA irradiation (35 J/cm^2) was associated with a decrease in intracellular glutathione and an increase in H_2O_2 production as well an increase in several stress-response-related processes, e.g., levels of p53, expression of p21, and phosphorylation of the MAP kinase p38
- oxidative stress was thought to be involved in the effects of UVA irradiation on NHM in culture

Symposium III: Intracellular Trafficking and Organelle Biogenesis
By Vijayasaradhi Setaluri

This symposium highlighted the recent advances in intracellular sorting of lysosomal and melanosomal proteins, biogenesis of melanosomes and their transport in melanocytes. The speakers illustrated how a wide range of experimental approaches, including mouse genetics and molecular genetic analysis of human pigmentation disorders, are helping us understand the intricate mechanisms of assembly and intracellular transport of organelles. Appropriately, the symposium opened with a talk by J. Bonifacino (NIH) on the molecular machinery for biogenesis of lysosomes, the most extensively studied organelles. Discussion of lysosome biogenesis is also relevant for pigment cell biology in light of many similarities between melanosomes and lysosomes. Bonifacino described the role of a new class of proteins known as Golgi-localized, gamma-ear containing, ARF-binding proteins (GGAs) in sorting of mannose 6-phosphate receptors (MPRs). Binding of the amino terminal VHS domains of clathrin-associated GGAs, specifically to the di-leucine sorting signal in the cytoplasmic tails of MPRs was shown to mediate sorting of MPRs from the trans-Golgi network (TGN) to endosomes. AP-1, the adaptor protein which was originally thought to mediate this sorting, is now relegated to a less important position in sorting MPRs and thereby lysosome biogenesis.

The ongoing debate over the relationship between lysosomes and melanosomes was addressed by Micheal Marks (Univ. Pennsylvania). Using immunogold electronmicroscopy as a principal tool, Marks suggested that in pigment cells, melanosomes represent a lineage of organelles distinct from conventional endosomes and lysosomes. The most significant findings described include the possible involvement of a Pmel17 enriched coated-endosome like structures in melanosome biogenesis, and the observation that melanosomal proteins are segregated from the late endocytic pathway.

While the early events in the biogenesis of melanosomes are still being worked out, much progress has been made in understanding the molecular mechanisms involved in the polarized transport of melanosomes toward keratinocytes. N. Jenkins (NCI) described the genetic approaches that led to the identification of melanophilin, a protein encoded by leaden (ln) gene. In ln mice melanin synthesis is normal but melanosome transport is impaired resulting in clumping of melanosomes, a phenotype similar to that found in dilute (d) and ashen (ash) mutant mice. Jenkins proposed that melanophilin, a novel Rab effector protein, functions as part of a transport complex with MyoVa and Rab27a proteins encoded, respectively, by d and ash loci. Data on candidate genes for dilute suppressor, a locus that suppresses ashen and leaden was also presented.

Understanding vesicular transport has implications for not only pigmentation but also other human disorders. Defects in vesicle formation and trafficking manifest as hypopigmentation and storage pool deficiencies. Whereas Griscelli syndrome and Chediak-Higashi syndrome result from vesicle trafficking, defects in vesicle formation appear to be responsible for Hermansky-Pudlak syndrome (HPS), a group of disorders characterized by oculocutaneous albinism and platelet storage pool deficiency. William Gahl (NIH) described the molecular characterization of HPS-1, HPS-2 and HPS-3 genes and a candidate HPS-4 gene. Among these, the function of only HPS-2 gene product, a subunit of adaptor complex (AP-3), in vesicle formation is understood.

It is becoming increasingly clear that exit of melanosomal proteins from the endoplasmic reticulum (ER) is a regulated event, and some pigmentary disorders are ER retention diseases. R. Halaban (Yale Univ.) presented data that suggests proper folding and exit of tyrosinase from the ER is induced by its substrates DOPA and tyrosinase. V. Hearing et al. (Toyofuku, NCI) analyzed intracellular processing of tyrosinase and TRP-1 in mouse melanocyte lines expressing mutant tyrosinase or mutant TRP-1, and proposed that OCA1 and OCA3 are ER retention diseases where mutation of one melanogenic protein affects the maturation and stability of others in the melanogenic pathway. S. Orlow and his coworkers (B. Shen, NYU) expressed wild type and mutant Oa1-GFP in heterologous COS cells and showed that Oa1 affects structure of late endosomes. Setaluri and coworkers (Wake Forest U.) presented data that suggests a role for GIPC, a PDZ-domain protein, in sorting and targeting of TRP-1.

Slide Session V: Cutaneous Pathology and Vitiligo
By Gisela F. Erf

Dr. G. Emilia Costin presented data on the assessment of drug-delivery systems using N-butyldeoxynojirimycin (NB-DJN) inhibition of tyrosinase as an end-point. NB-DJN is an inhibitor of ER a-glucosidase known to inactivate tyrosinase in B16-F1 melanoma cells. However, high concentrations of NB-DJN (5 mM) were required to effectively inhibit tyrosinase, suggesting inefficient cellular uptake of NB-DJN. Cellular uptake of NB-DJN could be greatly increased by encapsulating NB-DJN in liposomes. The most effective delivery system for NB-DJN was found to be pH-sensitive liposomes, requiring 100 to 1000 times less NB-DJN for inhibition of tyrosinase activity. Empty pH-sensitive liposomes carriers did not affect tyrosinase activity and were not toxic to the cell. Hence, the pH-sensitive liposome is a highly efficient carrier for delivery of ER-targeted drugs.

Dr. Guido W. Swart presented data on novel cDNAs identified when comparing mRNA expression profiles at various stages of human melanocyte transformation. One of the transcripts picked up during RT PCR-based subtractive hybridization is pCMa1which was localized to the distal, telomere proximal region on the short arm of chromosome 11.p15.1-2. cDNA clone pCMa1 (0.45 kb) did not contain a unique long reading frame and Northern blot analyses revealed multiple complementary pCMa1 transcripts of different lengths. *In situ* hybridization with an arbitrarily defined minus strand cRNA probe known to bind to a 4.0 kb plus transcript of pCMa1 revealed differential expression of pCMa1depending on the stage of neoplastic progression of melanocytes. The level of plus transcripts was highest in melanocytic nevi (10/10), variable in primary melanoma lesions (5/6), and negative in normal skin melanocytes and most (3/4) metastatic melanoma. The transient expression of pCMa1 in the neoplastic progression of melanocytes suggests that pCMa1 is a molecular marker for early stages of melanocyte transformation.

Dr. Rangaprasad Sarangarajan reported data on the role of the pro- and anti-apoptotic proteins of the Bcl-2 family in melanocyte apoptosis induced by 4-tertiary butyl phenol (4-TBP) in the etiopathology of contact vitiligo. Expression of four members of the Bcl-2 family (i.e., Bcl-2, Bcl-x, Bax, and Mcl-1) in normal human melanocytes (NHM) cultured with or without 250 µM 4-TBP was analyzed by flow cytometry and immunofluorescence techniques. Exposure of NHM to 4-TBP altered Bcl-2 expression whereas expression of the other apoptotic proteins was unchanged. Western blotting for tyrosinase, TRP-1 and Bcl-2 in NHM cells exposed to 4-TBP for 24, 48, and 72 h revealed no detectable change in all three proteins at 24 h, whereas decreased levels of Bcl-2 and tyrosinase were observed at later time points of 4-TBP exposure. Considering the anti-apoptotic role of Bcl-2, a minimal increase in Bcl-2 expression at 24 h may be an effort to protect the melanocyte from apoptosis induced by 4-TBP, whereas the drop in Bcl-2 after prolonged exposure to 4-TBP may promote cells to undergo apoptosis.

Ms. Xiaoli Wang presented two papers on the etiopathology of autoimmune vitiligo in Smyth line (SL) chickens. In her first presentation, she reported data on demonstrating the presence of interferon gamma (IFNγ) in the feather (the site of melanocyte destruction) of vitiliginous SL chickens using Northern blotting with an anti-sense chicken (ch)-INFγ-specific digoxigen-labeled riboprobe and immunoblotting with anti-chINFγ monoclonal antibodies. Using this approach, INFγ was detected in feathers of chickens with active vitiligo but not in chickens with stable vitiligo or chickens without vitiligo (non-vitiliginous SL chickens and normally pigmented parental Brown line controls). Based on flow cytometry, the INFγ producing cells in the feather included CD4+ lymphocytes. Taken together, these observations support a role of a Th1 dominated cell-mediated immune response in the loss of melanocytes in SL vitiligo.

In her second presentation, **Ms. Xiaoli Wang** showed data on *in situ* TUNEL and immunohistochemical staining of feather tissue obtained from SL chickens at various times prior to and throughout the development of visible vitiligo. In vitiliginous SL chickens, the numbers of apoptotic cells in the feather, especially in the epithelial barb ridge where melanocyte cell bodies are located, were higher than in non-vitiliginous SL and control chickens. The increased incidence of apoptosis was first observed at onset of vitiligo and was highest in active vitiligo, suggesting a close association between apoptosis and the disappearance of melanocytes. The number of CD8+ cells and MHC class II+ cell (including MART-1+ cells) increased two weeks prior to onset of vitiligo. Considering the temporal relationship and the close physical location between CD8+ feather infiltrating lymphocyte and TUNEL+ cells suggests that the apoptosis in vitiliginous feathers was induced by cytotoxic T cells.

Dr. Gisela Erf presented data on studies examining the role of turkey herpesvirus (HVT) in the expression of vitiligo in SL chickens. Using a time course approach, flow cytometry and virus reisolation techniques, it was found that HVT vaccination of SL chickens at hatch greatly increased the proportions of CD4+ splenocytes at 3 days of age and those of CD8+ splenocytes between 14 and 42 days of age. These changes in T cell profiles were suggestive of cell-mediated immune activity. Although HVT could be isolated from the thymus at 3, 6, and 9 days of age, the proportions among thymocyte populations were not affected by HVT. HVT did not affect lymphocyte profiles in the thymus and spleen of BL controls. However, HVT could be reisolated from thymus, spleen, bursa and blood at the same time points and at comparable amounts in both HVT-vaccinated SL and BL chickens. These observations suggest that SL chickens may have a heightened/inappropriate immune response to HVT that may play a role in triggering vitiligo.

Dr. Roger Bowers completed the session by presenting data from his research on other avian models for vitiligo, the Barred Plymouth Rock (BPR) and White Leghorn (WL) chickens. Premature death of melanocytes in BPR and WL chickens is due in part to low antioxidant superoxide dismutase (SOD) activity (50% and 75% of SOD activity in the wild type Jungle Fowl (JF), respectively). Molecular characterization studies of the CT Cu/Zn SOD gene, revealed 99% homology in cDNA sequence between the three types of chickens. A missense mutation observed in BPR may affect protein structure and, hence, SOD activity. SOD mRNA levels were lower in WL chickens compared to BPR and JF chickens, with SOD mRNA levels being highest in BPR chickens. It appears that the low SOD activity in WL chickens may be due to reduced transcription of the SOD gene. Whereas, the reduced BPR SOD activity must be due to post-transcriptional control of the SOD enzyme, because of the elevated levels of SOD mRNA in BPR compared to JF. SOD gene transcription may be increased in BPR in response to the reduced activity of SOD. Considering that WL chickens have both the barring gene (associated with a post-transcriptional decrease in SOD activity) and the dominant white gene (associated with reduced SOD gene transcription), Dr. Bowers suggested that this could explain why WL melanocytes are much more susceptible to premature cell death than BPR melanocytes.

Slide Session VI: Model Systems and Late Breaking Research
By William Oetting

The search for genes associated with albinism started in 1986 with the cloning of the tyrosinase gene, and has not shown any signs of ending. This session included two papers, one from Dr. Murray Brilliant, at the University of Arizona, and Dr. William Gahl, at the N.I.H. identifying two new genes in which mutations result in albinism in humans.

Dr Murray Brilliant presented a paper showing that the human homologue of the mouse *underwhite* locus, *underwhite-dominant brown* (UW^{db}) is responsible for a fourth type of albinism in humans, oculocutaneous albinism type 4 (OCA4). The UW^{db} phenotype looks like the *pink-eyed dilution* (*p*) locus in the mouse, the

human homologue of which is associated with OCA2. This UW^{db} allele is dominant; the heterozygote is less hypopigmented than the homozygote. The gene was cloned from both the mouse (chromosome 15) and the human (chromosome 5p). The protein has 12 membrane spanning regions and appears to be a membrane spanning transport protein that has some homology to a plant proton-sucrose transporter. One possible role for the protein is to balance the osmolarity in either the melanosome or the melanocyte. The human gene has been tentatively termed membrane spanning transport protein-1 (MSTP1). The human sequence is highly conserved to the mouse coding sequence. Two individuals with albinism, with residual pigmentation, were identified as having mutations in MSTP1 locus. One individual was homozygous for a splice site acceptor at exon 2, and the second individual had an in-frame deletion, that was thought to alter the protein structure. Sequencing of the tyrosinase gene (OCA1) and the P gene (OCA2) in individuals with albinism has shown that a significant percentage have no identifiable mutations in either of these two genes, showing that other genes associated with albinism most likely exist. TYRP1 associated with OCA3 and now MSTP1, associated with OCA4, have provided an explanation for the albinism in these individuals. It could be that this is only the beginning of an expanding list of genes associated with albinism.

A long list of genes associated with albinism is highly evident in genes associated with the Hermansky-Pudlak Syndrome (HPS). To date, two genes, HPS1 and ADTB3A (HPS2) have been identified. Dr. William Gahl now reported a third locus associated with HPS, HPS3. Individuals with HPS have albinism, along with platelet storage pool deficiency resulting in a bleeding disorder, and in some cases lysosomal ceroid lipofuscinosis, pulmonary fibrosis and granulomatous colitis. This newly identified gene is part of the very interesting story of HPS in Puerto Rico. The initial HPS gene, HPS1, was identified in a founder population in the Northwest corner of Puerto Rico. Affected individuals all shared a 16 bp duplication in the HPS1 gene. Although this mutation explained the HPS in some individuals in Puerto Rico, it was also known that there was a population of individuals in Central Puerto Rico that had HPS but did not have this mutation, or any other mutation in the HPS1 gene. Analysis of these individuals showed that their HPS mapped to another location. For these individuals a candidate gene was identified and cloned. The gene contains 17 exons and the coding sequence coded for a protein containing 1004 amino acids (113.7 kDa). No homology was found to other proteins. The HPS3 protein contains a clathrin binding site, an ER retention signal and a dileucine motif associated with protein trafficking to the melanosome. In the HPS population in Central Puerto Rico, a 3,904 bp deletion, including exon 1, was found in this gene. This deletion was found to be flanked by Alu repeats, which may describe the mechanism for the deletion. The deletion was thought to occur about 5.3 generation ago, or about 110 to 120 years. There are 15 known mouse loci that present with a HPS like phenotype, yet this gene was not any of the known mouse HPS loci. The HPS3 mouse homologue is the *subtle grey* locus. There is every reason to assume that other individuals with HPS will have mutations in these other genes, making the work of understanding the molecular basis of HPS a continuing story.

Symposium V: Phenoloxidases, Melanogenesis and Evolution
By Vincent Hearing

This Symposium was obviously scheduled to see who really, really couldn't get enough of pigmentation. It was held early on a Sunday morning, starting at 8 am on the final day of the meeting. Despite that, there was a good turnout and those who had the energy to attend were in for a treat. **Prof. Heinz Decker** (Univ of Mainz, Germany) was an invited lecturer who spoke on the structure, function and evolution of hemocyanin in the context of its relationship to tyrosinase. He notes that the enzymes tyrosinase, catechol oxidase and hemocyanin all share similar active sites (utilizing copper as the ligand), although their physiological functions are quite distinct. Tyrosinases in lower species (such as amphibians) are activated in vivo by proteolytic cleavage, which might open up substrate access to the catalytic site, and he made the interesting finding that if hemocyanin (typically found in arthropods) is subjected to similar proteolytic treatment in vitro, it shows a catechol oxidase activity reminiscent of that of lower forms of tyrosinase. Characterizing the structure of hemocyanin is an important model to understand the substrate active-site interactions of tyrosinases. Want more detail? Check out his recent reviews published in J Biol Chem (2001;276:15563-9) and Trends in Biochem Sci (2000;25:392-7). **Prof. Manickam Sugumaran** (Univ of Massachusetts, USA) moved up the evolutionary ladder to insects and discussed the role of phenol oxidases which play important roles in sclerotin formation, wound healing and defense reactions. It turns out that in addition to tyrosinase, insects also have a tyrosinase-related protein, called dopachrome isomerase. That latter enzyme is distinct from our favorite enzyme, dopachrome tautomerase, since the catalytic reaction in insects eliminates the carboxyl group rather than keeping it. Sugumaran's studies confirm the presence of a melanogenic complex between the phenol oxidase and dopachrome isomerase, and by forming that complex, the enzymes regulate each other's activity and control the levels of endogenous quinones produced. The complex is critically

important for the defense strategies of insects. Need to know more? Check out his recent paper in Adv Exp Med Biol (2001;484:289098) or wait for any early issue of Pigment Cell Research next year in which Prof Sugumaran will review this field.

Slide Session VII: Gene Regulation
By Vincent Hearing

The morning Symposium then continued with 6 talks selected from the submitted abstracts. **Dr. Brian Potterf** discussed Sox10, a transcription factor that activates expression of Mitf, another transcription factor that we all know regulates at least some of the melanogenic genes. Both Sox10 and Mitf play important roles during melanoblast development, and then reprise their roles to regulate melanocyte differentiation in later stages of life. Potterf and colleagues examined the effects of mutations in Sox10 on the development of neural-crest derived melanocytes; their evidence suggests that Sox10 is an transcriptional activator of Dct expression, which is consistent with the early expression patterns of Dct in mouse embryos. **Dr. Dong Fang** then reported on his work on the regulation of expression of Tyrp1; they found an upstream enhancer element in the Tyrp1 promoter and their results suggest that transcription of Tyrp1 is regulated not only by the M-box, but also by 2 novel elements in the Tyrp1 promoter. The Tbx2 transcription factor may function as an inhibitor of Tyrp1 expression, perhaps by blocking the binding of Mitf to the M-box of the Tyrp1 promoter. This repressor site is not found in the tyrosinase promoter, which may explain the coordinated but sometimes distinct expression patterns of those 2 genes. **Dr. James Lister** then discussed the duplicate Mitf genes that are found in zebrafish. There is a redundancy in their patterns of expression and they are expressed differentially in neural crest derived melanocytes and in the retinal pigment epithelium. One of them is similar to the mammalian 'A' form of Mitf, the other being similar to the 'M' form. These genes probably original from a single Mitf ancestor via duplication. **Dr. Thomas Hornyak** then discussed his work with Mash1 (a neurogenic transcription factor); it is a bHLH transcription factor that is involved in regulating neural crest development. Mash1 was found to negatively regulate Dct transcription. Expression of Mash1 in transgenic mice (regulated by the Dct promoter) led to the development of fewer neural crest-derived melanoblasts, although those did successfully localize in the hair follicles of adult mice. **Dr. S. Shriram** then presented the results of a study characterizing various mutations of the tyrosinase gene that are found in oculocutaneous albinism, but interestingly, focusing on cases of OCA1 in which no mutation has been identified, or only 1 allele is affected. They found (in a limited number of cases so far) that expression of only 1 allele (the known mutant) was found in the heterozygous cases, perhaps because of a mutation in the promoter region of the other allele which abrogates transcription of that other allele (which may encode a wild-type tyrosinase enzyme). It will be interesting to see how common this phenomenon is seen in such recessive diseases. And finally, **Dr. Caroline LePoole** presented a paper on the regulation of gp100 (sometimes called Pmel17, silver and/or HMB45) transcription. This completed the circuit of the known melanosomal-specific genes discussed in the Symposium. LePoole found that the gp100 promoter has a predicted upstream region (~ 1 kB upstream) that might bind CDK-2, and 3 upstream (~ 0.5 kB) potential E-box sites. However, Mitf was unable to activate the gp100 promoter. The sum of their results suggest that CDK2 is a negative regulatory element of gp100 expression and that Mitf is not involved in the regulation of expression of gp100.

In sum, this was an exciting session that showed the distinct and independent regulation of 4 genes which encode melanosome-specific proteins (tyrosinase, Tyrp1, Dct and gp100). It is clear that all 4 genes are regulated by positive and by negative regulatory factors in distinctive and complex patterns.

Positions - Wanted and Available :

Postdoctoral Position

Polarized Kit-ligand expression in the epidermis: Its role in human melanocyte homeostasis

A postdoctoral position (fully funded for the first year with the possibility of a 2 year extension) is immediately available in the Department of Pathology, Centre Medical Universitaire at the University of Geneva, Switzerland. The project is supervised by Dr. Bernhard Wehrle-Haller and Prof. Beat Imhof and is within the frame of a collaboration between the University of Geneva and Industry.

The aim of this project is to understand the role of kit-ligand in melanocyte homeostasis in the adult epidermis and how manipulation of kit-ligand expression or localization in keratinocytes affect melanocyte behavior. The project will employ cell-biological, pharmaceutical, biochemical as well transgenic approaches (mouse) to develop

methods to modify Kit-ligand localization (polarity and cell surface expression) in vivo and to study melanocyte behavior in response to such altered Kit-ligand presentation. For references and rational see Wehrle-Haller and Imhof (2001, J. Biol. Chem. 276, 12667-74) and Grichnik et al., (1998, J. Invest. Dermatol. 111, 233-38).

The Centre Medical Universitaire provides a stimulatory research environment located within the City of Geneva. Research in the department is centered around problems of autoimmunity, wound healing, inflammation, cell-cell junctions and cell migration. Geneva, located at the lake of Geneva in close proximity to the French Alps, provides a rich multicultural environment facilitating social integration.

Interested candidates preferably having experience in one or more of the aforementioned domains should send their CV (e.g. e-mail) including names and contacting information of two references to:

Bernhard Wehrle-Haller PhD
Department of Pathology
Centre Medical Universitaire
1. Rue Michel-Servet
1211 Geneva 4
Switzerland
Tel/Fax: 0041 22 702 5735 / 5746
Bernhard.Wehrle-Haller@medecine.unige.ch

Postdoctoral Research Position

A postdoctoral position is available immediately to study the transcriptional co-repressor and co-activator activities of the oncogenic protein Ski in human melanomas (PNAS (USA) 97:5924-5929, 2000). Seeking individuals with experience in EMSA, *in vitro* transcription-translation, site-directed mutagenesis and yeast two-hybrid screening. Interested individuals should send inquiries and applications (including CV, a brief description of past experience and future research interests, and the name of three references) to:

Estela E. Medrano, Ph.D.
Huffington Center on Aging
Baylor College of Medicine
One Baylor Plaza N-803.01
Houston, TX 77030

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Research Associate/Post Doctoral Fellow Position Available

Position available for either an entry level postdoctoral fellow or a more senior research associate to study the molecular and cellular biology of the melanocyte in general and the pathophysiology of vitiligo in specific. The research project will focus globally on the role of survival factors and apoptotic regulators on the viability of melanocytes in the skin and in culture. In addition, the project will focus on the genetic and cellular susceptibility of melanocytes from patients with vitiligo to under apoptosis in response to various stimuli. Postdoctoral fellow candidate should have experience with routine molecular and cellular techniques including cell culturing, site directed mutagenesis, and protein biochemistry. Research Associate candidate should have similar experiences utilizing the melanocyte system. Candidate will become part of an interactive research group focusing of various aspects of pigmentation in the Department of Dermatology and on skin physiology in the Skin Sciences Institute within the University of Cincinnati College of Medicine. Send curriculum vitae and list of three references to:

Raymond E. Boissy, Ph.D.
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Principal Scientist- Clinical Research - Skin Science Research

Unilever employs over 200 scientists at our New Jersey Laboratory who are dedicated to innovative and scientifically rigorous skin research programs. Our world sales exceed $40 billion so our programs have solid financial funding allowing for an innovative and challenging research culture. We currently have a full time opening that provides a unique opportunity to apply your basic science skills to human studies that impact the condition of skin for hundreds of millions people worldwide. We are seeking an expert in pigment biology or photobiology who can advance our knowledge and link laboratory research to clinically defined improvements of consumer skin problems. As a member of our skin research team, you will have an opportunity to work with other scientific experts in many fields including cell biology, biochemistry, measurement science and physical chemistry. You will also be encouraged to establish and maintain close ties to research in academic and government research communities.

We offer a competitive salary, benefits including tuition assistance and relocation, and a dynamic environment filled with learning and discovery beyond conventional scientific boundaries. Applicants must be authorized to work in the USA. For consideration please forward your CV to: Human Resources, Dept. CR-SID, Unilever Research US, 45 River Road, Edgewater, NJ 07020 or E-Mail: job.mca@unilever.com . Please place only the letters "CR-SID" as the subject of your e-mail. Unilever is an Equal Opportunity Employer m/f/d/v.

Postdoctoral Fellows - Cancer and Developmental Biology - Two NIH-funded positions are available for fellows interested in studying the Hedgehog signaling pathway in development and disease using skin as a model system. One project centers on defining the function of the Hedgehog pathway during skin appendage morphogenesis (Dev. Biol. 205: 1-9, 1999); a second project focuses on understanding how deregulated activation of this pathway gives rise to basal cell carcinomas (Nature Genet. 24: 216-7, 2000). Applicants should have a solid background in molecular and cell biology, with experience in transgenic animal models desirable but not required. Interested individuals should send a CV, letter of interest, and names of three references to: Dr. Andrzej Dlugosz, University of Michigan, Department of Dermatology and Comprehensive Cancer Center, 3310 CCGC, Box 0932, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0932 Email: dlugosza@umich.edu. The University of Michigan is an Equal Opportunity Employer.

Postdoctoral Research Associate - Position available to study the biology of human inherited disorders of pigmentation using gene transfer technology. The successful applicant will have a Ph.D. and/or M.D. with experience in cell biology and molecular biology. Experience in gene transfer/genome manipulation is preferred. Please send curriculum vitae along with the names of three references to Dr. Richard King, Division of Genetics, Department of Medicine, Box 485 Mayo, 420 Delaware St. S.E., University of Minnesota, Minneapolis, MN 55455. Equal Opportunity Employer.

Postdoctoral Position - Ph.D. in molecular biology, biophysics, genetics or biochemistry. Position available to conduct research on molecular mechanisms of cellular response to oxidative stress in human melanocytes and melanoma cells and its regulation for preventive and therapeutic indications. Contact Dr. Frank L. Meyskens Jr., Director, University of California-Irvine, Chao Family Clinical Cancer Research Center, 101 The City Drive, Orange, CA 92668, USA. Fax (714) 456-5039 Email flmeyske@uci.edu

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The Bibliography published in this issue covers the period June, 2001 through August, 2001. 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. We have attempted to highlight any publications which include a member of the PASPCR with a star (*sorry if we missed you but let us know and you'll get a free marked repeat in the next issue*).

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MELANOMA & METASTASIS

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