PASPCR Newsletter

Volume 7 Number 4 **December, 1999**

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 is the major, up-to-date source of current information for the **PASPCR** membership. The URL address to our home page is **http://www.cbc.umn.edu/paspcr**. This is a very active web-page, and as of December, the PASPCR home page has had over 15,000 'hits'. 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** is 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.

Note: The IFPCS webpage has a new URL address at http://www.cbc.umn.edu/ifpcs.

IN THIS ISSUE . . . . .

PanAmerican Society for Pigment Cell Research

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Calendar of Events :

Jun 25 - 28, 2000 IXth Annual Meeting of the PanAmerican Society for Pigment Cell Research, to be held in College Station, TX
Contact: Dr. Lynn Lamoreux, Department of Veterinary Pathobiology, The Texas Veterinary Medical Center, Texas A & M University, College Station, TX 77843-4467;
Phone: (409) 845-6084
Fax: (409) 845-9972
Email: llamoreux@vetmed.tamu.edu.

Sept 28 - Oct 1, 2000 9th Annual Meeting of the European Society for Pigment Cell Research, to be held in Ulm, Germany
Contact: Prof. R.U. Peter, University of Ulm (BWK) Dept of Dermatology Oberer Eselsberg 40 D - 89081 ULM
Tel: 49-731 502-3770
Fax: 49-731 502-3772
E-mail: ralf.peter@medizin.uni-ulm.de

Dec 5-6, 2000 13th Meeting of the Japanese Society for Pigment Cell Research, to be held in Sapporo , Japan,
Contact*:* K Jimbow

Feb 28, March 3, 2001 5th World Conference on Melanoma : Venice, Italy, February 28 - March 3
Contact: Dr Mario Santinami Secretary General 5th World Conference on Melanoma Casa di Cura S. Pio X Via F. Nava 31 I - 20159 Milano
Phone/Fax: 39-02-69516449
E-Mail : info@melanoma2001.org

Jun 25 - 28, 2001 Xth Annual Meeting of the PanAmerican Society for Pigment Cell Research, to be held in Minneapolis, MN
Contact: Dr. Richard A. King, Department of Medicine, Box 485 Mayo, 420 Delaware St. S.E., Minneapolis, MN 55455;
Phone: (612) 624-0144
Fax: (612) 624-6645
Email: king@mail.ahc.umn.edu.

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
Phone: 31-(71) 526 1952
Fax: 31-(71) 524 8106;
E-mail: SPavel@algemeen.azl.nl

Sept 3-7, 2003 XIth Annual Meeting of the PanAmerican Society for Pigment Cell Research, to be held in Wood's Hole, MA.

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.

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PASPCR Council Elections 2000

by Richard A. King

The election for three council positions will be held in January, 2000. Council members are elected for a three-year term, for the period 2000-2002. The Nominating Committee has selected the following candidates for this election and the names were announced at the November PASPCR General Membership meeting in Nagoya:

Mary K Cullen
Thomas Hornyak
Randall Morrison
Hee Young Park
Brian Potterf
Vijayasaradhi Setaluri

According to the PASPCR by-laws, five members of the Society may, by petition signed by each and accompanying a written statement of the nominee asserting his/her willingness to serve, nominate a candidate or candidates for the council. The Secretary/Treasure must receive such petitions not later than 60 days before the election.

19th International Pigment Cell Conference

The PASPCR and IFPCS invite members of the PASPCR to submit proposals for hosting the 19th IPCC. In 2005 the IPCC will be held in the Americas (North, Central or South). Those interested in hosting and chairing this meeting should prepare their invitation to present to the Council of the PASPCR meeting at College Station, Texas during the June 25-28, 2000.

The interested parties should present the advantages of hosting the meeting in their city and university; general plans and topics or themes; proposed levels of funding and sources of funding; plans for organizing the scientific meeting; conference facilities; hotels and recreation or other topics that will help the Council of the PASPCR select the best site for this meeting.

Vince Hearing at NIH and Jim Nordlund at Cincinnati both have indicated their interests in hosting the meeting. Others interested should contact Dick King at the University of Minnesota to indicate their interest.

The New Pigment Cell Research Editor

by Jim Nordlund

Vince Hearing is the new editor of the Pigment Cell Research. Munksgaard is keeping the price of the Pigment Cell Research constant this year. Every senior member of the PASPCR should subscribe to this journal and contribute articles. Some new and junior members will receive complementary copies.

We should all thank Jiro Matsumoto for the superb job he did with the Journal.

Mouse Loci Table

by Bill Oetting

A table containing coat color genes described in mice and their human homologues has been created and placed on the IFPCS web page. The site is at http://www.cbc.umn.edu/ifpcs/micemut.htm. Only those genes that have been cloned (at present 27 genes) have been included. There are also links to the Jackson Laboratory Mouse Genome Informatics Web page and Online Mendelian Inheritance in Man (OMIM) for each entry. I hope that this table is of use to you. If you have any corrections or additions, please let me know at bill@lenti.med.umn.edu and I will make the inclusions/changes. I would like to thank Drs. Dot Bennett and Vince Hearing for help in the table.

Positions - Wanted and Available :

Postdoctoral position - Ph.D. in molecular or cellular biology. Position available in the skin research center of Johnson & Johnson to study molecular and cellular mechanisms involved in pigmentation. Experience in tissue culture, molecular and cellular techniques and microscopy is required. Please send CV, brief description of experience and names of three references to Dr. M. Seiberg, 199 Grandview Rd., Skillman NJ 08558 or MSEIBER@CPCUS.JNJ.COM

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.

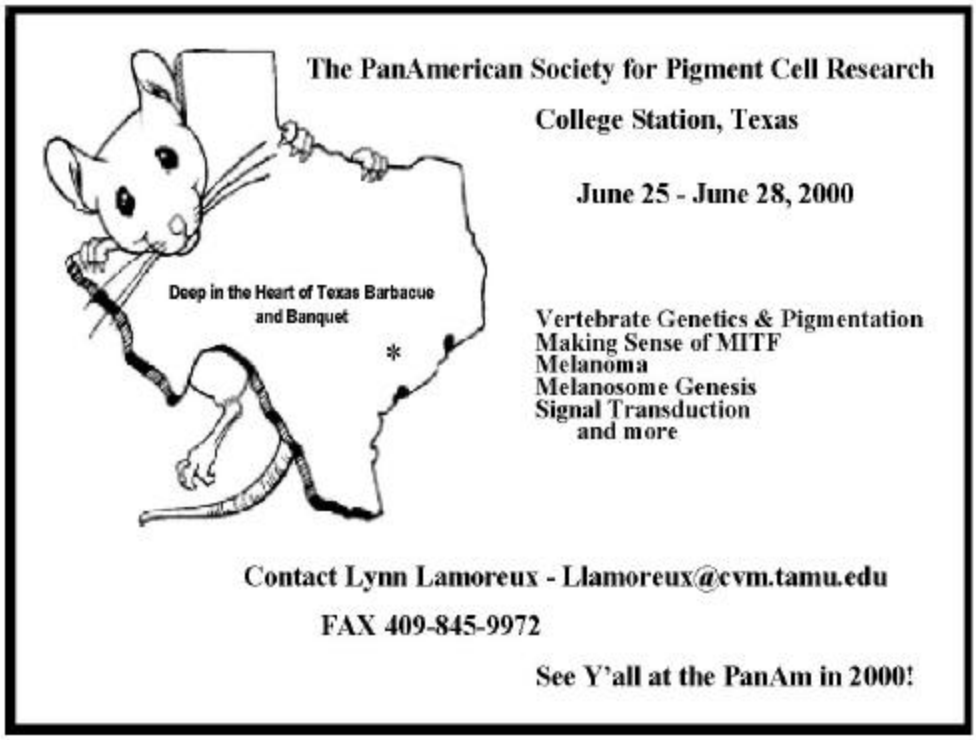
Postdoctoral Position - Ph.D. in molecular biology, biophysics, genetics or biochemistry. Position available to conduct research on molecular mechanisms of cellular response to oxidative stress in human melanocytes and melanoma cells and its regulation for preventive and therapeutic indications. Contact 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

Members in the News -

The **Myron Gordon Award** was presented to **Dr. Vincent J. Hearing, Ph.D**. at the International Pigment Cell Conference, in Nygoya, Japan, "In Recognition of His Biochemical and Physiological Studies on the Regulation of Melanin Formation in Mammalian Melanocytes".

The Myron Gordon Award was also presented to Prof. Shosuke Ito, Ph.D. "In Recognition of His Chemical and Biochemical Studies on Melanins and Melanogenesis".

Gregory S. Barsh - was awarded the **Takeuchi Medal** which was presented by Prof. Jiro Matsumoto (President, JSPCR) and Mrs. Chizuko Takeuchi on behalf of the JSPCR and the IFPCS at the International Pigment Cell Conference, in Nygoya, Japan



Session Reports from the XVIIth International Pigment Cell Conference and Satellite Meetings

Satellite Meeting No. 1
Vitiligo: A Manifestation of Apoptosis?
Report by James J. Nordlund

Symposium Chairmen: James J. Nordlund (University of Cincinnati) and Seung-Kyung Hann (Korean Institute for Study of Vitiligo and Yonsei University)

Goal of Symposium: This symposium on vitiligo emphasized one mechanism, i.e., apoptosis. The goal was to stimulate new ideas and approaches to the problem of vitiligo and its treatment.

Major Problems for Investigators: (James J. Nordlund, M.D., University of Cincinnati, USA) The most important goal for investigators is to find a safe, effective medication that will stop the spread of vitiligo when it first begins or that retains pigmentation after successful treatments. The second most important goal is to find better ways to transplant autologous melanocytes in those whose depigmentation affects glabrous (hairless) skin.

Mechanisms of Cell Death:

Ultrastructure of apoptosis: (Raymond Boissy, Ph.D., Caroline LePoole, Ph.D. and Ying Boissy, University of Cincinnati) Apoptosis is a programmed induced destruction of cells by which unneeded or senescent cells are

eliminated from the body without induction of an immune process. Necrosis is another form of cell death by which the cells are disrupted and release cellular antigens that might induce an immune response.

Apoptosis has morphological features including 1) alterations in membrane fluidity; 2) blebbing of the plasma membrane; 3) cell fragmentation in which apoptotic bodies are released into the environment; 4) vacuolization of the cytoplasm; 5) cellular shrinkage; 6) condensation of the chromatin along the nuclear membrane; 7) activation of calcium or potassium sensitive endonucleases that fragment DNA.

Apoptosis has been demonstrated as a mechanism of melanocyte death in a model system in which human melanocytes in culture are exposed to chemical toxins such as 4-tertiary butyl phenol (4-TBP). Melanocytes obtained from patients with vitiligo that are grown in culture also exhibit features of apoptosis especially if the cells are not maintained in very special conditions.

Apoptosis has not been clearly observed in the skin of patients with advancing vitiligo. However some melanocytes in the spreading lesion exhibit features that suggest cellular shrinkage and condensation of heterochromatin, features consistent with apoptosis.

Molecular Mechanisms of Apoptosis: (Yoshihide Tsujimoto, Ph.D., Osaka University, Japan) Apoptosis is a method of destruction of cells that must be selectively eliminated as part of tissue homeostasis, for morphogenesis or removal of other harmful cells such as cancers. The process is driven by a family of cysteine proteases called caspases. Caspases cleave a set of special proteins that initiate apoptosis. The Bcl-2, Bcl-x and Bcl-w are three of the better characterized anti-apoptotic proteins that inhibit apoptosis and protect a cell from destruction. Pro-apoptotic molecules include molecules such as Bid, Bik and Bim. The anti and pro apoptotic proteins form heterodimers inactivating each other.

Mitochondria play an essential role in apoptosis. The electrical potential across a cell destined for destruction by apoptosis is lost and cytochrome c and other factors are released. Bcl-2 prevents cytochrome c release, whereas Bax, Bak and Bid accelerate these processes.

Cytochrome c activates caspase 9 and ultimately caspase 3 releasing cytochome c through a permeability transition pore. The pro and anti apoptotic factors enhance or close pore permeability respectively. A newly discovered factor, Acinus, induces chromatin condensation after cleavage by caspase-3.

Apoptosis and necrosis share some common steps. The concentration of ATP within a cell is one factor that determines whether a cell undergoes necrosis or apoptosis.

Immune Mechanisms of Apoptosis: (Tatsuya Horikawa, M.D. and David Norris, M.D., University of Colorado) Cells exposed to toxins can die by either apoptosis or necrosis. Severe damage induces necrosis, intermediate damage initiates apoptosis. Many of the immune activated processes induce apoptosis such as TNF-α or TNF-β. Cytotoxic lymphocytes induce apoptosis through three distinct mechanisms. 1) coordinate release of perforin and granzymes adjacent to the target cell membrane; 2) cytokine release (i.e., IFN-γ, TNF-α, IL-1); 3) triggering of the Fas receptor.

Cells maintain complex anti-apoptotic defenses such as Bcl-2. Interruption of these defenses by immune mechanisms facilitate apoptosis in susceptible cellular targets. When activated cytotoxic lymphocytes encounter cells expressing high levels of ICAM-1, they bind to and engage Fas on the target surface. Those cells susceptible to apoptosis undergo programmed cell death. Others are destroyed by necrosis.

Apoptosis is a key mechanism controlling the balance among the highly changing interactive cell populations in the immune response. Activated lymphocytes expressing Fas ligand on their cell surface induce apoptosis of lymphocyte and macrophage targets bearing Fas. Apoptosis is a complex process involving multiple mechanisms of induction. But Fas-dependent lysis of cytotoxic T lymphocytes is the most efficient and highly developed form of immune cytotoxicity.

Mechanisms of repigmentation:

Melanocyte reservoir: (James J. Nordlund, University of Cincinnati) Data show almost conclusively that depigmentation of vitiligo is caused by loss of melanocytes. Histological data confirm absence of cells by routine, histochemical, and ultrastructural techniques. Attempts to culture cells from depigmented skin have been unsuccessful.

Glabrous skin (hairless skin) or depigmented skin with white hair do not respond to medical therapies for repigmentation. These areas do repigmented by surgical techniques. These data indicate that the hair follicle is the normal reservoir for repigmentation and that surgical transplants are a method to replace the follicular reservoir.

Mechanisms of melanocyte proliferation and survival: (Zalfa Abdel Malek, Ph.D., University of Cincinnati) Melanocytes can be induced to proliferate in response to stimuli such as ultraviolet light.
Many growth factors have been identified that stimulate growth of melanocytes. Some are synthesized in the epidermis, some in the dermis. Factors such as b-FGF, endothlin-1, α-MSH and ACTH are synthesized by keratinocytes and melanocytes.

Proliferation of melanocytes requires the activation of multiple signaling pathways. Together cAMP and activation of protein kinase C induce melanocyte mitosis. Endothelin-1 has a complex action including activation of protein kinase C, calcium mobilization and inositol triphosphate formation. These factors subsequently activate map kinase erk 1/erk 2 and the transcription factor CREB (calcium/camp response element binding protein) which are necessary for proliferation.

Endothelin 1 also enhances melanocyte motility and reduces adhesion to fibronectin. Mutations in receptors for endothelins such as endothelin-3 are responsible for a syndrome characterized by absence of both melanocytes and enteric neurons. Mutations in the c-kit gene are responsible for piebaldism.

Challenges for the future: (Seung-Kyung Hann, Vitiligo Research Center and Yonsei University). The causes and cures of vitiligo have remained elusive. It should be a disease of great importance to pigment biologists because the disorder provides clues to the normal function of the pigment cell with the other epidermal cells, the keratinocyte and Langerhans cells to form the KLM complex.

In this symposium we have suggested that apoptosis might be a mechanism by which the melanocytes are destroyed and we have reviewed the factors that can cause the cells to return to the depigmented skin. It is hoped that these presentations will be the stimulus for more discussion and conversations among pigment biologists to find new ways to solve the problem of vitiligo and its cure. One idea worth presenting is that there are weak and strong melanocytes in the skin of a given person. By identifying why some cells are stronger and resist vitiligo, we will find ways to prevent or halt the spread of vitiligo. When the human genome is mapped, it is hoped that the genes involved in vitiligo will be identified and that rapid progress on the cause and cure of this disease will be made.

PS1 - Biochemistry of Melanogenesis, Melanosomes, and Melanocytes

Report by John Pawelek

Dr. K. Jimbow presented the opening lecture "Signals and Molecules Involved in Melanosome Biogenesis and Melanocyte Differentiation". Melanosomes share many biological properties with lysosomes. Early, stage I melanosomes appear to be linked to endosomal vacuoles. Melanosomal proteins are glycosylated and are assembled through interaction with calnexin in the ER, eventually exiting through the trans Golgi network to the final melanosome compartments. Adapter protein-3 is important in intracellular transport of tyrosinase gene family proteins. Also, small GTP-binding proteins, e.g. Rab 5 and 7, as well as phophatidyl inositol 3-kinase regulate traffic. Thus, the cascade of melanosome biogenesis is regulated by several factors: 1) glycosylation of melanosomal proteins and correct folding and accumulation within the ER and Golgi, and 2) specific signals and molecules involved in intracellular transport and vesicular graffic of these glycoproteins from the Golgi to melanosomes.

Using HPLC and X-ray microanalyses, Smit et al. studied the relative proportions of pheo- and eumelanins in melanocytes from dark- and light-skinned individuals. Light-skinned individuals have a higher level of pheomelanins and lower level of eumelanins than those with darker skin. These differences can be accentuated if the cells are cultured with excess L-tyrosine. Cultured nevus cells from patients with dysplastic nevus syndrome

tend to produce predominantly pheomelanins, and again this phenomenon is enhanced if the nevus cells are cultured in high levels of tyrosine.

Solano et al. presented "New Insights on the Murine Silver Locus: On the Expression of the Transcript in Wild-Type and Silver Mutation and Function of the Protein". Wild type mouse cells express a gp87 silver locus protein that, though smaller, is similar to human gp100, whereas silver mutant cells express a truncated version of gp87, due to a premature stop codon at nucleotide 1808. Studies on the oxidation of DHICA by extracts of mutant and wild-type cells suggested that DHICA oxidation is catalyzed by TRP-1, and apparently not gp87.

Kobayashi and Hearing continued their studies on the stabilization of tyrosinase through binding interations with TRP-1, and here demonstrated direct interaction of the two proteins in vivo. Employing a chemical cross-linker to stabilize the association of tyrosinase with other cellular proteins, they showed by immunoblotting that TRP-1 was indeed associated with tyrosinase in amounts much greater than could be accounted for by nonspecific cross-linking. Together, the data indicated that TRP-1 interacts directly with tyrosinase, stabilizing it in vivo.

Toyofuku et al. studied aberrant folding and transport of mutant tyrosinases in type I oculocutaneous albinism (OCA1). Computer models suggest that some amino acid substitutions in OCA1 may alter folding of tyrosinase, but is it is not yet clear why this eliminates tyrosinase activity. Accordingly, wild-type and OCA1 mutant tyrosinases were transfected into COS7 cells. Some mutant tyrosinases were retained in the ER and not transported to lysosomes, the final destination of tyrosinase in cells other than melanocytes. Tyrosinases with temperature-sensitive mutations were transported appropriately to lysosomes, but not expressed at physiological temperatures. It was concluded that some aa substitutions altering the 3-D structure of tyrosinase result in temperature-sensitivity of the enzyme, while others result in trapping of mutant enzymes in the ER, preventing transport to melanosomes.

Peters et al. reported the presence of POMC-related peptides in melanosomes of cultured human melanocytes. Probing with specific antibodies they reported cross-reactivity with alpha MSH, proconvertases 1 and 2 (PC 1 and 2) and the PC2 regulatory protein, 7B2. Thus they identified elements of the POMC system in melanosomes, providing supportive evidence for their model of complex formation between MSH and co-factor 6BH4, which activates tyrosinase by releaving 6BH4 inhibition of the enzyme. Such a model suggests that MSH action does not necessarily involve MSH receptors.

CS2 - Chemistry and Biophysics of Melanin & Melanogenesis
Report by Patrick Riley

This session began with a Keynote Lecture given by the Chairman of the Conference, Professor Shosuke Ito. His talk, entitled “Chemical Analysis of Melanins and it’s Application to the study of Melanogenesis Regulation” began with a detailed review of a range of studies using the assay introduced in 1983 as a means of estimating the relative amounts of phaeomelanin and eumelanin. This assay is based on the conversion of DHICA moieties in eumelanin to the derivative pyrrole tricarboxylic acid (PTCA) by permanganate oxidation in approximately 2.8% yield, and benzothiazine moieties (in phaeomelanin) to 4-amino-3-hydroxyphenylalanine (AHP) by hydriodic acid hydrolysis in 20% yield under defined conditions of treatment of melanin samples. Professor Ito suggested that the proportional generation of phaeomelanin, assessed by these criteria, is inversely related to the level of tyrosinase activity. Application of this model to murine coat colour mutants was considered to be consistent with this general proposal. Professor Ito further suggested that the inner region of polymeric melanins consists of phaeomelanin with an outer layer composed predominantly of eumelanin. In response to questions Professor Ito suggested that at very low levels of tyrosinase activity any dopaquinone generated is rapidly converted to cysteinyldopa and eliminated from cells resulting in the absence of detectable melanin. With regard to the structural model of melanin proposed it was at the molecular level and would not be easily discernible by techniques such as electron microscopy.

Professor Patrick Riley then presented a talk entitled “The Source & Significance of Dopa in Phase I Melanogenesis” which outlined the overwhelming accumulation of evidence favouring the indirect generation of dopa by reduction of dopachrome in the initial steps of in vitro melanogenesis. He argued that this mechanism, coupled with the reduction of active site copper atoms, was able to account for the observed ‘lag phase’ kinetics of tyrosinase. In response to a question from Professor Frank Meyskens he agreed that UV-induced changes in tyrosinase synthesis may be significant but expressed doubts concerning the activation of tyrosinase by superoxide anion generated by UV exposure. In his view the intracellular proton concentration was more likely to be a

significant regulator of tyrosinase recruitment.

The next talk was given by Professor Tadeusz Sarna in which he outlined the functions of the retinal pigment epithelium (RPE) in providing metabolic support for photoreceptor cells. He drew attention to the decrease in RPE melanization as a function of age. Experiments on melanosomes obtained from differentially melanised bovine eye RPE demonstrate that photo-oxidation is more pronounced in the absence of melanin. Thus, decreasing retinal melanization may have a bearing on pathological conditions such as age-related macular degeneration.

Dr. Jun Matsunaga then presented evidence from clonogenic assays that a short (30-minute) exposure of B16 or Neuro2A cultures to selected melanogenic intermediates exhibited differential cytotoxicity. Of the agents tested the most toxic were dopachrome and dopaminachrome. This finding was interpreted to imply an important cytoprotective role for dopachrome tautomerase activity as demonstrated for migration inhibitory factor (MIF).

Dr.Malgorzata Rozanowska presented data from pulse-radiolysis and laser flash-photolysis experiments showing that carotenoid cation radicals are quenched by synthetic melanin. In other experiments it was shown that light- or chemically-induced lipid peroxidation was abrogated by the addition of a series of carotenoids and that their efficiency was increased in the presence of melanin.

Finally, Dr. Jeffrey Tosk gave an ebullient account of studies of Rayleigh scattering by suspensions of dopa melanin. Using a polarised light scattering technique the effects of microenvironmental alterations, such as pH and redox state, on the aggregation of the pigment could be demonstrated. These effects were considered to be relevant to the association between pigmentation and neuronal damage observed in Parkinson's disease. In response to a question from Professor Raimondo Crippa he agreed that the aggregation state may regulate the extent of the reactive surface of melanin.

PS2 - Basic Biology of Melanoma
Report by Frank Meyskens

The sessions on "Basic Biology of Melanoma" was represented by six platform and eleven poster presentations and covered a wide range of topics including keratinocyte / melanocyte/melanoma cross-talk and its importance in invasion, immunogenic properties of melanosomal proteins, angiogenesis, control of reactive oxygen species, and molecular genetic alterations.

Herlyn (USA) gave a superb overview of the topic of keratinocyte/melanocyte and biochemical interactions and regulation and its importance in maintaining tissue integrity. Substantial evidence was offered that the replacement of E- cadherin by N-cadherin during melanocyte transformation is a critical event that permits invasion to occur. Using a reconstructed model system MacNiel

(England) offers evidence that erosion of the basement membrane was necessary for invasion by melanoma cells and that this process was reduced by 17β-estradiol and estrogen. This observation is, of course, of great interest since longstanding clinical data clearly shows that young women with melanoma have a much better prognosis, even after adjusted for Breslow level. Related to this general topic were two papers on angiogenesis: Both calponin (Koganchiua, Japan) and $\alpha v\beta_3$ integrin (Kageshita, Japan) respectively were found to be altered expression in the blood vessels and melanoma cells. As is being documented by many investigators the role of angiogenesis is crucial in the pathophysiology of carcinogenesis and many new therapies are being developed based on such fundamental observations.

Papers were presented by four different groups (Kawasaki, Japan); Bartido, USA; Cochran, and Pawelick, all USA, New Haven) demonstrating the complexity of response of immune responses in melanocyte biology. Melanosomal proteins, dendrite cells, and T-lymphocytes all play a role and in a manner too complex to review here. Perhaps, the most intriguing of the observations is the necessary evidence being amassed by Pawelek & his group that metastatic melanoma cells may be a hybrid of host (macrophage) and melanoma cells. If this hypothesis can be proven, the theoretical and practical consequences would be enormous for tumor biology.

A group of papers also dealt with various aspects of biochemical controls including the inter-relationships between tyrosinase, trp-1, and δ-glutamyltranspeptidase (Chasuble, India), various oncogenes products

(Ueda, Japan) and the role of α-PKC in phospholipase alterations. Two complex papers (Takara, Japan; Andrs Germany) on the genetics of melanoma were presented as well.

Two posters were presented on the general topic of reactive oxygen species. Haycock (England) nicely demonstrated that α-MSH blocked the acute TNF or peroxide stress response in melanoma cells which has implications for the study of early inflammatory changes in melanocyte carcinogenesis. Our own group (Spillane, U.S.A) has presented the unique observation that apoptosis of melanoma cells is promoted by heavy ion chelators, inhibited by classical antioxidants, and that ferrous (anti-apoptotic) and ferric (pro-apoptotic) ions change the intracellular redox state in an opposing manner and affect apoptosis accordingly.

CS3 - Melanoma: Ultraviolet Light, Diagnosis and Treatment.
Report by Alistair J Cochran

CHAIRS: Alistair J Cochran, Bertil Kagedal, Juichiro Nakayama

Papers presented:
Understanding Regulation of NF?BAS as Basis for Melanocyte Transformation and Melanoma Cell Therapeutic Resistance, Frank L. Meyskens Jr., Susan McNulty, Niloufar Tohidian, and Julie Buckmeier, Chao
Effective Early Detection of Malignant Melanoma on the Sole, Toshiaki Saida,
Does PCR Detect Melanomas in Sentinel Nodes (SNs) that at Not Detected by Immunohistochemistry? J. Guo, J. Messina, D.-R. Wen, R.R. Huang, D. Reintgen, and A.J. Cochran,
Primary Cutaneous and Vulvar Melanomas are Dissimilar in Clinical and Histopathological Features, but Similar in TP53 Mutations, Boel Ragnarsson-Olding, Anton Platz, Sofia Karsberg, Lena Kanter-Lewensohn, and Ulrick Ringborg,

This session brought together a series of interesting if somewhat diverse papers.

Dr Meyskens reported that melanoma cell lines have elevated levels of reactive oxygen species relative to normal melanocytes. He and his colleagues studied nuclear factor kappa B (NFkB), a transcriptional regulatory complex that responds to reactive oxygen species and ultraviolet B, as a potential factor in melanoma progression and chemoresistance. UVB increases NFkB binding by normal melanocytes, but not by melanoma cell lines. Oxidative stress induces increased NFkB binding in both melanocytes and melanoma cell lines. The NFkB response of melanoma cells to UVB is apparently independent of oxidative stress and is mediated at the transcriptional level.

Dr Saida reported melanocytic nevi, visible as brownish black macules, on the soles of 8% of Japanese. These must be separated from early melanomas which may appear quite similar. With the exception of congenital nevi, most nevi on the sole are less than 7mm in diameter, leading to a recommendation that lesions larger than 7mm be excised. In contrast most melanomas are larger than 9mm in diameter. Epiluminescence microscopy (ELM) may provide further assistance in making this separation. Patterns seen on ELM that may be used to separate melanomas and nevi were reported. An algorithm for the management of these lesions has been developed.

The paper by Guo et al. described a study of the tumor status of sentinel lymph nodes (SN), comparing standard histology (SH), immunoperoxidase (IPX), RT-PCR (PCR), using a primer for m-tyrosinase and RT in situ PCR (ISPCR) (same primer). A series of 15 SN was studied. Five were positive for tumor by SH, IPX and PCR, 5 were negative for tumor by these three techniques and 5 were negative by SH and IPX, but positive by PCR. Additional sections were cut from the blocks of these 15 nodes and studied by ISPCR, using a primer for m-tyrosinase. In the 5 nodes that were negative by SH, IPX and PCR, ISPCR detected no tumor, but found neural tissue (Schwann cells containing m-tyrosinase) in 4 of 5 and a capsular nevus in one. In the 5 nodes positive by SH, IPX and PCR, ISPCR confirmed the presence of melanoma, but additionally found neural tissues in three. In the 5 nodes that were negative by SH and IPX, but positive by PCR, ISPCR demonstrated no melanoma, but all five contained neural tissue and two had a capsular nevus. It was concluded that sources of PCR signal for m-tyrosinase other than melanoma cells are present in lymph nodes. This must be considered in interpreting results from PCR studies of complex tissues such as lymph nodes.

Dr Ragnarsson-Olding reported a comparison of malignant melanomas (MM) arising on sun-exposed and non sun-exposed (vulvar) body sites and, within the vulva, on hair-bearing and glabrous skin. From a study of 219 patients the density of MM on the vulva is 2.5 times that on other areas of the body. On the vulva MM are often amelanotic. Mucosal lentiginous MM was most common, followed by nodular and superficial spreading melanoma, the reverse of the frequency on non-vulvar sites. In a study of TP53 mutations in 35 MM, 27% of those from sun-exposed and 34% from non-exposed sites displayed the C-T mutations at dipyrimidine sites that are considered fingerprints of UV radiation-induced DNA damage. It was concluded that the similarity in frequency of the TP53 mutations in MM from exposed and non-exposed sites points to a complex genesis for these alterations. The clinical and histologic differences between melanomas of the two sites are striking but inexplicable at this time.

Papers by Cascinelli and by Lee at al. were withdrawn

PS4 - Inter/Intracellular Signaling Pathways in Melanocytes
Report by Glynis Scott

The session on inter/intracellular signaling pathways in melanocytes was opened by Dr. Nishikawa who spoke about the microenvironment control of melanocyte migration and localization to the hair follicle. Their studies on the role of stem cell factor (SCF), c-kit and endothelin-1 show that SCF and ET-1 are critical growth factors for the localization of melanocytes to the skin. Their studies show that E-cadherin levels increase in melanocytes prior to entry of the melanocytes to the epidermis, and that this increase in expression is highly synchronized. They also show that overexpression of SCF through the use of transgenic mice results in population of melanocytes in the interfollicular areas. Dr. Nishikawa and co-workers show that the soluble and the membrane bound forms of SCF have differing functions in hematopeoitc and future work in their laboratory will focus on defining the effects of the soluble Vs membrane bound SCF on melanocyte migration and localization to the skin.

Dr. Thody and co-workers presented data on the regulation of melanocyte function by α-MSH. Dr. Thody reviewed findings confirming the importance of the MC-1 receptor in mediating the diverse effects of α-MSH on skin pigmentation. He then reviewed data showing that other POMC peptides, such as ACTH, are available ligands for the MC-1 receptor in the skin and may indeed have differing effects on melanocyte function compared with α-MSH. He shows that ACTH peptide 1-17 coupling to cAMP is greater than that seen with α-MSH and that certain ACTH peptides activate IP3 production. Another point of potential regulation is the levels and activity of proconvertase enzymes, which convert PMC to ACTH. Future studies will involve defining the dose response curve for POMC peptide effects on melanocyte function including melanogenesis, dendricity and adhesion, and the signaling intermediates involved. Dr. Medrano presented data on the effect of pigmentation associated genes on cell cycle and terminal differentiation in human melanocytes. Dr. Medranos' laboratory has made the observation that activation of cAMP results in senescence of human melanocy6tes and that senescence is accompanied by other markers of differentiation such as increased pigmentation. Their data indicates that changes in the levels of E2F/p130 repressor complexes is associated with terminal differentiation and increased pigmentation, suggesting a possible mechanism for increased melanoma susceptibility in light skinned individuals who cannot tan. Dr. Medrano also shows that cyclin E is markedly decreased in senescent cells, whereas it is increased in primary melanoma. Future work will be focused on defining the potential regulatory sites at which pigmentation associated genes affect cell cycle.

Dr. Tuma presented data on the role of the microtubule motor protein kinesin II and the actin binding protein myosin V on melanophore movement in Xenopus. By using dominant negative mutants of these two proteins fused to green fluorescent protein they show that cells expressing both mutants fail to exhibit any melanophor movement whatsoever. In cells expressing only the dominant negative kinesin mutant, melanophores failed to demonstrate the usual quick saltatations towards the periphery, but did show slow, random movements. Cells expressing the dominant negative myosin V mutant showed some movement of melanophores to the periphery, but melanophores fail to remain at the periphery. These results demonstrate the importance of these two proteins in melanophore movement and future studies will be directed to understanding the regulation of these motor proteins in melanophore movement.

Dr. Tada presented data on the signal transduction intermediates involved in ET-1, α-MSH and bFGF signaling in human melanoc7tes. A main point of their presentation is that CREB activation may occur through two distinct signaling pathways: one that is mitogen activated and ERK2 dependent and one that is stress induced and p-38 dependent. They show that ET-1 and bFGF, but not α-MSH, induce CREB phosphorylation, and that ERK2

activation is necessary for ET-1 induced CREB phosphorylation. Ultraviolet light also resulted in CREB activation, but through phosphorylation of p38 rather than ERK2. These results highlight the importance of CREB phosphorylation as a signaling intermediate in mitogen induced proliferation/differentiation and in response to stressors such as UV light.

Mr. Wagner presented the final talk in the session from Dr. MacNeils laboratory. In the studies presented the investigators demonstrated the effect of α-MSH on Ca+2 mobilization. Using the human melanoma cell line HBL as a model system, the investigators show that when cells were cultured on fibronectin, and when the α-MSH induced cAMP response was inhibited by an adenosine agonist, α-MSH induced increased intracellular Ca+2 levels in the majority of cells studied. This dual response of the MC-1 receptor to α-MSH is similar to that observed with the MC-3 receptor found in the brain. Future studies will be directed at determining the biological significance of these observations.

CS5 - Melanocyte Photobiology/Chemistry and UV protection
Report by Zalfa Abdel-Malek

Chairpersons: Zalfa Abdel-Malek, Masamitsu Ichihashi, Mauro Picardo

The melanocyte plays a central role in the cutaneous photobiological response to sun exposure. This response is determined to a large extent by constitutive pigmentation and subsequently by the tanning ability that confers photoprotection against further sun-induced DNA damage.

Gilchrest and Eller described the melanogenic response of S91 melanoma cells to the introduction of small DNA nucleotides into these cells. These DNA fragments enhanced to DNA repair and resulted in activation of the p53 pathway, which includes induction of p21, PCNA, XPA, XPC, GADD45, and tyrosinase.

Hill and Hill emphasized the differences in the responses of melanoma cells synthesizing different types of melanin (eu- versus pheomelanin) to different UV spectra. Their presentation also emphasized the importance of comparing survival curves, as well as mutagenicity following exposure to different UV spectra. The conclusion was that melanin may be a sensitizer or a photoprotector depending on the UV wavelength, form of melanin, and the assays used to determine the function of melanin.

The correlation between skin phototype and antioxidant levels are evaluated following sun exposure by Picardo et al. Although SOD/catalase ratio correlated with the MED, it was found that a specific allelic form of catalase is expressed at a high frequency in low skin phototypes.

Moro et al. reported that the differential sensitivity of melanocytes, keratinocytes, and fibroblasts to ultraviolet radiation (keratinocytes=fibroblasts>melanocytes) might explain the higher incidents of basal and squamous cell carcinoma than melanoma, and the photoaging response to sun exposure. Keratinocytes are also more sensitive than melanocytes to the cytotoxic effect of sodium arsenite, which results in basal and squamous cell carcinoma, hyperpigmentation, but not melanoma.

Smit et al. showed that in cultured human melanocytes, formation of cyclobutane dimers and 6,4-photoproducts in response to UVB light correlated directly with melanin content. However, no significant differences were found in the rates of DNA repair or in survival among melanocytes with different melanin contents.

CS6 - Ocular/Extracutaneous Melanin and Melanogenesis
Report by Dan-Ning Hu

A Symposium on Ocular/Extracutaneous Melanin and Melanogenesis was chaired by Dan-Ning Hu and Shosuke Ito. Dan-Ning Hu (USA) delivered the keynote lecture. The methods for cultivation and studying uveal melanocytes have been established in the past 10 years. Human uveal melanocytes grow well and produce melanin *in vitro*. The growth and melanogenesis of cultured uveal melanocytes are regulated by various biologic substances. The stimulators consist of some growth factors (etc. bFGF, HGF), Endothelin, adrenergic agonists and various

prostaglandins. The inhibitors consist of TGFβ, cholinergic agonists and IL-6. The uveal melanocytes are similar to epidermal melanocytes except in their response to α-MSH and ACTH. Both hormones stimulate the growth and melanogenesis of epidermal but not uveal melanocytes in cAMP-elevating agents deleted medium.

Giuseppe Prota (Italy) and Hu's work on types of ocular melanin was presented, they found that the iris pigment epithelium contains mainly eumelanin. Iridal melanocytes contain both eumelanin and pheomelanin, the ratio being variable depending on iris color. The pheomelanin/eumelanin ratio is higher in growing cultured uveal melanocytes than those in senescent cells. Kazumasa Wakamatsu (Japan) used an improved alkaline peroxide oxidation method to study neuromelanin. They found that neuromelanin consists mostly of dopamine with 10-20% incorporation of cysteine and that its structure is rather complex as compared to synthetic melanin.

Raymond Boissy (USA) reported that α-MSH does not stimulate the growth of uveal melanocytes *in vitro* and they could not detect receptors of α-MSH in uveal melanocytes by northern blot analysis and immunocytochemical studies. Khaled Abul-Hassen (UK) reported the transfer of gene to retinal pigment epithelium by a liposome-based method and to uveal melanocytes by adenoviral victor. After gene transfer, tyrosinase activity of melanocytes responds to various factors, but pigment epithelium lacks a factor for post transcriptional and/or translational modification of tyrosinase. Joan Roberts (USA) reported that cultured uveal melanocytes eliminate exogenous nitric oxide, an important regulator in ocular, neural and vascular tissues. Clearance of nitric oxide is directly related to melanin content. In the discussion, S. MacNeil (UK) mentioned that although α-MSH does not simulate growth and melanogenesis of cultured uveal melanocytes, intracellular calcium is elevated by α-MSH when the cell is cultured on fibronectin and adenosine agonist is added into the medium.

Hot Topics Symposium
Report by Vince Hearing

This Symposium was an innovation of the XVIIth IPCC and attempted to give a special forum to the most interesting and exciting abstracts submitted. As you know, all abstracts were judged blindly by the cochairs of each Symposium to select the best 3 to be presented orally in that Symposium. The highest scoring abstract from each topic was then considered for the 'Hot Topics Symposium' and the top 5 were selected for this special forum (in other words, it was quite an honor to present here not to mention that fact speakers got an extra 5 minutes).

Robert Hoffman (a PASPCR member) presented the first paper and reported his group's attempts towards regulating pigmentation using a *tyrosinase* gene encapsulated within liposomes for delivery to follicular melanocytes. The *tyrosinase* gene used was from *Streptomyces* and was linked with an internal ribosome entry site to allow expression (the bacterial enzyme was used rather than the mammalian enzyme because of its significantly smaller size). Albino mouse skins in organ culture were used as targets and some hair repigmentation was observed following this gene therapy approach. Since hair and skin melanocytes are relatively accessible to such targeting, the potential use of such gene therapy is a tantalizing goal for correcting pigmentary defects. A similar approach using antisense strategy would potentially down-regulate pigmentation, and their future research is aimed at increasing the efficiency and application of this approach.

Bernhard Wehrle-Haller next reported his group's work on stem cell factor (SCF), an important paracrine signaling factor for melanoblast survival. Various segments of the cytoplasmic tail of SCF were deleted in order to characterize the role(s) of various motifs on intracellular processing and secretion by keratinocytes. As an approach to identify where the mutant SCFs went, he incorporated green fluorescent protein (GFP) into the extracellular part and used fluorescent microscopy to track their localization. Wild-type GFP-SCF was transported to the cell surface where c-kit (the receptor) positive melanocytes would bind to it. Deletion of various segments of the cytoplasmic tail identified a short sequence required for this specific processing and distribution. That sequence is completely conserved in avian and mammalian SCF and Dr. Wehrle-Haller postulates that this motif is required for SCF function and correct melanoblast localization during development. In co-culture experiments, melanocytes and melanoblasts actively associated with wild-type SCF expressing fibroblasts, but not with mutant SCF expressing fibroblasts, leading to the hypothesis that SCF is not only important for localization of melanoblasts towards SCF-positive cells, but also that it might play other roles in cross-talk between these types of cells, perhaps even facilitating melanosome transfer.

Masashi Kato next described their further studies with the *ret* transgenic system in which *ret*-overexpressing mice have high rates of spontaneous melanoma generation. He now reported that the increases in *ret* expression were accompanied by increases in MAP kinases and c-Jun, as well as in matrix metalloproteinases. Their group proposes that increased expression of ret disrupts normal intracellular signaling which may play a role in malignant transformation of melanocytes. He used this melanoma system as an appropriate model to examine the efficacy of agents targeted against melanoma, and he reports that an herbal medicine (active component = ???) delayed the onset of tumors, and significantly decreased metastasis of melanomas to various organs.

Miri Seiberg (another PASPCR member) reported interesting studies that are attempting to sort out factors responsible for melanosome transfer to keratinocytes. She reports that they have recently found that the protease activated receptor-2 (PAR2) is important to this exchange, and that agents which inhibit or stimulate the function of PAR2 have dramatic effects on melanosome transfer in vitro, and also in vivo in a Sinclair swine model. PAR2 is expressed on the surface of keratinocytes (not melanocytes) and seems to play an important role in regulating melanocyte-keratinocyte interactions. Her results further suggest that increased transfer has a feedback mechanism that stimulates the melanocytes to produce more melanin, and vice-versa. Physical contact between melanocytes and keratinocytes is essential for these effects and co-culture of those cells separated by a permeable membrane prevented those effects. This study is an important first step in understanding mechanisms involved in the physical transfer of pigment granules from melanocytes to keratinocytes, a process that heretofore has essentially been poorly understood.

Shigeru Sato presented the final paper in this session, which dealt with the characterization of the mutation in *Mitf* found in the *Black-Eyed White* mouse. As we know, Mitf not only plays an important role in the regulation of melanoblast development, but also plays an important role in regulating differentiation of functional melanocytes. Null mutants of *Mitf* have a complete loss of pigment cells in all normally pigmented tissues, but the *Black-Eyed White* mutation is an interesting one wherein mutant mice have a normally pigmented retinal pigment epithelium, but lack melanocytes in the skin and inner ear. This mutation was shown to result from an insertion into intron 3 of *Mitf*, which affected the distribution of *Mitf* isoforms. *Mitf* is now known to be transcribed in 3 active forms, Mitf-A (predominantly expressed in the RPE), Mitf-H (predominantly expressed in the heart) and Mitf-M (predominantly expressed in non-RPE melanocytes). The *Black-Eyed White* mutation affects the processing of these isoform mRNAs, leading to only slight decreases in Mitf-A and Mitf-H, but to complete down-regulation of Mitf-M, which explains its dramatic effects on melanocytes in the skin and inner ear, and lack of effect on RPE. This study demonstrates the critical nature of the Mitf-M isoform for normal melanocyte development.

In sum, this Hot Topics Symposium was a novel venue to highlight the most topical and important abstracts submitted to the IPCC. It will be interesting to see if this becomes a traditional feature of future IPCC.

CS8 - Control of Hyper/Hypopigmentation
Report by Ray Boissy

The development of facultative cutaneous pigmentation is under the regulation of extramelanocytic factors generally produced by the keratinocytes of the epidermis, that can in turn be modulated by the environment, predominantly by ultraviolet irradiation. In order to begin to assess the facultative development of skin hyper/hypopigmentation analyses using co-cultures of melanocytes and keratinocytes is beginning to be exploited. Presentations in this seminar focused on such model systems. "Keratinocyte-melanocyte co-cultures and pigmented reconstructed epidermis as models to study skin pigmentation and its modulation" presented by R. Schmidt began the session. He reviewed techniques develop at L'Oreal to screen for inhibitors of melanization. He specifically discussed the following. [a] Cultured melanocytes are routinely developed using a medium reported by Dr. Olsson of Sweden designed for the culturing and expansion of vitiligo derived melanocytes. [b] Total cellular melanin was recovered from sonicated cells using a DEAE cellulose filter. [c] Keratinocyte-melanocyte co-cultures were established using a 10:1 ratio in keratinocyte specific medium resulting in successful melanosome transfer. [d] A technique using C^{14}-thiouracil to assess rate of melanin synthesis was developed. [e] A solar simulator was used to irradiate melanocyte cultures and co-cultures in which the threshold for increased melanogenesis was lower in the latter condition demonstrating that keratinocytes are a major mediator of UV induced cutaneous hyperpigmentation. [f] A reconstructed skin equivalent model was presented which was utilized to investigate the effects of sunscreens and UVR, Kojic acid, IBMX, and melanocytes from various ethnic donors on pigmentation of the model system. M. Kim presented "Modulation of melanin neosynthesis by plant extracts in human keratinocyte-melanocyte co-culture

system" in which a Transwell® system was used to test for diffusible molecules mediating the keratinocyte regulation of melanocytes. They demonstrated that the hypopigmentary effect of two specific plant extracts occurred only in the co-culture system and not in pure melanocyte cultures. The keratinocyte affect appeared to be modulated by IL-1a, IL-5 and IL-6. A. Hachiya presented "A paracrine role of stem cell factor/c-kit linkage in UVB-induced pigmentation" which investigated the expression of SCF and c-kit in co-cultures. They demonstrated that transcript and protein expression of SCF (the membrane bound form only) and c-kit were upregulated by UVB in a dose dependent manner. This upregulation was confirmed immunocytochemically *in vivo*. In addition, using a guinea pig skin system, UVB-induced hyperpigmentation could be inhibited by subepidermal injection of anti-c-kit antibody.

Melanocyte stimulating hormone and the agouti protein are also extramelanocytic regulators of cutaneous pigmentation via the receptor, MC1R. Z. Abdel-Malek presented "The melanocortin-1 receptor is a key regulator of human cutaneous pigmentation" in which she reviewed data demonstrating that MSH and ASP could increase and decrease respectively the activity of cultured human melanocytes in response to ultraviolet irradiation. Significant data was presented demonstrating that cultured human melanocytes homozygous for an Arg160Trp mutation in the MC1R failed to respond to the effects of both MSH and ASP. ASP is a ten fold larger molecule than MSH. V. Virador presented "Bioactive domains and expression patterns of the agouti signal protein" in which the ASP was molecularly dissected to identify its bioactive domain. Synthetic 15mer segments of the ASP were assessed for their ability to reduce melanization of cultured melanocytes. A region containing KKVARPR, just outside of the basic domain of ASP, was most effective. A model was presented suggesting how ASP binds to the MC1R to alter the pocket used for MSH binding. In addition, a synthetic peptide (αPEP16) was developed which demonstrated reactivity in hair follicles consistent with ASP being secreted by keratinocytes.

Successful cutaneous pigmentation is the result of the transfer of melanosomes from the dendrite tip of the melanocytes to the neighboring keratinocytes. This process has remained molecularly elusive. G. Scott presented "Dendrite formation and melanosome transfer - beyond the electron microscope" which clearly demonstrated in transfection studies that a member of the Rho family of molecules associated with actin assembly (i.e., Rac 1) is involved as a downstream regulator of dendrite extension. UVR and MSH can also influence rac-1 function. Rac 1 function appears to be regulated by TIAM-1. Analysis of sucrose density purification of melanosomes demonstrated expression for specific SNARE attachment protein receptors for vesicle fusion (i.e., SNAP 23, SNAP 25, syntaxin 4, and VAMP-2) along with a SNARE associated docking protein (Rab 3a). These molecules putative mediate the fusion of the melanosome with the plasma membrane of the melanocyte and its transfer through the plasma membrane of the recipient keratinocyte. Regulation of these molecules may ultimate underlies the development of hyper/hypopigmentation of the skin and hair.

Satellite Meeting 4

Sentinel Node mapping and dissection in the Staging and Treatment of Melanoma.
Report by Alistair J Cochran

Chairs: Alistair J Cochran , M.D., FRCP, FRCPath, and Toshiaki Saida, M.D., Ph.D.

Meeting Program:

Lymphatic Mapping and Sentinel Node Surgery, Alistair J. Cochran, M.D., FRCP, FRCPath, Department of Pathology and Laboratory Medicine, 13-145 CHS, UCLA School of Medicine, Los Angeles, California, 90095.

Sentinel Node Dissection for Melanoma, Richard Essner, M.D., FACS, Assistant Director of Surgical Oncology, John Wayne Cancer Institute, Santa Monica, California.

The role of Lymphoscintigraphy and Other Radionuclide Techniques in the Localization of Sentinel Lymph Nodes, E.C. Glass, R. Essner, A.J. Cochran, Haigh, D. Morton, John Wayne Cancer Institute, Santa Monica, California.

Occult melanoma micrometastases in the regional lymph nodes: Their detection, distribution and clinical implication, Minoru Takata and Naohito Hatta, Department of Dermatology, Kanazawa University School of Medicine, Kanasawa, Japan.

Clinical Experience with the Sentinel Node Technique in Japanese Patients with Melanoma, Naoya Yamazaki National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-Ku, Tokyo 104-0045, Japan.

Clinical Experience with the Sentinel Node Technique in Non-melanoma Skin Cancers, Yoshio Kiyohara, Masahito Taguchi, Tadashi Suzuki, Tetsuya Tsuchida, Department of Dermatology. Saitama Medical School, Saitama, Japan

Dr Cochran presented the background and significance of techniques that were the subject of the meeting. The management of high-risk (deep, thick) primary melanoma, clinically localized to the primary site, has been unsatisfactory. Treatment options were elective nodal dissection, an operation with substantial morbidity, that is probably unnecessary for 80% of patients or a policy of "wait and see" that delays definitive treatment for the 20% of patients who eventually recurred. Lymphatic mapping and the selective removal and close evaluation of the sentinel node (SN) provides a more rational approach. The symposium brought together experts who were active in originating and developing the techniques and clinicians involved in their application. Areas covered included localization of the SN, evaluation of the SN for tumor by histology, immunohistology and molecular techniques and the treatment and prospects of patients with tumor-positive SN. Current clinical experience in the US and Japan was presented.

Dr Essner described the surgical aspects of the approach noting that success requires close cooperation by skilled surgical, nuclear medicine and pathology personnel. There are three separate components: mapping of the direct lymphatic route from the primary site to the regional lymph node basin, identification of the first lymph node in that basin that receives lymph via the direct lymphatic (the sentinel node) and selective excision of the SN, leaving the non-sentinel nodes in place. Complete lymph node dissection is reserved for individuals with tumor in the SN, those most likely to benefit from node dissection. Identification of the SN originally depended on visualization of the afferent lymphatics and target node based on their blue color after injection of a blue dye (isosulfan blue). The technique is more accurate and easier to master when the blue dye is combined with preoperative identification of the lymphatics and SN by early read (dynamic) lymphoscintigraphy and intraoperative detection of the SN by a hand-held gamma probe. It was stressed, however, that the technique requires an initial learning period during which the performance of surgeon, pathologist and nuclear medicine personnel will improve quite rapidly. Since its development by Morton et al (1992) the effectiveness of the approach has been widely validated by other workers. The technique has also been applied to many other tumors, such as breast cancer, vulvar cancer and colon cancer. Lymphatic mapping and sentinel lymph node evaluation is at least as efficient as elective node dissection as a staging technique and may be superior as it permits the pathologist to focus on a limited number of nodes and apply special approaches, such as immunohistology and molecular pathology to this limited target. Two major studies are in progress. The Multicenter Selective Lymphadenectomy Trial randomizes patients to receive either wide local excision or wide local excision and lymphatic mapping and selective lymphadenectomy. If the sentinel node contains tumor the patient receives a complete lymphadenectomy. The Sunbelt Melanoma Trial is examining the role of SN evaluation in determining patients likely to benefit from treatment with interferon-alpha. From the results of these trials the therapeutic role of selective lymph node dissection will become clear.

Dr Glass provided an overview of the role of the nuclear medicine physician. Preoperative lymphoscintigraphy (LS) is essential to avoid the errors implicit in clinical assessment of likely lymphatic drainage patterns, to chart the route of the afferent lymphatic and to identify the SN within the relevant nodal basin. The site of the SN can then be marked on the skin to facilitate placement of the surgical incision. Preoperative LS requires the intradermal injection of radiopharmaceuticals such as Tc99m antimony trisulfide colloid, Tc99m albumin nanocolloid or Tc99m sulfur colloid. Optimal agents feature rapid migration times, good retention in the SN, minimal spillover into non-sentinel nodes and low radiation dose to the patient. After intradermal injection imaging with a scintillation camera should begin immediately to capture images of the afferent lymphatics and SN. Body outlines and the position of the SN are to be clearly marked to assist the surgeon in localizing his approach. The optimal arrangement is to undertake surgery within two hours of LS, obviating the need for a second perioperative injection of isotope. Unusual drainage paths are not uncommon. Special attention is to be paid to cervical, facial, epitrochlear, popliteal, umbilical and scapular nodes.
Problems encountered by new users are most often due to relatively simple factors. These include the use of excessive tracer (>18MBq), too long a period between tracer injection and imaging, poor positioning of the patient, failure to mark the outline of the body and failure to accurately mark the position of the SN on the skin. With attention to detail and moderate experience satisfactory results may be expected.

Dr Cochran outlined the role of the pathologist who, once the surgeon and nuclear medicine physician have identified and removed the SN, has the critical responsibility of determining whether the SN contains tumor. A single SN will be provided from 67% of patients, two SN from 25% and three or more from the remaining12%. Because

of the relative difficulty of interpreting frozen section material and the likelihood of losing diagnostic material because of distortion during freezing and thawing and tissue removal to obtain "full face" sections the use of frozen sections is not recommended. Sentinel nodes are carefully bisected through their longest circumference and ten serial full-face sections removed from each cut face. Sections 1, 3, 5 and 10 are stained with hematoxylin and eosin, section 2 with S100 and section 4 with HMB-45. Tumor cells are to be separated from capsular and trabecular nevus cells, paracortical dendritic cells, macrophages and intranodal nerves. It is essential to use immunohistochemistry to avoid missing up to 24% of positive SN. In numerous studies between 18-20% of SN have been found to contain tumor. The risk to personnel from technetium 99 at the doses used is considered slight, but standard radiation precautions should be utilized. Studies with molecular biology approaches are of great interest, but have not yet become standard. In providing material for experimental studies pathologists should divide the tissues in such a manner that the diagnostic process is not compromised.

Drs Takata and Hatta reported a study of 436 nodes from 32 patients. HMB-45 detected tumor in the nodes of 15/24 patients who were negative by HE. In 23 nodes nested PCR for tyrosinase was more sensitive than a combination of single round PCR for the melanoma associated markers tyrosinase, MART-1, Pmel-17, TRP-1 and TRP-2. Tyrosinase mRNA was detected in 6 nodes that were negative by HE and HMB-45.
Using HMB-45 and nested RT-PCR for m-tyrosinase, maps of distribution of microscopic and "submicroscopic" metastases were generated for 13 inguinal basins. The authors reported considerable variation in the distribution patterns of occult metastases in the node basins studied. The authors conclude that the main role of molecular biology is to identify the subgroup of patients whose nodes are negative by histology and molecular biology and who require no additional treatment.

Dr Yamazaki reported on clinical experience at the National Cancer Center Hospital, Tokyo. In a study of 14 patients with acral lentiginous melanoma, using the dye patent blue V alone, the SN was identified in 13/14 cases. Sensitivity and accuracy were similar to those reported previously and the authors found the approach "feasible and successful."

Dr Kiyohara and his colleagues reported their experience with the techniques in the management of 24 patients with non-melanoma skin cancer (squamous cancer, porocarcinoma, invasive Bowen's disease and invasive Paget's disease) at Saitama Medical School. In 11 cases the SN contained tumor and a complete lymph node dissection was undertaken. In no case was a non-sentinel node found positive in the presence of a negative sentinel node. A single sentinel node was found in 76% of patients and two in 24%. The authors conclude that the approach is "reasonable and reliable."

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The Bibliography published in this issue covers the period August, 1999 through October, 1999. 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*).

MELANINS, MELANOGENS & MELANOGENESIS

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International Federation of Pigment Cell Societies

Officers: Shosuke Ito (JSPCR, *President*); Stan Pavel (ESPCR, *Vice-President*); Richard A. King (PASPCR, *Secretary/Treasurer*)

Council Members: Sally Frost-Mason (PASPCR); Sheila Mac Neil (ESPCR); Masako Mizoguchi (JSPCR); James J. Nordlund (PASPCR); Patrick A. Riley (ESPCR); Shigeki Shibahara (JSPCR); Vincent J. Hearing (*Ex Officio* member as the Editor of Pigment Cell Research)

A Letter from the IFPCS President to the PASPCR members

As the chair of the **17th International Pigment Cell Conference (IPCC)** held in Nagoya this fall, I wish to express my sincere thanks to PASPCR members and others who came a long distance to attend the meeting. We were very pleased to welcome 71 participants from the North American continent (2 countries), 69 from the European continent (13 countries), and 28 from the Asian continent (4 countries), in addition to 139 from Japan. Interest and attendance at the symposia and satellite meetings were great and stimulating discussions were held during and between the formal sessions throughout the meeting. We do believe that most, if not all, of the participants learned new advances in pigment cell research and also enjoyed the social programs.

The outgoing and new members of the **IFPCS** Council held two official meetings during the Nagoya IPCC and elected, as Officers for the next 3 years, Shosuke Ito (JSPCR) *President*, Stan Pavel (ESPCR) *Vice-President* and Richard A. King (PASPCR) *Secretary/Treasurer*. The election was based on the rotation cycle that began 9 years ago when the IFPCS was established at the Kobe IPCC. I am very honored to serve as the President following the successful completion of the terms of the previous 3 Presidents, Drs. Yutaka Mishima, Giuseppe Prota, and Vincent J. Hearing. On behalf of the Officers, I wish to assure you that we will work hard with the Council to continue the growth and interactions initiated during the first 3 IFPCS administrations. We want to congratulate the departing Officers, President Vincent J. Hearing, Vice-President Yoshiaki Hori, and Secretary-Treasurer Patrick A. Riley for their outstanding work and achievements in the last 3 years. Their efforts greatly helped the IFPCS grow and initiate new activities that make the IFPCS more effective in fostering scientific exchange among members. We also would like to welcome new Council members, Drs. Patrick Riley (who served as the Secretary/Treasurer following the untimely death of Dr. Bengt S. Larsson), Richard A. King, and Shigeki Shibahara and express farewell to departing Council members, Drs. Yoshiaki Hori and Yutaka Mishima.

The IFPCS has established the following goals for the Federation (also available on the **IFPCS Web page** at **http://www.cbc.umn.edu/ifpcs)**:

1. To encourage the dissemination of knowledge related to pigment cells by the establishment, sponsorship and support for the publication of books, bulletins, newsletter, journal, reports or other means.
2. To organize a tri-annual international meeting, to honor outstanding contributions in the field by awarding the Myron Gordon award at that meeting, and to select a scientist who has made recent and significant advances in the field to present the Seiji Memorial lecture.
3. To foster and enhance research on pigment cells and pigmentation among the regional Societies and to foster scientific collaboration, cooperation and communication among the regional Societies.

Goal #1 was achieved by establishing an official IFPCS-sponsored journal, ***Pigment Cell Research*** (**http://www.pigment.org**). Thanks to the efforts of the founding *Editor* Dr. Joseph T. Bagnara (1987-1994) and the subsequent Editors Drs. Takuji Takeuchi (1995) and Jiro Matsumoto (1996-1999), the journal has grown steadily and shown continued improvement to the point that it now has an Impact Factor score of 1.3. I wish to congratulate Dr. Jiro Matsumoto for his outstanding job in promoting the progress of the journal during his 4-year term as Editor. The journal will now enter a new era under the leadership of Editor Dr. Vincent J. Hearing (2000-2004) who will be supported by a new panel of 15 Associate Editors. To further promote the growth of the journal, it is essential that the numbers of subscribers and submitted papers be increased. I wish to urge all PASPCR members to subscribe to ***Pigment Cell Research,*** as this is the official journal of the Federation.

With your help, I am confident that the 5-year editorship of Dr. Hearing will produce even further progress in the rank and value of ***Pigment Cell Research***.

Goal #2 may be the most visible one among the several efforts that the **IFPCS** has been making. Starting with the Nagoya IPCC, the Federation has established the rule that the (International) Scientific Program Committee should include the IFPCS President and 3 Council members, allowing the Local Organizing Committee to work closely with representatives from the Federation in selecting speakers and Symposium topics. As the Chair of the 17th IPCC, I found this system to work very smoothly and effectively. Much of the credit for the scientific success of the Nagoya IPCC should be given to Dr. Hearing and other members of the International Program Committee. As the President of the Federation, I am now looking forward to working closely with the Chair of the 18th IPCC, Dr. Stan Pavel. I am happy to inform you that the venue of the 18th IPCC, to be held in September 2002, is a splendid, five star hotel in Scheveningen on the North Sea coast of the Netherlands.

Goal #3 is being achieved through three related and important initiatives that the IFPCS has taken in the past several years. **Special Interest Groups** have been established and are providing substantial benefits to our scientific community, as shown on our Web page. We now have Special Interest Groups in the subdisciplines of **Biology of Melanoma, Developmental Biology, Genetics of Pigmentation, Hypo/Hyperpigmentation, Ocular/Extracutaneous Pigmentation,** and **Vitiligo**. As the Chair of the 17th IPCC, I was very pleased that three of those groups held Satellite meetings at the IPCC under the themes of 1) Vitiligo: A Manifestation of Apoptosis? 2) Regulation and Genetics of Pigmentary Genes, and 3) Cellular and Molecular Control of Pigment Cell Development. All the satellite meetings were well attended and appreciated. The Federation Council has decided to continue these Interest Groups as a mechanism to promote pigment cell research.

Another initiative to achieve Goal #3 was the establishment of the **IFPCS Visiting Scientist Award**. The grants, established in 1997, are intended to support investigators from one of the regional Societies who wish to visit the laboratory of an investigator in another regional Society to learn specialized techniques and/or to establish collaborations. You will find a full description of the program, the name of generous corporate donors, and the name of awardees on the IFPCS web page. The program was established with funding for 9 visiting scientist awards, with each regional Society being allotted 3 awards for the 3 years' period beginning in 1997. To date 5 individuals have received an award of $3,000 each to cover expenses for their travel and accommodation. The initial 3-year period of the program will end next year, but we hope to continue this program with a renewal of corporate donations.

The third initiative is the establishment of the **InterPig DataBase,** which collects data on research reagents and resources available to the pigment cell community. The database is available to all researchers, especially to members of regional Societies. It includes 115 biochemicals, cell cultures, immunological and molecular biology reagents, and mouse mutants. I hope that PASPCR members will take advantages of the database and will consider adding their new and/or valuable reagents to the database so that these reagents are available to other investigators. This will make the database more useful and will promote pigment cell research collaborations among the scientific community.

Finally, I sincerely hope that we will see healthy and steady progress in our 3 regional Pigment Cell Societies, **ESPCR, JSPCR,** and **PASPCR** as our term on the IFPCS Council extends to the 21st century. I urge each of you to contribute to your Society in any way you can: submitting your abstracts to the regional Society meetings, publishing your papers in the ***Pigment Cell Research***, collaborating with other members, and recruiting others scientists and clinicians to join us.

Shosuke Ito
President, IFPCS