PASPCR Newsletter

June 2004
Vol. **12** Number **2**

Introduction...
by Bill Oetting

NOTICE - 3, 2, 1 - go

Only 3 more issues of the Bibliography of the ***PASPCR Newsletter*** remain - **UNLESS** - we can enlist the help of someone to take over. If you have a subscription to Current Contents (or any other literature awareness service), you could do this in just 1-2 hours every 3 months. The current PASPCR Bibliographer, after 11 years, has decided that other more pressing issues, such as organizing the IPCC in 2005, will consume too much of his time, and this literature search will end unless a volunteer steps forth to take it over. We would be happy to provide you with the searching keywords and algorithms used to generate the different categories of references listed in the PASPCR Bibliography. Want the adulation of your peers for years to come? Contact Bill Oetting or Vince Hearing.

The ***PASPCR Newsletter*** is published quarterly and is intended to serve as a means of communication for the members of our Society. You are invited to contribute articles, or other information you feel will be of interest to members of the **PASPCR**. If you attend a scientific meeting and have heard results which you think will be of interest to the membership of the PASPCR, please write a few paragraphs summarizing what was presented and share it with us. Any information on upcoming meetings of interest will be added to the "Calendar of Events". This is your newsletter, and we depend upon you to help us make sure it best serves the Society's needs. Contributions and comments can be sent to me, preferably by E-mail, to bill@lenti.med.umn.edu.

The PASPCR Web Site can be found at:

http://paspcr.org

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

New Internet Addresses

The web server for the PASPCR and IFPCS websites has been changed. The direct internet address for the PASPCR website is now paspcr.med.umn.edu and the address for the IFPCS web site is now ifpcs.med.umn.edu. Of course, **paspcr.org** and **ifpcs.org** will take you directly to the home page for each.

The domain name **ipcc.info** will take you to the IPCC web site, providing you the most up to date information on the International Pigment Cell Conference, which will be held on September 18 - 22, 2005 at the Hyatt Regency Hotel in Reston, VA. Information includes preliminary program information and a list of invited speakers.

In this Issue . . . . .

The PanAmerican Society for Pigment Cell Ressarch

C/O Dr. Raymond E. Boissy
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Calendar of Events:

June 24-27, 2004 XII[th] Meeting of the PanAmerican Society for Pigment Cell Research, to be held in Irvine, California.
Contact: Frank Myskins.
E-mail: flmeyske@uci.edu
Web: www.paspcr.org

July 22-24, 2004 International Skin Cancer Conference, Zurich, CH
President: Günter Burg
Contact: Reinhard Dummer
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Web: www.skincancer.ch

Sept 22-25, 2004 XII[th] Meeting of the European Society for Pigment Cell Research, to be held in Paris, France.
Contact: Dr. Lionel LaRue
E-mail: Lionel.Larue@curie.fr
Web: http://espcr2004.curie.fr/

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

Sept 18-22, 2005 XIVth International Pigment Cell Conference (IPCC), to be held near Washington DC, USA.
Contact: Dr. Vince. Hearing
E-mail: hearingv@nih.gov
Web: www.ipcc.info

If you know of future meetings that you feel would be of interest to the PASPCR membership, please let us know.

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

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Corporate Sponsors
by Raymond E. Boissy

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

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New Members
by Raymond E. Boissy

The PASPCR would like to welcome these new members to the society:

Andrew Aplin	Albany Medical College
Sreenivasulu Chintala	Roswell Park Cancer Institute
Aea Kyung Enu	Seoul, Korea
Esther Guzmán	Henry Ford Hospital
Jennifer Hauser	University of Cincinnati College of Medicine
Ernest Hixon	University of Maryland
Becky Lockhart	University of Arkansas
Michael Pratt	Pfizer
Kang Sangjin	Household & Healthcare Research Park, Korea
Susan Taylor	Columbia University
Dilshika Wijesekera	University of Arkansas
Sun Yang	University of California-Irvine Medical Center

New Editor for *Pigment Cell Research*
by Vince Hearing

Pigment Cell Research is pleased to introduce Prof. Colin R. Goding as its Editor as of Jan 1, 2005. The transition to the new Editorial Office in the UK will occur over the remainder of this year.

As of June 1, 2004, all new manuscripts should be submitted directly to Prof. Goding at the email address noted below.

All manuscripts currently in review or in revision will continue to be handled in my office.

Submit articles to:

Prof. Colin R. Goding
Pigment Cell Research Editorial Office
Marie Curie Research Institute
The Chart, Oxted
Surrey, RH8 0TL, UK
email: pcreditor@mcri.ac.uk

I look forward to the continued growth of the journal under Prof. Goding's direction,

Vince Hearing

We are looking for:

items to include in the ***PASPCR Newsletter***. Please send in information that you have on:

Meetings of interest
Reports on meetings you have attended
News about PASPCR members
Short stories
Interesting graphics

or anything else you think that the PASPCR membership would be interested in reading. Please email your contributions to bill@lenti.med.umn.edu.

Thanks!

Research in the PASPCR

In this section we will highlight the major research focus of laboratories of PASPCR members. Our hope is that this information will be useful to all within the PASPCR by presenting the major research project in our laboratories and possibly opening doors for collaboration. In this issue, **Bryan Fuller** describes some of the projects in his laboratory.

Understanding the Regulation of Tyrosinase in Human Melanocytes

Research efforts in my laboratory have, for several years, focused on elucidating the biochemical mechanisms which control melanin production in human melanocytes. More specifically, our studies have been directed toward identifying the molecular events which are responsible for differences in pigmentation in Black and White skin. Our research has led to the following discoveries: 1) although tyrosinase activity in the melanocytes of Black-skinned people is 10 times higher than that measured in White skinned individuals, the abundance of tyrosinase mRNA and tyrosinase protein is the same, 2) the mRNAs of tyrosinase from Black and White melanocytes are identical in sequence, 3) the catalytic activity of tyrosinase in White but NOT Black melanocytes can be markedly increased by treating melanocytes in culture with weak bases, such as ammonium chloride, or with ion gradient disrupters such as monensin or nigericin, 4) the catalytic activity of tyrosinase in White but NOT Black melanocytes rapidly increases upon treatment with bafilomycin, an inhibitor of V-ATPase, the enzyme responsible for organelle acidification, and 5) the pH within melanosomes of White melanocytes is acidic and inactivates tyrosinase, while the pH in melanosomes of Black melanocytes is more neutral, which favors high tyrosinase activity. Our conclusion from these results is that the activity of tyrosinase in melanocytes from different racial skin types is controlled primarily by the pH environment of the melanosome and that some hydrogen ion exchanger which controls the efflux of H^+ ions and therefore regulates intraorganelle pH must be differentially expressed in Black and White melanocytes. In a new article in Experimental Cell Research (in press) we report on immunohistochemistry and co-localization studies which reveal that melanosomes of both Black and White melanocytes contain a V-ATPase, a finding which suggests that melanosomes from both racial skin types are capable of being acidified. In this paper we also show that at least 5 sodium hydrogen exchangers (NHEs) are expressed in human melanocytes. Further, treatment of melanocytes with the NHE inhibitor amiloride causes a rapid loss in tyrosinase activity in Black but NOT White melanocytes. This suggests that the melanosome membrane in Black melanocytes likely contains an amiloride sensitive NHE that is responsible for extruding the hydrogen ions pumped into the organelle by V-ATPase. By removing intra-melanosome hydrogen ions, the NHE produces a more neutral pH which is optimal for tyrosinase activity. Because of the absence of amiloride sensitivity in White melanocytes, it seems likely that the amiloride sensitive form of NHE present in Black melanosomes is either absent or inactive in White melanosomes. Finally, we report that at least one NHE isoform, NHE-7 is found in melanosomes of Black melanocytes suggesting a possible role for this exchanger in reducing the concentration of hydrogen ions within the organelle.

In addition to our studies concerned with the molecular basis for differences in racial skin color, we have focused our research efforts toward determining the biochemical mechanisms responsible for the forskolin/ cAMP induced increase in tyrosinase activity in human melanocytes. Unlike mouse melanocytes or mouse melanoma cells, we have found that the tyrosinase gene is NOT induced by cAMP in human melanocytes. The tyrosinase gene is constitutively active in most human melanocyte cell strains, with the possible exception of melanocytes derived from red-haired individuals where tyrosinase gene activity is low. Although treatment of human melanocytes for 72 hours with either forskolin or IBMX can lead to a 15 fold increase in tyrosinase activity, the abundance of tyrosinase mRNA and protein does not increase. However, as reported by others, the level of phosphorylated MITF does increase in cells treated with either of these compounds. Our research suggests that the cAMP induced increase in tyrosinase activity does require gene transcription and efforts are underway to identify the gene or genes which are activated through a cAMP mediated signaling pathway.

The Rest of the Story

In a past issue of the PASPCR Newsletter (March, 2001), we included an article by Dr. Willys Silvers on how he became involved in writing his book, *The Coat Colors of Mice*. Now, a digital copy of his book has been included with the Mouse Genome Informatics (MGI) database at The Jackson Laboratory. Paul Szauter is responsible for text entry, graphics, and HTML adaptation. Here is his story about how *The Coat Colors of Mice* ended up on the web.

Online Version of The Coat Colors of Mice at MGI

By Paul Szauter
Mouse Genome Informatics, The Jackson Laboratory

Mouse Genome Informatics (MGI) has recently released an online version of *The Coat Colors of Mice* by Willys K. Silvers. The entire text of the book, including all tables, figures, and references, is available at: **http://www.informatics.jax.org/wksilvers/**

This project grew from an attempt to "do something" about coat colors at MGI. Our database has a number of tools for retrieving genes and alleles by phenotypes. These include 1) searches using a controlled vocabulary of phenotype terms, 2) searches of text fields in the Mouse Locus Catalog, OMIM, and the notes field of Allele Detail Pages, and 3) searches of text fields in a set of strain descriptions. Unfortunately, none of these tools does full justice to the complex phenotype of coat color, which involves the interaction of different alleles at many different genes. The very things that make the study of the genetics of coat color so interesting (allelic series, gene interaction, and epistasis) seem to thwart our attempts to represent this phenotype in a database in a way that is friendly to biologists.

The best way to gain an understanding of coat color is to read a comprehensive review by an expert. There is no resource quite like *The Coat Colors of Mice* by Willys K. Silvers, published in 1979. This book has long been out of print, and copies at The Jackson Laboratory regularly go missing from the library or the offices of individual researchers. We were able to obtain Dr. Silvers' permission to create an online version of the book, and began to work on the project about a year before its release.

Much has been learned since 1979, and the molecular nature of the products of many coat color genes is now known. We decided to incorporate this information into the online version not by writing additional text, which would require both comprehensive expertise on the subject and regular maintenance, but by linking to dynamic data at MGI and NCBI. Links to MGI Gene and Allele Detail Pages are embedded in the text. These links take the user to pages that provide map positions, information on orthologous genes in other mammals, DNA and protein sequences, references, and other information. The text also contains links to pages listing all currently known alleles of each gene described in the book. The references cited in the text are linked to references in MGI or PubMed. The user can discover more recent publications on the same subject using MGI's references or PubMed's "Related Articles" search.

To provide an overview, we created a table listing all of the genes discussed in the text, with links to the relevant parts of the text, as well as to Gene Detail and Allele Summary Pages at MGI. At the top of this table is a link allowing the user to retrieve all genes with one or more alleles currently known to affect coat color at MGI. This table, referred to by the project team as the "Rosetta Stone Table," can be seen at: **http://www.informatics.jax.org/wksilvers/frames/frameRST.shtml**

There is a User's Guide at: **http://www.informatics.jax.org/wksilvers/userguide.shtml**

In a sense, this book grows every day as additional information is added to MGI, PubMed, and other databases. We are currently working on second release of the book that will contain the massive subject index, with links to the relevant parts of the text.

It has been very rewarding to be a part of this project, which seeks to combine Dr. Silvers' expert insights into the biology of mouse coat color with the latest tools in bioinformatics. We welcome your comments and suggestions at MGI User Support (mgi-help@informatics.jax.org).

The Va/+ mouse
Image from the Coat Colors web site, courtesy of Paul Szauter, The Jackson Laboratories

Va, varitint-waddler (**mucolipin 3, Mcoln3)**
Heterozygotes show normal/diluted/white hair patches, circling, hyperactivity, deafness, and reduced fertility. Homozygotes are white with small patches of color and show severe behavioral abnormalities, poor postnatal viability and are nearly infertile.
From the MGI database

12th European Society for Pigment Cell Research – Paris – Septembre 2004

Dear Fellow Members,

The organizers of the upcoming *12th **E**uropean **S**ociety for **P**igment **C**ell **R**esearch* have decided to give an award to the best poster presented over the Meeting.

While reading the presentations the jury will take several criteria into consideration including scientific quality, iconography and answers to questions formulated by the members of a nominated jury to be able and select the winning communication.

The award will consist in a French surprize and a free registration for the *19th **I**nternational **P**igment **C**ell **C**onference* to be held in **Reston, Va.** From **September 18th** through **22nd, 2005**. (www.palladianpartners.com/IPCC05)

We wish you luck and look forward to meeting you in Paris.

Best regards,
Dr. Lionel LARUE
Institut Curie

Mouse News
by Lynn Lamoreux

A glance at the report of the meeting of the developmental biology interest group of the IFPCC, held last month at NIH, is enough to convince the the most reluctant reader that the laboratory mouse model has come of age – for many reasons and many applications. For some of these applications it makes little difference whether or not the mice are inbred or congenic with models used by other investigators. In other instances, our work will be very much more fruitful if we each use the same mouse – same at all loci – to ask different questions of the same locus. Some of the reasons are presented below.

Those of us who heard Heinz Arnheiter's vision of our work, ultimately to understand how the genomes function within their environment and over evolutionary time, may find some similar thoughts below.

LL

THE UNITARY MOUSE MODEL
by M. Lynn Lamoreux

The mouse model, of course, can be used to study biological phenomena at all levels of organization from the molecular to the organismal. Our *Unitary Mouse Model* of pigmentation consists of all the available *inbred* mice mutant at loci that affect mouse pigmentation, put to their effective use by the us – the community of scientists. These mice can be obtained from certain individuals, from Mouse Mutant Research Resources (MMRRC), where my colony is now preserved, and of course from The Jackson Laboratory (JAX). I am preparing a CD that will consist of a searchable database of photographs, phenotypes and location or source of individual genotypes of mice –it will be essentially a summary of the unitary model. An interim, or draft, CD, not quite complete and not yet searchable is available.

(Continued next page)

The uses of the *Unitary Model* include the following.

Study of a Gene and its Functions

The availability of the model means that you can evaluate, for example, the *himalayan (Tase)* DNA; while your colleague in Japan may be more interested in the cellular level of function, the melanocyte; a colleague at NIH might prefer to study the same mutant gene at the level of the organ, perhaps development of the eye; while I will prefer to relate all these observations to the overall organismal phenotype

The laboratory mouse is the model of first choice for most purposes, primarily because it is available inbred.

This means that you and I and our colleagues at NIH and Japan and elsewhere, if we work with mice that are genetically the same as each other, can confidently compare our results at all of the levels of organization from the molecular through the organismal because we will all be working with the same gene within the same background genome.

When we wish to learn more about the *Tyrosinase* gene, again at the multiple levels of organization, there are some types of modifications of that gene that we can create. NIH has recognized C57BL/6J as an inbred background that is suggested for such creations, so that they can be used as described. Modifications that we can not create may be found in the *series of natural mutations that are also available on the same genetic background.* One example is found in Reference #1. Another example is found in reference #2 (using C57BL/10 in part because some alleles differ on that background).

Study the Effect of Background Genome upon the Functions of a Gene

The *same mutant gene can be studied congenic with different inbred strains*. For example, it would be useful to know why the JU strain background (compared with C57BL/6J) decreases both yellowness and obesity in mice that are yellow because of mutation at the *agouti* locus. Similar questions relate to the patterns of migration and survival of melanocytes during embryogenesis in white-spotted mice (see picture at the end of the article). One example of this application of the model is found in reference #3 (using C57BL/6J inbred mice contrasted with JU/CtLm inbred mice carrying the identical mutant gene).

Climbing up the Ladder of Organismal Complexity (cell, tissue, organ, organism)

Certainly the the higher levels of organismal function require genic interaction in vivo; it is already clear that genic interactions can be unpredictable and may represent more than the sum of their components. Therefore, *congenic combinations of mutants* will be essential to evaluation of higher levels of biological organization. A good example of genic interaction can be seen in the interactions of *silver (si)* and alleles at the *brown (Tyrp1)* locus, whose phenotype on a C57BL/6J background is strikingly different from that published in the literature.

For study of genic interaction, multiple mutant combinations can be created using congenic mice, in order to make direct comparisons of specific phenomena (Reference #4, for example).

Panels of mice can be created that represent every possible combination of two mutant loci and their normal counterparts. If the mice are congenic, the resulting data can be confidently attributed to actions and interactions related to the specific loci that differ. For a real example, it was noted that mice that are *brown* ($Tyrp1^{b}/Tyrp1^{b}$) and chinchilla ($Tyr^{c\text{-}ch}/Tyr^{c\text{-}ch}$) are the same pigment phenotpe as mice that are *brown* but not mutant at the *Tyr* locus, suggesting an interesting genic interaction. Primary melanocyte cultures were created using congenic mice with various combinations of alleles at these two loci and the cells were used to evaluate their interactions in normal cellular function. (References #5, #6, #7 and #8 report examples of this type of research).

Congenic immortalized cell lines are also readily available to the scientific community and have been

widely used (reference #9). Wellcome Trust Functional Genomics Cell Bank http://www.sghms.ac.uk/depts/anatomy/pages/WTFGCB.htm

Climbing Down the Ladder of Evolution

As implied by the mammals above, mutants can also be used for interspecific comparative genetics. In these cases congenesis is not an option.

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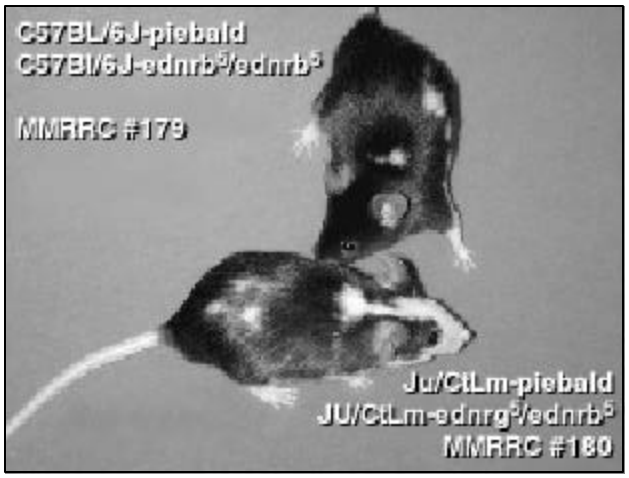
Wellcome Trust Functional Genomics Cell Bank
http://www.sghms.ac.uk/depts/anatomy/pages/WTFGCB.htm

http://WWW.MMRRC.org

This colony of mice would not have survived were it not for much support.

With thanks to:
Dr. Seth Orlow
Dr. Ray Boissy
Dr. Vince Hearing
Dr. Dot Bennett
Dr. Rick Ermel
Dr. Jim Womack
PASPCR
and the entire pigment cell community



Positions - Wanted and Available

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

Postdoctoral position

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

Albany Medical College is located in the scenic Hudson River Valley, offering affordable housing, easy commutes and quick access to cultural (e.g., Saratoga, 45 min; Tanglewood, 1 hr), and outdoor activities (Adirondack State Park, 2 hr).

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

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

The Albany Medical College is an equal opportunity, Affirmative Action Employer

Postdoctoral Associate Position

A postdoctoral research position is available for work on the development of melanocytes and their malignant progression to cutaneous metastatic melanomas in this laboratory's melanoma-susceptible transgenic mouse model. The basis for newly recognized phenomena will be investigated in the areas of apoptosis, imprinting, hypoxia-inducible gene expression, and cell migration. Some of the results are expected to provide a basis for novel experimental treatments of mice with malignant melanoma. A recent Ph.D. or M.D./Ph.D. degree is required, with strong specialization in molecular and cell biology. Please send a C.V., summaries of publications, and names of three references to:

Dr. Beatrice Mintz
Fox Chase Cancer Center
7701 Burholme Avenue
Philadelphia, PA 19111 USA
FAX: (215) 728-3574
E-mail: beatrice.mintz@fccc.edu

Department of Dermatology Chair

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

Frank L. Meyskens, Jr., M.D.
Chair, Dermatology Search Committee
c/o Kit Scott
UCI College of Medicine
Dean's Office
246 Irvine Hall
Irvine, CA 92697-3950

The University of California is an Equal Opportunity Employer committed to excellence through diversity.

Postdoctoral Position

A Postdoctoral Position is available to study the role of UV radiation in the development of primary melanoma. The project will use transgenic and pigment cell mutant mice and cell cultures to study molecular mechanisms of melanoma initiation and progression. A strong background in pigment cell biology, cellular mechanisms of toxicology, carcinogenesis, or molecular biology is desired. Send curriculum vitae, names of 3 references, and a brief summary of research interests to:

Faith M. Strickland, Ph.D.
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Henry Ford Hospital
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E-mail: FSTRICK1@hfhs.org
Phone: 313-874-3385
FAX: 313-874-3770.

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Postdoctoral Research Associate

Fox Chase Cancer Center.

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

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

XIXth INTERNATIONAL PIGMENT CELL CONFERENCE (IPCC)

A Focus on Human Pigmentary Diseases

September 18–22, 2005
Hyatt Regency Reston, Reston, Virginia

For more information: Please go to the IPCC web site
http://www.ipcc.info

Bibliography:

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

MELANINS, MELANOGENS & MELANOGENESIS

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