PASPCR

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Newsletter

The **PASPCR *Newsletter*** is published three times a year and is intended to serve as a regular means of communication for the members of our Society. The PASPCR Newsletter is distributed via e-mail, in pdf format, on the first of April, August and December and it will continue to be posted on the web site of the Society.

We hope you had a great time at the PASPCR Meeting. The meeting report of the 15th Annual Meeting of PanAmerican Society for Pigment Cell Research is published in this issue and will also be available on the PASPCR website (go to http://www.paspcr.org and click on the "PASPCR Information" tab).

Preparations for the 16th Annual Meeting of the PASPCR, spear-headed by Youwen Zhou are progressing well. The meeting will be held in Vancouver, Canada on September 29 - October 3, 2010. Further information on the meeting can be found on page 13 of this newsletter.

We hope you enjoy this issue. We encourage you to send us your comments at our email address paspcr.newsletters@gmail.com. Let us know what you would like to see in the letters, suggest sections you think would be useful to include, and recommend any changes that you would like to see. We also encourage you to let us know about meetings that you think would be of interest to members of the Society. If you attend a scientific meeting at which you heard about work 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. Also, keep us updated on any "*Members in the News*" so we can spread the word of your successes. This is **your *Newsletter***, and we depend upon you to help us ensure it best serves the Society's needs. We look forward to hearing your ideas and suggestions and to continue working together to compile the Newsletters for our Society.

The PASPCR Newsletter Editorial Team would like to thank to all our contributors for their columns submitted to us for inclusion in the letters.

We wish you Happy Holidays and a great 2010!

PASPCR Newsletter Editorial Team

The PASCR Web Site can be found at:
http://www.paspcr.org

In this Issue . . . . .

The PanAmerican Society for Pigment Cell Research

C/O Andrzej T. Slominski, M.D., Ph.D.
University of Tennessee Health Science Center
Department of Pathology and Laboratory Medicine,
930 Madison Avenue; Room 525 (Clinical Office),
Memphis, TN 38163

Officers:

Frank Meyskens
President

Greg Barsh
President-elect

Andrzej Slominski
Secretary/Treasurer

Council Members:

Robert Cornell	(2010-2012)
Gisela Erf	(2009-2011)
Thomas Hornyak	(2009-2011)
Marjan Huizing	(2008-2010)
Ana Luisa Kadekaro	(2008-2010)
Prashiela Manga	(2008-2010)
Michael Marks	(2010-2012)
Miri Seiberg	(2009-2011)
Richard Spritz	(2010-2012)

IFPCS Representative:
Caroline Le Poole (*Treasurer*)
John Pawelek (*Immediate Past-President*)

Calendar of Events

2010
20th Annual Cutaneous Malignancy Update
Date and place: January 16-17, San Diego, CA, USA
Contact: med.edu@sprippshealth.org
Web-site: http://www.scripps.org/events/melanoma-annual-cutaneous-malignancy-update

2010
The 70th Annual Meeting for the Society for Investigative Dermatology
Date and place: May 5-8, Atlanta, GA, USA
Web-site: http://sidnet.org/Annual_Meeting.asp

2010
The 16th Annual Meeting of ESPCR
Date and place: September 4-7, Hinxton-Cambridge, UK
Contact: wtmeetings@wtconference.org.uk
Web-site:
https://registration.hinxton.wellcome.ac.uk/display_info.asp?id=176

2010
1st Vitiligo World Congress
Date and place: September 23-25, Milano, ITALY
Contact: info@vwc2010.com

2010
16th Annual Meeting of PASPCR
Date and place: September 29 – October 3
Vancouver, BC, CANADA
Contact: Youwen Zhou, M.D., Ph.D.
E-mail: cpd.info@ubc.ca
Web-site: http://www.paspcr2010.org

2010
The 22nd Annual Meeting of JSPCR
Date and place: December 5-6, Fukuoka, Japan

The *PASPCR Newsletter* is published three times a year (April, August and December) by the PanAmerican Society for Pigment Cell Research. All views are those of the authors. For further information or to submit articles, please use the e-mail address paspcr.newsletters@gmail.com.

Publication Committee

Corporate Sponsors

By Andrzej Slominski

The PASPCR would like to acknowledge and thank our Government and Corporate Sponsors; the list below reflects contributions made during the year of 2009. In the past, financial gifts from our Sponsors have allowed our Society to increase benefits to the membership far out of proportion to the actual dues collected from members. Money contributed by these Sponsors have been used to support the 15th PASPCR Annual Meeting held in Memphis, including the meeting travel stipends, scientific program and educational activity and any additional meeting expenses, and also for funding our Young Investigator Award program. We gratefully acknowledge the contributions as follows:

GOVERNMENT PATRON

National Institutes of Health (NIAMS, NCI, NIEHS)

CORPORATE PATRONS

DIAMOND Corporate Patron
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Methodist Health Care
University of Tennessee HSC

We also thank for the $1,000 donation from a contributor who wishes to remain anonymous.

PASPCR Members/Changes in contact info

By Andrzej Slominski

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

Robert A. Cornell

University of Iowa

Iowa City, IA

Michael F. Holick

Boston University School of Medicine

Boston, MA

Comnuan Nokkaew

Morehouse School of Medicine

Atlanta, GA

Russel J. Reiter

University of Texas Health Science Center

San Antonio, TX

Uma Santhanam

Avon Products, Inc.

Suffern, NY

Jeremy A. Sunseri

University of Utah School of Medicine

Salt Lake City, UT

Yanhui Zhang

University of Tennessee Health Science Center

Memphis, TN

Letter from PASPCR President

The Council for PASPCR consists of nine members, with three rotating each year on January 1. It is the responsibility of the President and the Nominating Committee (led by the President-elect Greg Barsh) to assure that the Council is well-balanced. Typically a call for nominees goes out in August or September with review by the Nominating Committee. The bylaws allow either selection by the Nominating Committee or an open election, particularly if there are a large number of candidates. Most of the time an election is then held while other times the Nominating Committee selects three candidates and recommends them to the President who then checks whether they would be willing to serve. This year we have decided on the latter approach. There has been some concern expressed by a member that the bylaws be revisited and an election be required. We will do that at the next Council teleconference, but the nominees for this year have been selected and notified. These are:

Richard Spritz, M.D. who is Professor of Pediatrics and Director, Human Medical Genetics Program, University of Colorado. He is a long term member of PASPCR and was previously on the Council (2006-2008). His major research area is the genetics of vitiligo, albinism, and related hereditary diseases. He is world-renown for his seminal contributions to this important area of research, prominently represented in PASPCR.

Michael S. Marks, Ph.D. is Associate Professor, Department of Pathology and Laboratory Medicine and Physiology, University of Pennsylvania. He received the Aaron Lerner Lectureship award for 2009 and gave a terrific talk in Memphis and is now a new member of PASPCR. He has contributed fundamental information about Pmel17 and other proteins that have allowed a better understanding of the biogenesis of the melanosome – the dark organelle. His "outside" perspective will be valuable to the Council.

Robert Cornell, Ph.D. is Associate Professor, Department of Anatomy and Biology, Carver College of Medicine, University of Iowa. He is a developmental biologist who has contributed to our fundamental recognition of the neural crest and melanocyte origins and development, using zebra fish as the model organism. His unique and important perspective will undoubtedly lead us to a better understanding of "stem cells" and their importance.

We also wish to thank Caroline Le Poole, Lidia Kos, and Raymond Boissy who are rotating off the Council for their contributions. Caroline will remain on the Council as *ex officio* as she is the treasurer of IFPCS. And of course, Ray will remain a spiritual presence, having served as Secretary Treasurer from 2002 to 2008.

PASPCR Council Members

Term			
2008 - 2010	**Marjan Huizing**	**Ana Luisa Kadekaro**	**Prashiela Manga**
2009 - 2011	**Gisela Erf**	**Thomas Hornyak**	**Miri Seiberg**
2010 - 2012	**Robert Cornell**	**Michael Marks**	**Richard Spritz**

Frank L. Meyskens, Jr.
President, PASPCR

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Letter from PASPCR Treasurer and Secretary

From September 4 to 7, Hamilton Eye Institute at the University of Tennessee Health Science Center (UTHSC) hosted the 15th PanAmerican Society for Pigment Cell Research (PASPCR) conference. The conference theme was "The Pigmentary System: Securing a Place Under the Sun," and the program represented a unique

blend of basic, translational and clinical science. It attracted more than 130 of basic science researchers from both academic and industrial backgrounds, clinicians, pathologists, ophthalmologists, residents and graduate students interested in current problems in pigment cell research from the USA, Canada, Japan, Europe, Asia and Australia. As the organizers we are greatly honored that the Council of the International Federation of Pigment Cell Societies including European, Asian, Japanese and PanAmerican representatives has chosen this conference for its meeting where important decisions relating to the IFPCS have been made.

The conference was opened by myself, Dr. Frank Meyskens, President of the Society, Dr. Steven Schwab, Dean of the Medical School and Dr. Charles Handorf, Chair of the Department of Pathology. The conference was marked by an outstanding scientific program, exceptional oral and poster presentations as well as outstanding key note speakers (Drs. S. Grando, M Holick, L. Pfeffer, M. Kastan, R. Paus, J. Arbiser, M. S. Marks, R. J. Reiter, E. Blalock, G. Barsh, A. Slominski, D. Johnson) who are the leaders in their corresponding fields of science and medicine. The conference provided a venue for physicians and scientists as well as specialists from related fields to participate in new advances in pigment cell biology within such areas as neurobiology, endocrinology, immunology, photobiology and cancer research. The high quality of science was recognized by NIH with sponsorship by NIAMS, NCI and NIEHS, by pharmaceutical and cosmetic industry and local health care system through generous sponsorship from Johnson and Johnson, Unilever, the Amway Corporation, L'Oreal, Memphis Dermatology Clinic, Proctor and Gamble, Avon Products, Inc., Baptist Memorial Health Care Corp. The clinical and educational content was of great value as the Methodist Health Care has designated this educational activity for a maximum of 26 AMA PRA Category 1 Credits. We thank all of the attendees and members of the national and local organizing committees for their contribution to this great scientific and educational success.

Specifically, I thank Dr. Barrett Haik and Dr. Charles Handorf for their support and contribution. Dr. Haik as the Chair of the Hamilton Eye Institute has provided its facilities for the conference as well as supported it financially and organizationally. Dr. Handorf, a long supporter of the PASPCR, has provided administrative and organizational support for the conference and, together with Mrs. Miriam Handorf, opened their residence for the welcome reception on September 3, 2009. I can fully attest that every attendee was grateful for this and very much impressed by the southern hospitality. I also thank Dr. Peter Netland for his support and organizational contribution. Importantly, we thank Dr. Blazej Zbytek as well as Ms. Barbara Frederick, Ms. Leslie Ingram and Ms. Deborah Trapp for their tireless administrative and organizational work. We also thank our fellows and residents Drs. Radoslaw Bieniek, Jiong Zhang, Amanda Mullins and Dianne Kovacic for their voluntary help. The scientific success was made possible because of outstanding and hard work of the National Organizing Committee and chairs of the sessions including Drs. Frank Meyskens, Gertrude-Emilia Costin, Prashiela Manga, John Pawelek, Tom Hornyak, Vincent Hearing, Zalfa Abdel Malek, Ana Luisa Kadekaro, Marjan Huizing, James Grichnik, Sancy Leachman, Youwen Zhou, Lidia Kos, Connie B. Lin, Vijayasaradhi Setaluri and Caroline Le Poole.

Another important aspect was represented by social events. On September 3, 2009 we learned that Elvis Presley is still alive and enjoyed southern hospitality in Handorf's residence. On September 5, we had a gala dinner in the Texas de Brazil. Many of us enjoyed Beale Street with its blues, jazz and rock music.

Again it was a big privilege for us to host this meeting in Memphis that brought the distinguished scientists and clinicians who are the leaders in their corresponding fields of science and medicine as well as outstanding trainees interested in pigment cell biology.

Andrzej Slominski, Secretary/Treasurer

Membership Application

PANAMERICAN Society for Pigment Cell Research

Please see the back for description of membership categories and remittance required with application. Mail, fax or e-mail completed application and remittance to the Secretary-Treasurer's office

Type or print.

Name _____ Degree(s) _____
last first middle

Faculty Title (if applicable) _____ Yr of Appt _____

Department _____

Institution _____

StreetAddress _____

City, state, zip _____ Phone (_____)_____

Fax (_____)_____ E-Mail _____

Please check category for which you are applying. *See the back for definitions and dues schedule.*

___ Regular ___ Student

Student Sponsorship: Sponsors of Students verify herewith that the applicant is a bona fide graduate student or postdoctoral fellow.

Sponsor signature _____ Printed name _____

Sponsor Institution _____

Area of Research: We would appreciate your providing the following information. Please check your research interests.

_____ Cell Biology	_____ Physics	_____ Comparative Biology
_____ Biochemistry/Chemistry	_____ Clinical	_____ Melanin
_____ Molecular Biology	_____ Melanoma	Other: _____

Please list the clinical areas in which you are certified: _____

_____

Signature and membership start date

I, the undersigned, wish my membership in the PANAMERICAN Society for Pigment Cell Research to begin January 1, 2009.

_____ _____
Applicant's signature *Date*

-OVER-

MEMBERSHIP CATEGORIES AND DUES SCHEDULE

To apply for membership, please send to the office of the Secretary-Treasurer:

- Completed application form, including sponsor signature;
- Remittance for one year's dues.

Dues are payable on a calendar year basis. Please check the appropriate category.

- ☐ Regular ($224/yr) *($77 for PASPCR, $28 for International Federation of Pigment Cell Societies and $119 for both printed and electronic subscription to the journal Pigment Cell and Melanoma Research)*
- ☐ Regular ($154/yr) *($77 for PASPCR, $28 for International Federation of Pigment Cell Societies and $49 for an electronic subscription to the journal Pigment Cell and Melanoma Research)*
- ☐ Student ($40/yr) *($12 for PASPCR; $28 for International Federation of Pigment Cell Societies) [includes free subscription to the journal Pigment Cell and Melanoma Research]*
- ☐ Second membership (if IFPCS dues are paid through another local society) ($77/yr)

** Students receive electronic free journal subscriptions when joining or renewing membership prior to January 31st each year)

Method of Payment (please indicate total amount):

$ _____ **Check** Please send check or money order in U.S. funds drawn only on a U.S. bank. Checks drawn on a non-U.S. Bank will be returned. Make check payable to: **PANAMERICAN Society for Pigment Cell Research** or **PASPCR**.

$ _____ **VISA** Card #: _____

$ _____ **MasterCard** Exp. Date _____

Signature: _____

Return to: Andrzej T. Slominski, M.D., Ph.D.
Secretary-Treasurer, PASPCR
Department of Pathology and Laboratory Medicine
University of Tennessee Health Science Center
930 Madison Avenue, Suite 599
Memphis, TN, 38163
Phone: 901-4483741; Fax: 901-4482435; e-mail: aslominski@utmem.edu

PANAMERICAN SOCIETY FOR PIGMENT CELL RESEARCH

2010 DUES

INVOICE DATE: December 1, 2009 **DUE DATE: December 15, 2009**

1. Contact Information *(Please be sure all contact information is current and correct, including e-mail address)*

Current Address

☐ **Corrections** ***(please print CLEARLY)***

_____
_____
_____
_____
_____

Phone: _____
FAX: _____
E-mail: _____

☐ **No Corrections Needed**

2. Dues *(Please mark the appropriate category below)*

☐ Regular ($224/yr) *($77 for PASPCR, $28 for International Federation of Pigment Cell Societies and $119 for both printed and electronic subscription to the journal Pigment Cell and Melanoma Research)*

☐ Regular ($154/yr) *($77 for PASPCR, $28 for International Federation of Pigment Cell Societies and $49 for an electronic subscription to the journal Pigment Cell and Melanoma Research)*

☐ Student ($40/yr) *($12 for PASPCR; $28 for International Federation of Pigment Cell Societies) [includes free electronic subscription to the journal Pigment Cell and Melanoma Research]*

☐ Second membership (if IFPCS dues are paid through another local society) ($77/yr)

Members of the SMR are exempt from the mandatory subscription of the PCMR through PASCPR, after certifying that the subscription has been paid as a part of the dues to the SMR, they pay $105.

3. Method of Payment *(Please **mark the total amount** next to the preferred method of payment)*

$_____ **Check** Please send check or money order in U.S. funds drawn only on a U.S. bank. Checks drawn on a non-U.S. Bank will be returned.
Make check payable to: **PANAMERICAN Society for Pigment Cell Research** or **PASPCR**.

$_____ **VISA**** Card #: _____ Exp. Date _____
$_____ **MasterCard**** Card #: _____ Exp. Date _____
*****BE SURE TO SIGN*** Signature: _____

PLEASE SUBMIT YOUR DUES BY December 15, 2009

Return to: Andrzej T. Slominski, M.D., Ph.D., Secretary-Treasurer, PASPCR, Department of Pathology and Laboratory Medicine, University of Tennessee Health Science Center, 930 Madison Avenue, Suite 599, Memphis, TN 38163; Phone: 901-4483741; Fax: 901-4482435; e-mail: aslominski@utmem.edu

Please return this form with your payment

PCMR Journal Corner

Confessions of an Editor
By Colin Goding

On a cool grey day in Oxford in the autumn 2003 I went to meet for the first time the journal manager and other members of the team that managed Pigment Cell Research for the publisher Blackwells. I'd prepared a few ideas that I might have scribbled on the back of an envelope, if I had thought it really mattered. I was after all being interviewed for a job I didn't really want. As I sipped an espresso on arrival in Oxford earlier that morning, I had contemplated what, or rather who, had got me into this situation in the first place. Dot Bennett. The mother of melanocyte biology had benignly approached me a year before and gently intimated that the next editor of Pigment Cell Research was to be a European, and that I would be a wonderful choice for the position. I was flattered, though not enthusiastic. But the seed of the idea had been planted and was duly watered by a succession of colleagues, each of whom spun me the same line. It is difficult to resist such a coordinated massaging of the ego. In time I began to contemplate the challenge that running a journal might bring. And especially how little work was involved. After all only 50 papers a year had been published. A mere 1 per week. I could handle that.

What I hadn't counted on were the hidden extras. The other manuscripts that I would need to find referees for that were not going to be published; finding a cover image; setting the running order; writing editorials; checking proofs and figure quality; responding to authors; helping publicise the journal; choosing reviews and chasing authors; Editorial board meetings; dealing with Society issues; helping to authors rewrite abstracts and indeed papers if the English wasn't quite up to scratch…..and all this with an editorial office comprising just myself and a computer. I had a lab to run too. But once I said I was going to do the job, I thought I needed to give it my best shot.

It helped that I had a clear vision for what the journal should be: A focus for the entire pigment cell community, which would provide a high quality service. The question was how could the best service be implemented? Clearly publishing papers that no one would read was not going to provide a service, while publishing papers that were appearing in high impact journals, and which presumably were being read, was not immediately achievable. How then does one attract high quality papers and reviews? Clearly my predecessor, Vince Hearing, had faced the same issues and had achieved the success of increasing the impact factor by the simple strategy of publishing a couple of highly read and cited reviews per issue. The result was an increased profile for the journal and better quality papers. The impact factor, which reflects the citations attracted to a journal is a disproportionate presence in the psyche of science; it is a major determinant in where we try to publish, and is used by funding agencies and potential employers to get a sense of the quality of work of the individual under review. Love it or hate it, the impact factor is a powerful influence. That of Pigment Cell Research had improved substantially but still remained low at around 3. The journal clearly wasn't serving the community as much as it should. But how does one increase an impact factor? Publishing more reviews was not an option as most topics seemed to have been covered already. I needed a minimum of 30 reviews to take me through the 5 years and given the nature of the field, there were only a limited number of topics that were left. The only strategy I could come up with was twofold: to increase the readership, and thereby generate more citations, which would raise the impact factor and consequently attract more papers; and to publish fewer papers. The danger of an impact factor-based strategy was pointed out to me by a member of the IFPCS who suggested that if the impact factor increased too much, many members of the pigment cell biology would feel too intimidated to submit manuscripts for fear of rejection, and those currently submitting to higher impact journals would still not submit to PCR. The result would

be no papers. And indeed in the second year, this prophecy came close to being fulfilled with one of the issues containing only two reviews and two papers, one of which was from my lab. But then things began to change, the impact factor did rise, and immediately after the announcement the submissions went up substantially. At present the numbers of papers being submitted is around 4-fold higher than when I took over, though in part that has been achieved by increasing the readership and broadening the appeal of the journal.

When I first took office, I was astonished to find that there were no melanoma papers or reviews in PCR. When I asked why, no one seemed to put forward any particular reason, other than another journal, Melanoma Research, existed. I took a look at the first issue of PCR that was published 22 years ago and found that it had around 50% of its contents based on melanoma. The melanoma community was large, yet was not aware of Pigment Cell Research, didn't publish in it, didn't read it, and didn't cite it. I decided therefore to take the journal back to its roots and sought out melanoma reviews, which at least increased the numbers of topics that were available to me. That then began to process of raising awareness in the melanoma community culminating in the eventual adoption of the journal by the newly-formed Society for Melanoma Research (SMR). The proportion of melanoma reviews and articles is now around 50%, back to where it was when the journal began. The result was again a raised awareness of the journal and an increase in submissions that mean the journal has a secure future, and double the number of readers with both the SMR and the IFPCS memberships taking compulsory subscriptions. The price was simply a name change to incorporate the word melanoma in the title. Melanoma Research continues, but retains a distinct identity in publishing papers with a more clinical orientation.

The increased subscriptions, melanoma coverage, and association with the SMR meant more work for me. I tried to turn around papers as fast as possible and get referees comments back to authors within 2 to 3 weeks. This was made easier by knowing personally many members of the research community and personalising the letters inviting reviews or the 'opportunity' to review a paper: 'Hi Bill….' is much more effective at eliciting a positive response than a standard letter beginning 'Dear Dr. Pavan….' . Because I was a member of the community I was seeking to serve rather than a professional editor, I think the journal maintained a more intimate contact with its audience. However, the increased workload meant that it was no longer possible for me to provide the kind of service that I wanted to give. The editorial board was re-organised accordingly with the appointment of two executive editors, a decision that in retrospect was one of the best I made. Both Sho Ito and Ze'ev Ronai, representing the pigment cell biology and melanoma interests respectively, immediately took some of the load of my shoulders by taking responsibility for commissioning reviews. Ze'ev then initiated the highly successful News and Views section, which again raise the profile of the journal substantially by getting eminent scientist within the community to contribute, and again fulfilled the commitment to providing a service to the readership.

Concerns about the workload, again led to another major change: the recent adoption of the online submission system. Personally, I detest online submission systems, as I can never remember all the passwords, and get sick of entering the details required and uploading files. But, the sheer number of submissions dictated something had to be done. The incoming Editor-in-Chief was also in favour of adopting some kind of system since the workload was becoming too great and the service would suffer as a consequence. In designing the system, Ze'ev and I, together with the publisher, have tried to keep it as simple as possible, though it is difficult to beat the simple instruction to authors that I initially adopted 'send a PDF to the editor'. Nevertheless it seems to be working reasonably well and I hope is not proving a burden to authors or referees.

5 years have passed and the journal is a very different beast. Colour covers and altered format, News and Views, melanoma content, support from both the SMR and the IFPCS, raised impact factor and increased readership, and an editorial board uncoupled from Society affiliations, have all gone some way to improving the journal and providing a better service. At the beginning I was perceived as developmental biologist or melanoma specialist who would change the journal, and downgrade traditional topics such as melanin chemistry. I have changed the journal, but think I also maintained the commitment to publish on every aspect of pigment cell biology and keep the diversity that is so highly valued. Change is good, but so is continuity.

Now that I have stepped down I don't have to worry about journal deadlines and making sure I get manuscripts reviewed in a timely fashion. I can happily retire to the broad sunlit uplands of running my lab.

I'll end with an observation: In the days of the Roman Empire there was a succession of three emperors: Augustus, Tiberius and Caligula. Augustus was a dictator, but his successor Tiberius, a tyrant. During the reign of Tiberius, the population looked back upon the era under the dictator Augustus with a fond recollection of better times, and damned Tiberius. But Caligula was a monster. And so, during his reign the population remembered the good days of Tiberius. One's place in pantheon of the great can be assured by simple expedient of ensuring that one's successor is worse than oneself. Whether this applies to editors is for the readership to judge. This editorship is over, the next has just begun…..

Colin Goding

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Access to on-line contents of PCMR Journal

The following details have been provided by Lluis Montoliu, webmaster of IFPCS website, to facilitate the access to the on-line contents of PCMR Journal.

As you know, all IFPCS members (all members of ASPCR, ESPCR, JSPCR and PASPCR) are entitled to browse, read and download full online contents of our scientific journal, Pigment Cell & Melanoma Research (PCMR).

Access has been set from the members' area of the IFPCS web site. To access the members' area of the IFPCS web site you would need your username and your password. These have been sent to you at the time of registering you as IFPCS member. However, if you have forgotten or lost the message indicating these parameters you simply have to visit the IFPCS website and request an automatic reminder, providing only your email address. Upon confirming that this email address is present in the IFPCS Members database the system will send a reminder, with your username and your password, to your email address.

Simple procedure to access to PCMR online through IFPCS web site:

1) From the IFCPS home page (http://www.ifpcs.org) go to members' area of the IFPCS website: http://www.ifpcs.org/index27.php

2) Click on "**MEMBERS-ONLY AREA**" and provide your username and password. Alternatively, if you don't know or can't remember them, simply set a reminder to be sent to you by clicking on "I am a member of IFPCS but can't remember/don't know my username/password to access" and provide your email address. Direct URL to set reminders: http://www.ifpcs.org/requestpass.php

3) Once inside the "Members-only area", select "**access to PCMR**" in the left menu bar (orange colour).

4) Finally, click on the PCMR journal's logo or onto "**Access to on-line PCMR contents**" and the implemented script will drive you to the archive of the journal, where you will be able to select any issue and open/download any paper or report published since 1987 to 2009.

The entire access procedure takes only a few seconds. It is very simple and straight-forward. However, if you experience any difficulty or face any unexpected problem, please contact Dr. Lluis Montoliu at montoliu@ifpcs.org.

Announcement – 16th Annual PASPCR Meeting – Vancouver, CANADA

Pigmentation & Melanoma Research Congress

VXI Annual PASPCR Meeting

"New Developments in the Pathogenesis and Treatment of Pigment Conditions & Melanoma"

September 29—October 3, 2010

The University of British Columbia - Robson Square, Vancouver, Canada

Local Organizing Committee

Dept. Dermatology & Skin Science, UBC

Youwen Zhou, MD, PhD (Chair), David McLean, MD, and Harvey Lui, MD, Haishan Zheng, PhD, Catherine van Rammsdonk, PhD

Scientific Committee

Youwen Zhou, MD, PhD, Greg Barsh, PhD, Frank Meyskens, MD, Andrzej Slominski, MD, PhD, Caroline La Poole, PhD

Preliminary Key Topics:

(As of August 21, 2009 - pending approval and modification by PASPCR):

- Dyschromia, photoaging, and photobiology
- Lasers and light source treatment for pigmentation diseases
- Melasma and other hyperpigmentation diseases
- Melanocyte development and melanogenesis
- Pigmentation genetics and research models
- Melanin biochemistry, biophysics and photonics
- Oxidative stress in pigment diseases and melanoma
- Melanoma: What's new in pathogenesis
- Melanoma: What's new in diagnostic and prognostic markers
- Melanoma: What's new in immunology and therapy
- Vitiligo: Recent Advances in Genetics and genomics
- Vitiligo: Pathogenesis
- Vitiligo: Recent advances in therapies
- Pigmentation/Melanoma epidemiology and cancer prevention

Pigmentation & Melanoma Research Congress is jointly held by:

- Pan American Society of Pigment Cell Research and,
- Department of Dermatology and Skin Science, University of British Columbia

Sponsored in part by:

- VGH Photomedicine Institute

Who should attend?

This year's congress will attract dermatologists, pathologists, basic science researchers from both academic and industrial backgrounds, residents, students interested in current problems of pigment cell research.

Contact: Dr Youwen Zhou, MD, PhD via University of British Columbia Continued Professional Development (CPD)

Email: cpd.info@ubc.ca

Tel: 1(604) 875-5101

UBC Dermatology
Care · Teaching · Research

The Division of Continuing Professional Development
Faculty of Medicine

www.paspcr2010.org

MEETING REPORT - THE XVTH ANNUAL MEETING OF THE PANAMERICAN SOCIETY FOR PIGMENT CELL RESEARCH – "THE PIGMENTARY SYSTEM: SECURING A PLACE UNDER THE SUN"

MEMPHIS, TN - SEPTEMBER 4-7, 2009

SESSION 1: Biochemistry, Chemistry and Biophysics of Melanin Pigmentation
Chairs: John Pawelek, Gertrude-Emilia Costin and Vincent Hearing
By Vincent Hearing

Jason Belitsky (Oberlin College) began the session by reporting his studies trying to analyze the molecular structure of melanins to further understand their physical properties. He noted that melanins are among the more poorly understood large biomolecules (e.g. compared to proteins and DNA), and he stated that his thinking about this project was heavily influenced by the recent studies of Simon's and Ito's group of eumelanins and their proposed structures. He is particularly interested in the interaction between various types of melanins and their capacities to bind various compounds, particularly heavy metals such as lead. These may have critical importance to the function of neuromelanin in the brain and its dysfunction in patients with Parkinson's disease. He is trying to unravel the processes by which eumelanin self-assembles into a large polymer and what effect that has on its subsequent binding of metal ions and organic compounds. In addition to synthetic melanins generated by the oxidation of DOPA, he is also studying natural melanins purified from human hairs, an easy and plentiful source. He then coats those melanins on PVDF disks, which are heavily visibly pigmented; the binding of compounds of interest to those filters can then be readily measured. He compared binding of lead to those melanins at various pHs (4.5, 5.0 and 5.5 were shown) and the binding was relatively high but not dramatically affected within that range of pHs. The binding and color is reversible by treatment with EDTA. He is developing this screening method as a model for the study of neuromelanin and its role in Parkinson's disease, and also for the study of organic pollutants and other compounds that bind to melanins.

Wen Li (University of Tennessee Health Science Center) discussed their studies using nuclear magnetic resonance (NMR) to analyze metabolic changes in human and hamster cells. The rationale for the study is that levels of pigmentation can affect the behavior and responsiveness of melanoma cells. The authors used changes in tyrosine levels in the medium to induce pigmentation in amelanotic (hamster) and in melanotic (human) melanoma cell lines and increased pigmentation was generally seen in 3-5 days. The density of the melanin and its weight in pigmented cells causes relatively rapid sedimentation of the cells which is a big challenge for this technology. They used various C13-labeled precursors to study different cellular processes, for example, C13-glucose to study energy metabolism and C13-sodium acetate to study lipid synthesis. Interestingly, increasing pigmentation enhanced lipid metabolism. Further studies will use such specifically labeled precursors to investigate the effects of inducing pigmentation on the metabolism of melanoma cells.

Vince Hearing (National Cancer Institute) reported their most recent study comparing the effects of repetitive exposure to UVA and/or UVB on human skin, with particular respect to whether the tans induced provide any photoprotective benefit. The skins of subjects (types II-III) were irradiated daily over a 2 week period with sub-MED doses, which induced comparable tans at the doses used, and 3 days later, subsites of the tanned areas (and the unexposed control) were challenged with a 2 MED dose

of SSR. Biopsies were taken immediately after that and melanin content, expression of melanocyte-specific markers and DNA damage (in the form of CPDs) were assessed. The mechanisms of UVA- or UVB-induced tans were distinct, UVB stimulating the melanogenic pathway leading to increased melanin synthesis. In contrast, UVA had little or no effect on melanin content or the expression of melanocyte markers. The mechanism of UVA-induced tans probably reflects oxidative-induced changes of existing melanin and melanogenic intermediates similar to the mechanism responsible for the rapid and transient color change know as immediate pigment darkening.

John Pawelek (Yale School of Medicine) discussed his work on the relationship of melanin (in various forms) and the aggressive growth of melanomas. He noted that cutaneous melanomas often are pigmented much more dramatically than the surrounding normal skin. He reviewed the occurrence of 'coarse' melanin, large complexes of melanins that were initially described many decades ago, but are now known to be due to autophagy (self-eating of subcellular organelles) due to stress. The coarse melanin can be seen in melanocytes, keratinocytes and melanophages in normal skin, and is typically very dark in melanoma cells. The darker melanin seen in melanoma cells is thought to be eumelanin compared to the lighter melanins found in adjacent normal light skin which is thought to be more pheomelanic in nature. He discussed the role of β1,6-branched oligosaccharides, which are associated with autophagy. For those interested in this topic, Pawelek and Chakraborty recently published a review on the role of fusion of melanoma cells with macrophages in Nature Rev Cancer [2008 8(5):377-86] and on the specific topic of dark pigmentation in melanomas in Exp Derm [2009, in press].

T. L. Scott (University of Kentucky) reported on a new approach to culturing melanocytes from Mc1r-deficient (e/e) mice. Mc1r plays an important role in regulating pigmentation in melanocytes, and modulates the amount of melanin produced and also the ratio of pheomelanin (yellow/red) to eumelanin (brown/black). The goal was to avoid including factors normally added to melanocyte culture medium that affect cAMP levels and thus complicate studies of MC1R function, which depend on the cAMP pathway. Such factors include dibutyryl cAMP, MSH, IBMX and cholera toxin. In place of those, they used SCF since it is known from mouse models that SCF has no effect on e/e mice, and they also added ET1 and TPA to assist cell growth. The pheomelanin/eumelanin ratio in e/e melanocytes cultured in that manner was 10X higher than in black melanocytes but still did not approach the dramatic changes in that ratio seen *in vivo*. They feel this is an important first step in defining growth medium that will allow such effects to be seen that more closely reflect the physiological situation.

KEYNOTE LECTURE 1: Sergei Grando – Cutaneous Cholinergic System: Lessons for Skin Pigmentary System

By Vincent Hearing

Sergio Grando (University of California Irvine) concluded the Symposium with the first Keynote lecture of the meeting entitled "Cutaneous cholinergic system: lessons for skin pigmentary system". He reviewed the cholinergic system and noted that the effects of acetylcholine (ACh) on non-neuronal signaling have existed more than 3 billion years whereas its function in the neuronal system has existed only for the past ~1/2 billion years. Thus we need to think of this ligand: receptor signaling cascade as functional far beyond the neuronal system. ACh receptors are expressed in many non-neuronal cells and tissues, and there are 2 classes of those receptors, muscarinic receptors (GPCR type) and nicotinic receptors (gated ion channel type), both of which are expressed by melanocytes. ACh decreases

pigmentation, reported at least for uveal melanocytes. Melanocytes are able to synthesize and metabolize ACh and also respond to that from other sources. ACh modulates cutaneous pigmentation due to its effects on the regulation of genes encoding melanogenic proteins and those regulating intracellular melanosome movement. In lower species, such as amphibians, ACh markedly affects the distribution of melanosomes in melanocytes/melanophores. Dysregulation of ACh metabolism has been proposed to be involved in the depigmentation seen in vitiligo (cf his recent review in Life Sci, 2007; 80:2248-52). Expression and function of ACh and its receptors are highest in the basal layer of the epidermis, both in melanocytes and in keratinocytes. Further studies on the role(s) of ACh functions in the skin should provide important insights into the regulation of normal pigmentation as well as conditions of hypo- and/or hyper-pigmentation.

SESSION 2: Cell Biology of Melanin Synthesis
Chairs: Zalfa Abdel Malek, Ana Luisa Kadekaro and Marjan Huizing
By Marjan Huizing

K. Kalleberg (Unilever R&D, Trumbul, CT) presented how multispectral imaging can be beneficial when certain stains/images are hard to acquire or characterize. A spectral camera can detect and separate different spectra of various stains and colors. Multispectral imaging is more sensitive than the traditional Fontana Masson stain for detection of melanin/melanosomes in the different layers of the skin in histology samples. Several applications of spectral imaging were presented, including imaging of living skin or Melanoderm, spectral quantitation, and separation of colocalized stains.

Francois Rouzaud (Florida International University, Miami, FL) presented how the nano-indentation technique can be used for detecting mechanical properties of individual cells (melanocytes vs melanoma) in culture, which provide information about their plasticity and adhesive properties. Mechanical properties were measured with a nano-indenter, which can detect different membrane parameters: stiffness, cytoplasm viscosity, membrane rupture load, and membrane rupture depth. Examples of the use of this technique were presented including the stiffness and rupture load of melanocyte membranes increases in the presence of α-MSH, membrane stiffness increases when cells are grown on a fibronectin coating, and cytoplasm viscosity higher in mouse melan-a cells than in mouse B16 melanoma cells. Other potential applications include responses to UV radiation, metastatic processes, and hormone or drug treatments.

Prashiela Manga (New York University School of Medicine, NY) investigated the activation of the unfolded protein response (UPR), which is indicated in several diseases of melanocytes (OCAs and melanoma). She investigated whether UPR-mediated apoptosis could be targeted by different drugs (thapsigargin or tunicamycin) for potential melanoma therapies. First all three pathways of UPR activation (IRE1, PERK or ATF6 release) were assessed in drug-treated wild type mouse melanocytes (mel-a, mel-b and mel-c). Mel-a cells showed the strongest response in turning on all three pathways. Investigation of this response in melanoma cells is ongoing.

Ganesh Diwakar (Amway Inc., St Ada, MI) presented the development a mammalian tyrosinase assay (versus the existing mushroom tyrosinase assay) for screening of tyrosinase modulating agents that can be used for pigmentation/whitening cosmetics. A CRE (cyclic AMP response element) activation assay was used (CRE-luciferase stably transfected in B16 mouse melanoma cells) as a primary drug screen.

Confirmation of potential candidates was performed on a cell-based mouse melan-a assay. The system was validated using known tyrosinase inhibitors β-arbutin and licorice.

James Grichnik (University of Miami Health System, Miami, FL) presented a case report of a 40 year old white male melanoma patient with multiple dysplastic nevi. The patient self-administered synthetic α-MSH ('Melatonan', heavily marketed to body builders) for tanning. Three weeks after starting Melatonan treatment he developed new moles and darkening and growth of existing nevi. Some moles faded after discontinuing melatonin use. Likely, the α-MSH analog drove already mutated melanocytic stem cells to produce new atypical nevi. Thus, the use of synthetic α-MSH should be approached with caution since neoplastic melanocyte cells can be driven to proliferate in predisposed patients.

Nityanand Maddodi (University of Wisconsin, Madison, WI) studied the effects of MAP2 (microtubule associated protein 2) gene regulation on melanoma neuronal differentiation and tumor progression. MAP2 concentrations are inversely correlated with melanoma aggressiveness. During melanoma progression, the MAP2 promotor is methylated, resulting in silencing MAP2 expression and increased metastatic behavior. Hyperactivation of BRAF-MEK signaling not only downregulates the neuronal transcriptional repressor HES1, but also demethylates the MAP2 promotor. These results suggest that BRAF oncogene activation may regulate melanoma neuronal differentiation.

KEYNOTE LECTURE 2: Michael Holick - Shining Light on Skin Pigment, Vitamin D and Health

By Marjan Huizing

This keynote lecture emphasized the importance of vitamin D on human health. The major source of vitamin D for humans is exposure of skin to sunlight, which triggers the conversion of 7-dehydrocholesterol in several steps to vitamin D3. Melanin absorbs UVB radiation in the skin, but thereby reduces vitamin D3 production. As humans evolved from the equator to higher latitudes, gene mutations may have occurred that favored light skin (more vitamin D production). Vitamin D deficiency and being prone to vitamine D deficiency (by living on higher latitudes) may increase risks for chronic diseases including common cancers, multiple sclerosis, diabetes, heart disease and infectious diseases. It is therefore of importance to receive regular screening for vitamin D levels, especially for those individuals who spend most of their days indoors.

KEYNOTE LECTURE 3: Lawrence Pfeffer – NF-kB Signaling: Implications For Skin Cancer

By Gertrude-Emilia Costin

Lawrence Pfeffer (University of Tennessee) started the day of Saturday, September 5th, 2009 with the Keynote Lecture entitled "NF-kB signaling: implications for skin cancer". Dr. Pfeffer provided a thorough overview of interferon (IFN) properties and its involvement in selectively regulating the gene expression through several signaling pathways. It was emphasized that interferons play critical roles in the host defense by modulating gene expression through the IFN-dependent activation of STAT and NF-kB transcription factors. Data from Dr. Pfeffer's group placed TRAF2 directly in the signaling pathway transduced through the IFNAR1 subunit of the IFN receptor. Data showing that TRAF2 is directly coupled to the signal-transducing IFNAR1 subunit of the IFN receptor were persented. These findings provided an important insight into the molecular mechanisms by which IFN generates signals

to induce its biological effects. In the second part of the talk, Dr. Pfeffer discussed data that established that IFNα/β activates NF-κB to promote cell survival through a phosphatidylinositol 3-kinase (PI3K)/Akt pathway, which involves serine phosphorylation and degradation of IκBα. Dr. Pfeffer presented data describing a second pathway by which IFNs activate NF-κB that is independent of IκB degradation. This pathway involves NF-κB-inducing kinase (NIK) and the tumor necrosis factor receptor-associated factor-2 (TRAF2) and results in IFNα/β-induced processing of the p100/NF-κB2 precursor into p52. IFNα/β stimulates NF-κB DNA binding and NF-κB-dependent transcription. Whereas expression of NIK and TRAF2 constructs causes NF-κB activation, expression of dominant negative NIK and TRAF2 constructs blocks IFN-promoted NF-κB activation and IFN-stimulated κB-dependent transcription and IFNα/β-induced processing of the p100/NF-κB2 precursor into p52. In contrast, PI3K does not mediate IFNα/β-induced p100 processing, although PI3K is involved in the pathway resulting in IκBα degradation. Moreover, whereas IFN promotes cell survival in lymphoblastoid cells, expression of dominant negative NIK and TRAF2 constructs enhances IFN-induced apoptosis. IFN was therefore shown to induce NF-κB activation to mediate IFN-dependent cell survival signals through a "canonical" pathway of IκBα proteolysis mediated by PI3K/Akt and a "noncanonical" pathway of p100 processing mediated by NIK/TRAF.

SESSION 3: Malignant Transformation of the Melanocyte and Melanoma Progression
Chairs: James Grichnik, Sancy Leachman and John Pawelek
By James Grichnik

Rossitza Lazova (Department of Dermatology, Yale School of Medicine) presented on "Autophagy In Cutaneous Malignant Melanoma". These researchers presented data that reveal that invasive and florid *in situ* malignant melanoma cells display autophagy. This was detected through immunohistochemistry for the autophagosomal marker LC3B (microtubule-associated light chain 3B), and by electron microscopy. Increased activity seemed to be correlated with progression and 90% of the lymph node metastases were positive. Autophagosomes contained the Golgi 58k protein and 1,6-branched oligosaccharides, indicating that at least some of the autophagosomal proteins were glycosylated by the Golgi enzyme GnT-V. Some also contained contained melanized melanosomes, accounting for the phenomenon of "coarse melanin" in malignant melanoma. This process is thought to be driven by endoplasmic reticulum stress and provides the cell with an energy source and may be a therapeutic target.

Feng Liu (Department of Medicine, Department of Biological Chemistry, Chao Family Comprehensive Cancer Center, University of California-Irvine School of Medicine) presented on "A Role Of Mitf In UVR-Mediated DNA Damage Response Via $p21^{cip1}$ In Normal Human Melanocytes And Melanoma Cells". These researchers presented data demonstrating that MITF is phosphorylated at serine 73 with UVC radiation, followed by a proteasome-mediated degradation. A mutant MITF-S73A was unable to be phosphorylated and did not appear to be targeted for degradation after UVC exposure. A375 cells expressing MITF-S73A mutant showed less p21CIP1 accumulation compared to cells expressing wild-type MITF after UVC. These cells also had an elevated percentage of BrdU-labeling. These data suggested that MITF mediates DNA-damaging UVR signal through p21CIP1 and facilitates DNA repair.

Zoran S. Pavicevic (Department of Neurosurgery, University of Tennessee Health Science Center) presented the lecture entitled "MDA MB 435 Melanoma Cell Line – Derived Cancer Stem Cells (CSC) Show Increase in expression of ABC Transporter Family Drug Resistance Genes not Previously

Implicated in Tumor Growth and Progression". These researchers presented data that the POU5f/Oct4 promoter driving expression of green fluorescent protein (GFP) in MDA MB 435 cells allowed for the identification of positive cells with a high potential for tumorigenesis and metastasis. The GFP+ cells were also more resistant to Taxol. Gene expression analysis revealed increased expression of ABCA10, ABCC5 ABCD1, ABCD3, ABCE1, ABCF2, ABCF3 in the GFP+ cells. These ABC transporter family members may be playing a role in tumor growth and metastasis and may represent potential therapeutic targets.

Youwen Zhou (Department of Dermatology and Skin Science - University of British Columbia) presented the lecture entitled "The Expression Of Acute Phase Reactant Proteins Correlates With Melanoma Invasion And Predicts Poor Survival In Stage III And Stage IV Melanoma". These researchers presented data showing that acute phase reactant protein was virtually absent in normal nevi, dysplastic nevi and melanoma *in situ* but its expression was dramatically increased as lesions progressed to primary and metastatic melanoma ($p<0.001$). Increased expression of this protein strongly correlated with poorer survival in metastatic melanoma, with a mean survival of 46.2 months for patients with weakly stained lesions compared to 14.9 months for strongly stained lesions ($p<0.05$). Downregulation of this protein through siRNA knockdown resulted in decreased Matrigel invasion, but did not inhibit cell proliferation, migration, or survival. This acute phase reactant protein may to contribute to melanoma invasion and metastasis and may be a novel prognostic marker for metastatic melanoma.

Deborah Lang (Department of Medicine, University of Chicago) presented the lecture entitled "PAX3 And SOX10 Activate MET Receptor Expression In Melanoma". These researchers presented data that PAX3 synergistically activates MET expression with SOX10 in melanoma cells. Expression of MET was found to be highly correlated with PAX3 and/or SOX10 expression. PAX3 and SOX10 bind to the MET promoter and inhibition of PAX3 expression lead to a >50% reduction in MET protein levels. Blocking SOX10 protein levels significantly reduced HGF-dependent phospho-MET expression. Thus these two factors were found to regulate the MET gene promoting migration, invasion, resistance to apoptosis, and tumor cell growth.

Ashley Daniels (Marshall University) presented the lecture entitled "Retinoic Acid Induces The Inhibitor Sfrp1 In Human Melanoma". These researchers presented data that retinoic acid (RA) treated SBCl2 melanoma cells induced Wnt signal inhibitor secreted frizzled-related protein 1 (SFRP1) protein expression 1.6- to 5.6-fold from 4h to 4d of treatment and cell growth was 50% lower. SFPR1 knockdown was found to inhibit the capacity of RA to reduce cell numbers. SFRP1 inhibits Wnt/ß-catenin signaling, including translocation of ß-catenin to the nucleus. Treatment of the melanoma cells with SFRP1 (100-200 ng/ml) for 48 h reduced cell numbers by 25-37% suggesting that SFRP1 is able to directly inhibit melanoma growth. Thus RA affects SBCl2 melanoma cell growth in part through induction of the Wnt inhibitor SFRP1.

Sandeep S. Joshi (Department of Biochemistry and Microbiology, Marshall University) presented the lecture entitled "The Normoxic Expression Of HIF-1α In Human Melanoma Cells: Biologic Effects And Lack Of Regulation Of The Erk 1/2 MAPK Pathway". These researchers presented data that HIF-1α mRNA and protein was increased in RGP vs melanocytes, VGP vs RGP and metastatic vs VGP melanoma cell lines. They also identified expression of a HIF-1α mRNA splice variant in WM1366 and WM9 melanoma cells that lacks part of the oxygen-dependent regulation domain. Over-expression of HIF-1α increases in anchorage-independent growth and Matrigel invasion while inhibition resulted in decreases in both anchorage-independent growth and matrigel invasion. These findings suggested

that normoxic expression of HIF-1α expression may contribute to the malignant behavior of melanoma and may be an important therapeutic target.

Arup Kumar Indra (Oregon State University) presented the lecture entitled "Retinoid-X-Receptor α (RXR α) Signaling In Tumor-Microenvironment During Melanoma Formation". These researchers presented data that RXR ablation in epidermal keratinocytes ($RXR\alpha^{ep-/-}$) of adult mice modulated the expression of keratinocyte-derived growth factors known to be involved in melanocyte mitogenesis and melanomagenesis. A bigenic mouse ($RXR\alpha^{ep-/-}$/CDK4R24C/R24C) was created with an activated cyclin dependent kinase 4 gene. Bigenic mice subjected to DMBA/TPA exhibited more aggressive and metastatic melanocytic tumors compared to $RXR\alpha^{ep-/-}$ mice alone. Thus their results demonstrated the cooperative effects between keratinocytic RXRα and CDK4 in mediating melanocyte proliferation and melanoma formation implicating an important role of the tumor-microenvironment.

KEYNOTE LECTURE 4: Michael Kastan – DNA Damage Responses: From Molecular Mechanisms to Clinical Interventions
By Prashiela Manga

Michael Kastan (St. Jude Children's Research Hospital, Memphis) discussed recent progress made in understanding the molecular pathways that regulate DNA repair and potential therapeutics that can be used to improve this response. A key protein in eliciting the repair response is p53, which Kastan *et al* found to be increased following DNA damage and caused G1 arrest. The first downstream target of p53 was found to be GADD45. Kastan *et al* subsequently demonstrated that p53 is a substrate for the ataxia-telangiectasia protein kinase which upon DNA damage phosphorylates serine 15. ATM in its inactive form is a homodimer that is activated by autophosphorylation. A number of additional targets for ATM have now been identified and pathways activated by specific damaging agents such as ionizing radiation delineated. Cells that lack functional ATM are hypersensitive to ionizing radiation, since in addition to p53 ATM targets SMC1, CHK2, MDM2, BRCA1, FANCD2 and NBS1, some of which have been implicated in multiple cancers and cancer syndromes. The ATM pathways represent important targets for both chemoprevention and cancer therapies. One potential agent is choloroquine, which activates the ATM-p53 pathway in the absence of DNA damage and without causing DNA damage itself. This drug has been shown to be effective for the treatment of metabolic syndrome. Chloroquine effectively improved the condition of a mouse model for this disease (ob/ob and db/db mice). Thus the ATM may prove an important target for future drug development.

SESSION 4: Cell Surface and Nuclear Receptors and Their Ligands
Chairs: Prashiela Manga, Andrzej Slominski and Zalfa Abdel Malek
By Prashiela Manga

Alejandro Conde (Florida International University) presented a discussion focused on the cross-talk between GPCR pathways. MC1R, a critical GPCR protein in the melanocyte regulates constitutive and facultative pigmentation. In addition, a second GPCR, endothelin receptor B can also impact behavior of the melanocyte. The ligands for these GPCRs, MSH and Endothelin-3 have been shown to have a synergistic effect on expression of tyrosinase mRNA, but not on MITF. A potential mechanism accounting for the disparate responses is through PKC-mediated signaling. PKC acts downstream of GPCR/PLC/phosphoinositol signaling. One isoform in particular, PKC-β, may play a role in regulating

melanin synthesis in the absence of MC1R signaling, thus providing a target for rescuing the red hair/fair skin phenotype which is associated with significant increases in melanoma susceptibility.

Zorica Janjetovic (University of Tennessee Health) discussed the biological activity of vitamin D3 hydroxyderivatives. 1,25-Dihydroxyvitamin D3 ($1,25(OH)_2D_3$) and its analogs can inhibit cellular proliferation and may thus be useful anti-tumor properties. There are however cancer lines that are resistant to the effects of $1,25(OH)_2D_3$. This resistance may be the result of variation in activity of the vitamin D receptor (VDR). Binding of the receptor has been shown to be reduced in some melanoma lines. Differential VDR expression, altered by changes in culture media which change levels of melanin synthesis, correlate with response to $1,25(OH)_2D_3$. The authors thus propose $1,25(OH)_2D_3$ as a candidate for development of a melanoma therapeutic.

Jianjun Chen (University of Tennessee Health) discussed 3β-Hydroxy-androsta-5,7-diene-17β-carboxylic acid (17-COOH-DHA), a novel steroidal 5,7-diene derivative. 17-COOH-DHA was synthesized and tested for potential as an anti-melanoma treatment. Human keratinocyte (including HaCat cells), melanocyte and melanoma lines were tested for sensitivity to 17-COOH-DHA. Dose dependant reductions in proliferation were observed. In addition, the compound inhibited colony formation in the melanoma line SKMEL188. It was found to stimulate involucrin, Bcl-2 and EGFR expression and to reduce cyclin E-1. 17-COOH-DHA therefore demonstrates potential as an anti-melanoma agent.

Linda Eastham (Marshall University) discussed epigenetic silencing and reactivation of retinoic acid receptor, RARβ2 in human melanoma cells. The anti-tumor effects of vitamin A derivatives, retinol and retinoic acid are mediated through receptors with several isoforms. RARβ2 is thought to mediate the anti-proliferative effects of retinoic acid. However some melanoma lines are resistant to retinoids. Retinoic acid was found to inhibit proliferation and increase expression of RARβ2 in melanocytes and some sensitive melanoma lines. Lines in which the RARβ2 was hypermethylated were resistant to the effects of retinoic acid. Treatment with 5'-aza-2'-deoxycytidine, a demethylating agent, promoted RARβ2 expression and response to retinoic acid.

Zalfa Abdel-Malek (University of Cincinnati), reported on the correlation between MC1R genotype and response to UV. MC1R variants associated with loss of function have been implicated in determining pigmentation of the skin and hair as well as the capacity to respond to UV induced damage by upregulation of melanin synthesis and activation of DNA repair mechanisms. A panel of human melanocyte cell lines expressing MC1R variants were established by Abdel-Malek *et al* and correlative studies preformed to determine the effects on these cells. Melanocytes expressing two alleles associated with significant loss of activity, the so called Red Hair alleles, did not demonstrate an increase in cAMP and tyrosinase expression following treatment with MSH, while lines heterozygous or these alleles did not show a compromised response. Wildtype or heterozygous melanocytes reversed the effects of UV irradiation (hydrogen peroxide formation, CPD generation and induction of apoptosis) more rapidly and efficiently than cells homozygous or compounds heterozygous for loss of function alleles.

Jillian Vanover (University of Kentucky) presented evidence of repigmentation in hair of mice homozygous for the c2j tyrosinase mutation following stem cell factor expression. A K14-SCF transgenic mouse model was used in this study. Upon expression of SCF, expression of tyrosinase mRNA and protein were greatly increased. Despite previous reports that c2j is a loss of function

mutation, progressive increases in pigmentation were observed in these model animals suggesting that rescue of the hypopigmentation phenotype is possible, which may prove to be useful in the management of melanoma risk.

KEYNOTE LECTURE 5: Ralf Paus – Neuroendocrinology of the Hair Follicle
By James Grichnik

Neuroendocrinology of the hair follicle was presented by Ralf Paus from the University of Lubeck. Hair abnormalities including pigmentary changes have been noted in patients with thyroid disorders. Further HPA (hypothalamic-pituitary-adrenal) – like systems appear to be present in skin as evidenced by the melanocortin system. This led Dr. Paus to investigate the presence of a thyrotropin-releasing hormone, thyroid stimulating hormone, and thyroid hormone axis in the hair follicle. He utilized a human hair explant model in which the hairs continued to grow *in vitro*. He was able to show that T3 and T4 prolonged anagen, decreased apoptosis, increased keratin 6, decreased keratin 14, and increased pigmentation. He was also able to show that the TRH receptor was present and that TRH stimulated hair growth and melanization. Thus the hair follicle does appear to have a partial HPA axis equivalent in terms of TRH and response to T3 and T4.

SESSION 5: Melanocyte Maturation/Differentiation: Developmental and Cellular Biology
Chairs: Tom Hornyak, Youwen Zhou and Lidia Kos
By Tom Hornyak

Greg Bonde (Cornell lab at the University of Iowa College of Medicine) presented on "Transcription Factor Activator Protein 2 Epsilon (TFAP2E) Functions Redundantly with TFAP2A to Promote Differentiation of Melanocytes in Zebrafish Embryos". TFAP2A and TFAP2E are transcription factors of the AP2 family, and Tfap2 has been shown to affect growth and differentiation of melanocytes. Tfap2 binds the *Kit* promoter, and interestingly there is a similar loss of early melanocyte precursors between *tfap2a*$^{-/-}$ zebrafish embryos and embryos lacking *kit.* However, as development proceeds, the phenotypes of the embryos diverge, with melanoblast number in the *tfap2a*$^{-/-}$ embryos approaching wild-type levels. These observations suggested that another factor might be partially redundant with *tfap2a* to compensate for its loss. In this presentation, evidence was presented to demonstrate that *tfap2a* seems to function alone through *Kit* to regulated early melanoblast cell division and migration in zebrafish, with *tfap2a* and *tfap2e* functioning more redundantly later to activate *mitf* for differentiation and survival.

Hayoung Hwang (Hornyak lab in the Dermatology Branch of the National Cancer Institute, NIH) presented on "Functional Properties and Characterization of Melanocyte Label-Retaining Cells". An analysis of the distribution and properties of quiescent, label-retaining melanocytes in doxycycline-regulated transgenic mice driving expression of an H2BGFP fusion protein from the *Dct* promoter was presented. Evidence was presented to support the localization of quiescent melanocytes in the secondary hair germ, in addition to the bulge or lower permanent portion, region of the telogen murine hair follicle. These cells demonstrate stem cell properties *in vivo*, by virtue of their ability to confer pigmentation to amelanocytic follicles derived from *Mitf* mutant mice.

Lidia Kos (Florida International University) presented on "Interaction Between the Transcription Factor, Sox10, and Endothelin Receptor B in the Melanocyte Lineage". The study was prompted by the

desire to answer the following question: do Sox10 and Ednrb interact? Previous evidence suggested that the answer to this question is yes in enteric neurons and melanocytes, but no in melanoblasts. To address this *in vivo* using genetic means, intercrosses of mice each heterozygous for deficiencies in *Ednrb* and *Sox10* were performed. Compound heterozygotes on a normalized genetic background exhibited white belly spots greater than the sum of those observed in individual heterozygous mutants, an indication of a synergistic interaction between *Ednrb* and *Sox10* in melanocyte development. This might be explained by the known binding of Sox10 to the *Ednrb* promoter, perhaps ascribing a developmental regulatory role to this interaction. Surprisingly, a *Dct-Ednrb* mouse completely rescued the spotting phenotype observed in *Sox10* mutant heterozygotes. Embryonic analysis showed that the number of melanoblasts in the *Dct-Ednrb; Sox10*$^{+/-}$ background at E11.5 was considerably greater than in the *Sox10* heterozygous mutant alone, although not as large as the number observed in wild-type embryos. *Sox10*-compromised melanoblasts, reduced in number, appear to retain sufficient resiliency and responsiveness to a delayed *Ednrb* signal to be able to normalize substantially at later stages of development.

Andrzej Slominski (Department of Pathology and Laboratory Medicine at the University of Tennessee Health Science Center) presented information on "The correlation of TRPM1 (Melastatin) mRNA expression with microphthalmia associated transcription factor (MITF) and other melanogenesis related proteins in normal and pathological skin, hair follicles, and melanocytic nevi". Melastatin (MLSN; a.k.a. transient receptor potential cation channel, subfamily M, member 1 (TRPM-1)) can regulate melanocyte differentiation and proliferation. Its transcription is controlled by the essential melanocyte transcription factor MITF (microphthalmia-associated transcription factor). During melanoma progression, MITF expression is preserved while MLSN mRNA expression decreases or is lost in less differentiated or more aggressive melanomas. In melanocytic cells, MLSN expression generally correlated positively with the differentiation state of the cells, with MLSN strongly and significantly correlated with MITF and tyrosinase expression. MLSN was lower in acral skin and in older (>age 60) skin, and unlike other melanocyte differentiation markers, did not vary in sun-damaged skin. Another intriguing observation in this *in vivo* study of MLSN expression was that MLSN appeared to be downregulated relative to MITF in regenerating melanocytes (in wounds and in the hair follicle outer root sheath) and in less differentiated nevus-associated cells.

Ivana de la Serna (Department of Biochemistry and Cancer Biology at the University of Toledo Medical School) presented on "Heterogeneous SWI/SNF chromatin remodeling complexes promote expression of microphthalmia-associated transcription factor target genes in melanoma". SWI/SNF factors are ATP-dependent chromatin remodeling enzymatic complexes that modify chromatin structure to facilitate transcriptional activation or repression at specific genes. They can interact with histone-modifying enzymes to effect these changes and vice versa. They play a role in embryonic stem cell pluripotency, cellular differentiation, and can be linked to functions in melanocytes and melanoma by various observations that have been made. BRG or BRM are the ATPases in the hSWI/SNF complexes, and these were studied in MITF-mediated transcriptional activation. Using a system of overexpression of MITF in a fibroblast line that could also overexpress DN-BRG1, it was shown that Brg1 and other members of complex could be recruited to MITF-dependent loci. Members of the tyrosinase family of genes and Pmel17 could be expressed in these cells. Also, BRM was found to interact with Mtif and is recruited to MTIF target genes. One interesting suggestion from these studies is that there may be some specificity for Mitf target genes regulated by BRG1 or BRM, with BRG1 regulating MITF activity at melanocyte differentiation genes, but with BRM recruited to MITF-dependent genes more involved in cell cycle regulation, such as CDK2. Expression of BRG1 or BRM

is down-regulated in a subset of human melanoma cells, pointing to a possible role in malignant progression.

Lionel Larue (CNRS – Institute Curie in Orsay, France) delivered a presentation about how "Replacement of a large minority of smooth muscle cells by melanocytes during development in the ductus arteriosus (DA) does not allow its closure and leads to postnatal death". Experiments were described analyzing the contribution of melanocytes to the ductus arteriosus in the mouse. (Also for more relevant to this topic, see recent paper on Dct+ cardiac cells published in the Journal of Clinical Investigation). Lionel Larue presented evidence using a Cre-lox system that there is a common progenitor for certain DA smooth muscle cells (SMA+Dct-) and melanocytic cells (SMA-Dct+). Tyr-Cre-dependent activation of an oncogenic form of beta-catenin promoted the generation of a greater number of melanocytes at the expense of SMA-expressing cardiac cells in the DA. This appears to explain the failure of these mutant mice to close the DA after birth, resulting in left atrial dilatation and premature mortality.

AARON B. LERNER LECTURE: Michael Marks – Melanosome Biogenesis: Pmel17, Functional Amyloid and Construction of a Dark Organelle
By Tom Hornyak

The Aaron B. Lerner lecture was delivered by Dr. Michael S. Marks, Associate Professor of Pathology and Laboratory Medicine at The University of Pennsylvania. It was entitled: "Melanosome Biogenesis: Pmel17, Functional Amyloid and Construction of a Dark Organelle". In this lecture, Dr. Marks summarized 14 years of work devoted to understanding the construction of the melanosome, a member of the lysosome-related organelle family. He graciously acknowledged collaboration with Graca Raposo for substantial portions of this work. At the time he began his work, the dogma in the field held that melanosome were simply modified lysosomes because they shared certain proteins characteristic of lysosomes. However, through cell biological studies, it was possible to establish that the melanosome lineage is a separate lineage derived from the endosomal lineage. Melanosome cargo proteins are sorted from early endosomes via three distinct pathways, with Hermansky-Pudlak syndrome-associated protein complexes functioning in two of those three pathways. Differences between sorting requirements for key melanosomal proteins helped illuminate the determinants of these different pathways. For example, tyrosinase is missorted in HPS2 melanocytes, whereas Tyrp1 is sorted normally in these cells. This observation implied the existence of a distinct pathway regulating Tyrp1 sorting, one that was shown to be responsible not only for Tyrp1, but also ATP7A and OCA2 trafficking, regulated by the macromolecular protein complex Biogenesis of Lysosome-Related Organelles Complex (BLOC)-1 including HPS proteins 7 and 8. Interestingly, tyrosinase is sorted properly in BLOC-1-deficient melanocytes, but cannot function properly due to the lack of ATP7A-dependent copper transport. Exogenous administration of copper to these cells can restore their pigmentary phenotype. Dr. Marks then discussed the role of Pmel17/gp100 in the formation of the striated early stage melanosome. Pulse-chase labeling experiments have revealed that Pmel17 undergoes significant post-translational processing and cleavage while traversing the ER, Golgi, and post-Golgi compartment. The insoluble fragment "Ma", produced from proprotein convertase activity, may represent the fibrillogenic fragment responsible for generating the intralumenal striations, with the process in early stage 1 melanosomes emanating from the internal membranes. Structural similarities between domains of Ma and amyloid proteins suggest that Pmel17, or domains thereof, represents a physiological, non-pathological form of amyloid involved in organelle assembly.

KEYNOTE LECTURE 6: Jack Arbiser – Oxidative Stress, Melanocytes and Melanoma
By Gertrude-Emilia Costin

Jack Arbiser (Emory University) started the day of Sunday, September 6th, 2009, with the Keynote Lecture entitled "Oxidative Stress, Melanocytes and Melanoma" focused on the challenges of melanoma treatments. Dr. Arbiser emphasized the alarming increase in the new cases of melanoma and of death related to this disease. Dr. Arbiser presented the concept of the reactive oxygen-driven tumors; he further detailed on the signaling abnormalities described in melanomas, including β-catenin deregulation (mutation/mislocalization), p16 loss, MAP kinase activation and Akt activation. Dr. Arbiser's group initially proposed that tumor signaling pathways are dependent on the tumor suppressor gene profile, with p53 and p16ink4a being the most common tumor suppressor lost in advanced cancer. This theory was based on data on introduction of dominant negative map kinase kinase into p53 deficient angiosarcoma cells that led to an enhancement of cell growth, rather than the predicted tumor suppression, given that MAP kinase activation has most often been seen as oncogenic. Dr. Arbiser's group demonstrated based on the established oxidative carcinogen model of nickel sulfide that this oxidative carcinogen caused hypermethylation of p16ink4a and the activation of MAP kinase. These findings suggested that tumors caused by reactive oxygen induced carcinogens will likely have loss of p16ink4a rather than a mutation of p53 and also that MAP kinase activation occurs in a non-random fashion associated with p16ink4a loss. Finally, some treatment possibilities were outlined, one of which was based on sertraline, an antidepressant. One of the major reasons melanoma responds poorly to chemotherapy and radiation is the constitutive expression of Akt, which protects against apoptosis. Sertraline was found to be a potent cytotoxic agent against A375 human melanoma. Use of antidepressants that decrease Akt may therefore improve the efficacy of interferon and other therapies against melanoma.

SESSION 6: Oxidative Responses in Melanocytes and Melanoma Cells
Chairs: Frank Meyskens
By Frank Meyskens

Many investigators have become interested in the effects of oxidative stress in the carcinogenesis process as well as the development of inhibitors and activators of this process as a preventive and therapeutic strategy. Seven presentations addressed various mechanisms that regulate OSR, **Paulsen** (Iowa) offered compelling evidence from a zebra fish model that two TRMP ion channels detoxify ROS generated during melanin synthesis and suggest that mutation of a TRMP may be important in dopinergic neurons gone away in Parkinson's disease. Two presentations explored the role of α-MSH in OSR. This hormone was shown to regulate the early response of melanocytes to UVR by reducing oxidative damage to DNA via inhibition of hydrogen peroxide formation by a mechanism that was nevertheless mediated by MC1R (**Kadekaro**, Cincinatti). **Picardo** (Rome) demonstrated that MSH stimulation of MC1R led directly to increased catalase and its targeting to melanosomes and the melanin synthesis pathway. **Murapa** (Kentucky), using congenic mice demonstrated that mutant MC1R produced largely pheomelanin that generated high amounts of ROS in response to UVR. In normal MC1R MSH enhanced upregulation of a broad range of cellular anti-oxidant systems. Two papers from the Meyskens lab continued to explore the role of Ref-1/APE in regulating growth in human melanoma cells. **Z. Yang** presented evidence for a feedback loop in which NO enhances Ref-1 upregulation with downsteam activation of AP-1, Nf-KB, MMP and NOS with subsequent generation of more NO. Inhibitors of NOS abrogated this process. **S. Yang** presented an elegant paper that

continues her exploration of the function of Ref-1 and convincingly demonstrated the role of Ref-1 in melanoma progression via upregulation of a wide range of proliferation and invasion parameters. Finally, **Sarangarajan** (Worcester) demonstrated that GSH regulation changed during melanoma progression with upregulation occurring in the metastatic phenotype as compared to primary melanoma cells. Overall, the session was quite exciting and lays the groundwork for development of unique experimental and eventually clinical therapeutic.

SESSION 7: Solar Radiation and the Pigmentary System: Securing the Place Under the Sun
Chairs: Andrzej Slominski and Connie Lin
By Connie Lin

Dr. N. Box (University of Colorado) presented the 1st talk, entitled "p53 and pigmentation in mice: Coordinating Melanocyte and Keratinocyte Roles during the sunburn response. Dr. Box discussed the essential role of p53 during skin pigmentation (mediated by Kit ligand, EDN-1 and POMC in keratinocytes and tyrosinase in melanocytes) and outlined how p53 may participate in an inherent sensitivity to UV induced melanocyte transformation in individuals with low melanin synthesis capacity. Using melanoma cells with tyrosinase promoter-activated HRASV12G and with a heterozygous allele of Mdm4, which resulted in constitutively high P53 level, Dr. Box showed that P53 has no impact on the formation of pre-malignant nevi, but rather prevented malignant conversion from nevi to melanoma. Using hyperpigmented Sooty Foot Ataxia mouse model, he showed an important role for p53 in keratinocytes that resulted in tanning. These data suggested that skin tanning and pigmented lesion are tightly linked through the keratinocyte P53.

Dr. Anna Luisa Kadekaro (University of Cincinnati) presented the 2nd talk, entitled "α-MSH increases H2AX phosphorylation soon after UV irradiation in human melanocytes". Dr. Kadekaro's talk began with an introduction of UV-induced DNA damage and the cascade of DNA repair processes. She then presented data showing that H2AX phosphorylation is an initial event in DNA repair and can be increased by α-MSH via activation of MC1R. Dr. Kadekaro showed that UV irradiation led to a dose-dependent increase in the number of phosphorylated histone protein H2AX (cH2AX)-positively stained normal human skin cells (melanocytes, keratinocytes and fibroblasts). Pretreatment with α-MSH prior to UV irradiation led to a dose-dependent increase in cH2AX in normal melanocytes, but not in melanocytes with non-functional MC1R. She further demonstrated that the increased phosphorylation of H2AX is dependent on cAMP, since increased cH2AX staining can be obtained in melanocytes with non-functional MC1R. These data provide new mechanisms by which α-MSH protects skin cells from UV damage, and on the importance of functional MC1R in reducing the risk of melanoma.

G. Walker (Queensland Institute of Medical Research, Australia) presented the 3rd talk, entitled "Enhanced melanocyte proliferative response accompanies tumor initiation by UVR in neonatal melanoma-prone mice". Dr. Walker discussed UVR-induced melanocyte responses using a neonatal melanoma-prone mouse model. He presented data showing that a single UVR exposure induced melanocyte proliferation and repopulation from follicular outer root sheath (ORS) to the epidermal basal layer in the neonates (peak at day 3-5 poster UVR) but not in adult mice. Dr. Walker further demonstrated that depletion of melanocytes (including ORS transit amplifying cells but not bulge stem cells) by blockage of Kit receptor function with an antibody ACK2, prevented the activation of melanocytes upon UVR, suggesting that the Kit-positive ORS precursors might differentiate and

populate the epidermis upon UVR, and that neonatal mouse melanocyte stem cells cannot respond to UVR alone. Interestingly, melanoma-prone Tyr-Nras transgenic mice with ACK2-resistant dermal MC population did not have proliferative melanocytes upon UVR irradiation. The cell-of -origin of melanoma in these animals remains unclear.

Dr. M. Zmijewski (Dr. A. Slominski's lab, University of Tennessee) presented the 4th talk entitled "New secosteroidal (vitamin D-like) derivative as potential anti-melanoma therapeutics". The aim of the study was to screen a library of new vitamin D-like compounds with modulated side chain (with potentially reduced vitamin D-associated hypercalcemia) for their anti-proliferative activity using several melanoma cell lines. Results indicated that most compounds, including steroidal 5,7 dienes and other D,T,L-like secosteroids, showed an inhibitory effect on melanoma growth. Interestingly, pigmented and non-pigmented cells showed slightly but significantly differential responses to these compounds, suggesting the involvement of melanogenesis in drug resistance.

Dr. Kim (Dr. A. Slominski's lab, University of Tennessee) presented the 5th talk about **"20-hydroxyvitamin D2, a product of cytochrome P450scc hydroxylation, inhibits proliferation of human melanoma cells and keratinocytes".** He reviewed a novel metabolic pathway of vitamin D by cytochrome P450scc, by which plant derived ergosterol and its photoproduct Vit D2 are hydroxylated to form 20-hydroxyvitamin D2 (20(OH)D2). The purified 20(OH)D2 exhibited inhibitory activity on DNA synthesis using human melanoma cells (SKMEL-188) and HaCaT keratinocytes. Dr. Kim also showed that 20(OH)D2 altered gene expression of normal human keratinocytes undergoing differentiation. Moreover, Dr. Kim presented evidence that 20(OH)D2 stimulates CYP24 mRNA expression and hypothesized that it may modify local metabolism of 1,25(OH)2D (the active form of Vit D3). Further biological evaluation of these compounds could help to select the best candidate(s) with non-toxic side effects for potential treatment of hyperproliferative diseases (including melanoma and other cancers).

Connie B. Lin (Johnson & Johnson) presented the 6th talk, entitled" Unraveling the molecular mechanisms of senile lentigines". Dr. Lin described the classification of the progressive stage of senile lentigines (SLs) based on the histological analyses of melanin deposition and elongated rete ridges (the two hallmarks of SLs). Using this classification, she presented data showing the differential expression patterns of several critical proteins involved in cell proliferation and melanogenesis by immunohistochemistry: Ki67, KGF/KGFR, SCF/c-Kit and PAR-2 are highly expressed in the early SL stages and TYR levels are significantly increased in all SL stages. Dr. Lin further demonstrated that KGF might be involved in the initiation of hyperpigmentation and rete ridges formation by showing that treatment of KGF resulted in increased epidermal thickness and pigment deposition *in vitro*, and increased rete ridges elonagation and visible hyperpigmentation *in vivo* (human skin grafted onto SCID mice and pigmented swine). She hypothesized that UVB-induced KGF plays an important role in the initiation of hyperpigmentation and rete ridges formation of SLs.

Dr. A. Taieb (Inserm U 876 and National Reference Center for Rare Skin) presented the 7th talk, entitled "Xeroderma pigmentosum (XP)-C and XPC knockdown keratinocytes as a model to study the effects of ROS in photoprotection and cancer". Dr. Taieb discussed the importance and function of XPC protein in DNA nucleotide excision repair (NER). He developed a XPC reconstructed epidermis using XPC human keratinocytes with overexpressed catalase enzyme, based on the fact that the defect of XPC is associated with decreased catalase activity. He presented data showing a significantly decrease in UVB-induced sunburn cells, caspase-3 activation and p53 accumulation in this reconstructed epidermis overexpressing catalase. More interestingly, the XPC- reconstructed epidermis

with high levels of catalase was more resistant to UVB-induced apoptosis than normal reconstructed epidermis, indicating that antioxidant enzymes may reduce photosensitivity in XPC and probably in other disorders related to ROS accumulation. Dr. Taieb further discussed hypoxia-inducible factor-1 (HIF-1) as another important regulator for XPC and other NER genes.

Dr. T. Kunisada (Gifu University Graduate School of medicine, Japan) presented the last talk of this session, entitled "Differential signaling requirement for the maintenance of non-cutaneous and dermal melanocytes versus epidermal melanocytes". The objective of Dr. Kunisada's study was to better understand the regulation of non-cutaneous melanocytes (e.g., in eye, harderian gland, and inner ear) and to provide a molecular basis for the clear discrimination between non-cutaneous or dermal melanocytes and epidermal melanocytes. Dr. Kunisada showed that melanocytes from eye, ear and harderian gland are less sensitive to kit signaling than cutaneous melanocytes, but more responsive to endothelin 3 (ET3) or hepatocyte growth factor (HGF) stimulation or inhibition (by specific ET-3 or HGF antagonists). These were further supported by *in vivo* data: in transgenic mice with human K14-promoter over-expressing ET3 or HGF, the survival and differentiation of non-cutaneous and dermal melanocytes, but not of epidermal melanocytes, were enhanced. These data provide new insights into the regulation of melanocytes development and the pathogenesis of melanocyte-related and melanomas.

KEYNOTE LECTURE 9: Gregory Barsh – Novel Regulators of Melanin Pigmentation
By Prashiela Manga

Greg Barsh (Stanford University) presented a talk entitled "Novel regulators of pigmentation: model systems in a post-genomic world". This talk highlighted the importance of utilizing the most recent methodologies in our approach to understanding pigmentation and of identifying appropriate/novel model organisms. Using the dog as a study model, Dr. Barsh and his group identified a gene previously not know to play a role in pigmentation, β-defensin 103. The gene product has now been shown to prevent the agouti repression of the Mc1r receptor, which gives rise to the red/yellow hair band. Thus a mutation at the locus results in continued eumelanin production and the Black phenotype. This locus was also found to account for the black phenotype in wolves in the Yellowstone National Park. A new model being investigated currently is the zebra. The question being posed: are the stripes black or white? This question is being addressed using a next generation sequencing approach.

SESSION 9: Pigmentary System of the Eye
Chairs: Peter Netland, Barrett Haik and Charles Handorf
By Peter Netland

The last session of the 2009 Annual PASPCR Meeting, titled *Pigmentary System of the Eye*, presented an interesting cross-section of studies focusing on the important role of pigment cells in ocular health and disease. The location in Hamilton Eye Institute provided an appropriate backdrop for the session. The enthusiastic participants who stayed through to the end of the meeting were treated to lively question and answer sessions and new information about pigmentary cells in the eye. Here are highlights and take-home messages from the session.

Mike Anderson and colleagues (*Mutation of Lyst in mice recapitulates aspects of human exfoliation syndrome*) studied Lyst mutant mice with an interesting concentric transillumination pattern of the iris,

said to resemble the changes that may occur in exfoliation syndrome. Pigment dispersion is noted in these mice, with histological studies showing loss of stromal melanocytes and presence of macrophages. The mutation is a result of a three base pair deletion in the WD40 encoding region of the *Lyst* gene. Candidate-driven and phenotype-driven genetic modifier screens demonstrated that *Tyr* mutations rescue *Lyst*-mediated iris phenotypes while the DBA/2J genetic background enhances them, suggesting that pigment production is also an active factor. Further work is being done to strengthen the association with exfoliation syndrome.

Fridtjof Thomas and colleagues (*Demographics of patients with uveal melanoma in the mid-southern United States: socioeconomic status as a risk factor*) performed zip code analysis of 635 patients from the mid-south region. Limitations of zip code data were reviewed, and it was pointed out that population centers were more heavily represented in the data. A Poisson regression was fit to the retrospective data in this study of uveal melanoma counts in different zip codes. A zip code average house value was positively associated ($P = 0.0012$) with the number of observed uveal melanoma cases even after controlling for population size, proportion of non-whites, average persons per household, and State. Thus, a higher socioeconomic status of a given zip code was positively associated with the occurrence of uveal melanoma in zip code areas.

Ed Chaum and colleagues (*Quantitative analysis of gene regulation in response to serial oxidative stress in the retinal pigment epithelium: molecular proportional-integral-derivative control of gene expression?*) examined the mechanisms that modulate the cellular responses to chronic and repetitive oxidative stress in the human retinal pigment epithelium. Real-time qPCR studies confirmed different transcriptional responses to repetitive oxidative stress in the AP-1 family genes and immediate early genes. Genes with a rapid rise of transcription in response to oxidative stress include *c-Fos*, *EGR2*, and *EGR1*, while other genes (*AFT-3*, *Fra-1*, *JunB*, *HO-1*, and *FosB*) had slower rates of rise of transcription. This approach may allow rapid evaluation of proposed treatments to modify the response of retinal pigment epithelial cells to oxidative stress.

Gene Shildkrot and colleagues (*Long term survival in patients with large ciliary body and choroidal melanomas treated with iodine-125 plaque brachytherapy*) determined the all-cause mortality at five and ten years in patients with large ciliary body and choroidal melanomas treated with iodine-125 episcleral plaque brachytherapy. The overall mortality in 112 patients was 42.2% 5 yr and 60% 10 yr, which is very similar to results following enucleation (COMS: 42% 5 yr and 61% 10 yr mortality). These results suggest that eye-sparing treatment of large tumors with plaque brachytherapy is similar in efficacy compared with treatment by enucleation. The investigators are evaluating other adjunctive strategies to further improve survival.

Sancy Leachman and colleagues (*Selenium for the prevention and treatment of melanoma*) have used mouse and cell culture models of UV-induced melanoma and metastatic disease to explore the use of selenium for prevention and treatment melanoma. For prevention, they tested topical formulations of selenoaminoacids, finding a modest decrease in time required for tumor formation in animals treated with selenomethionine. In a xenograft model of melanoma metastasis, daily oral dosing with methylseleninic acid (MSA) reduced the size of tumors to 1/3 of that in untreated controls. The authors conclude that topical selenium has a modest impact on melanoma as a preventive agent, which might be applicable in situations of selenium deficiency. The anti-tumor activity of selenium in the form of MSA in the xenograft model is being studied in combination with other chemotherapeutic agents.

Scott Lawrence and co-workers (*A dual surgical approach to treatment for invasive iris melanomas*) evaluated outcomes of combined iridectomy and brachytherapy in large iris tumors. In this situation, primary excision may leave viable tumor at the posterior margin of resection, and brachytherapy alone may necessitate a large field and dose of radiation with associated toxicity to the cornea and lens. In this series, eight patients were treated with iridectomy (with or without anterior cyclectomy) followed by Iodine-125 plaque brachytherapy. After median follow-up of 28 months, there was no disease recurrence or metastasis in any patient. All specimens were positive for tumor cells at the posterior surgical margin, which was treated with mean brachytherapy dose of 82.5 Gy over 7 days with an effective dose rate of 49.0 cGy/hour. There was no significant change in visual acuity or intraocular pressure after surgery. These results indicate that combined surgical excision and brachytherapy provides effective local control for iris melanomas with diffuse anterior chamber involvement.

KEYNOTE LECTURE 11: Dianna Johnson – Retinal Pigment Epithelium Reaction to Oxidative Stress and Solar Radiation
By Peter Netland

The session 9 was started with a keynote lecture from renowned retinal neurobiologist and retinal pigment epithelium expert **Dianna Johnson, PhD**. Dr. Johnson presented new findings in her talk *Retinal stem cells previously identified as retinal stem cells are pigmented ciliary epithelial cells*, including her work in collaboration with Dr. Samantha Cicero, Dr. Mike Dyer, and other colleagues. She and her co-workers have isolated "retinal stem cells," finding that these cells have ciliary epithelial cell morphology and markers. Her hypothesis was that pigment ciliary epithelial cells may divide, make clonogenic spheres, then transdifferentiate into retinal neurons and glia. Dividing cells have characteristics of ciliary epithelial cells, and, in an interesting set of experiments, dual beam focused ion beam electron microscopy of spheres showed that all cells in spheres are pigmented in 3D reconstructed images. Dr. Johnson concluded that spheres formed by ciliary epithelium consist of pigmented ciliary epithelial cells that divide while maintaining a differentiated state, no stem cells or retinal progenitors were found in the spheres, and cells from spheres do initiate transdifferentiation, but fail to differentiate when transplanted. Her studies highlight the importance of shifting the focus away from studies on derived spheres toward improving techniques for using stem cells or retinal precursor cells for cell-based therapies to restore vision.

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AWARDS - THE XVTH ANNUAL MEETING OF THE PANAMERICAN SOCIETY FOR PIGMENT CELL RESEARCH

The following poster presentations have been awarded during the meeting and their lead authors have received free membership for PASCPR for the year of 2010:

First place: *F-Box Protein Co-Factors Cks1 and αB-Crystallin: B-RAF Regulation and Roles in Melanoma Cell Cycle Progression.* Rong Hu and Andrew E. Aplin, Department of Cancer Biology, Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA

Second place: *Timeline of Melanoblast Specification and Cell Behavior*. Harris M. L.[1], Thomas A. J.[2], Vitt J. R.[3], Kuo B. R.[2] and Erickson C. A.[3], [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]Utah State University, Logan, Utah, [3]University of California, Davis, Davis, CA.

Third place: *Expression of GFP Reporte Driven by Human Oct-4 Promoter in SKMELL 188 Non-Pigmented Cell Line Identifies the Most Aggressive Melanoma Cancer Stem Cells in Melanoma Progression.* Pavicevic Z. S., Slominski, A., Janjetovic Z., Ignatova T. N., Duntsch C. D., Kukekov V. G., Department of Neurosurgery and Department of Pathology, University of Tennessee Health Science Center, Memphis, TN.

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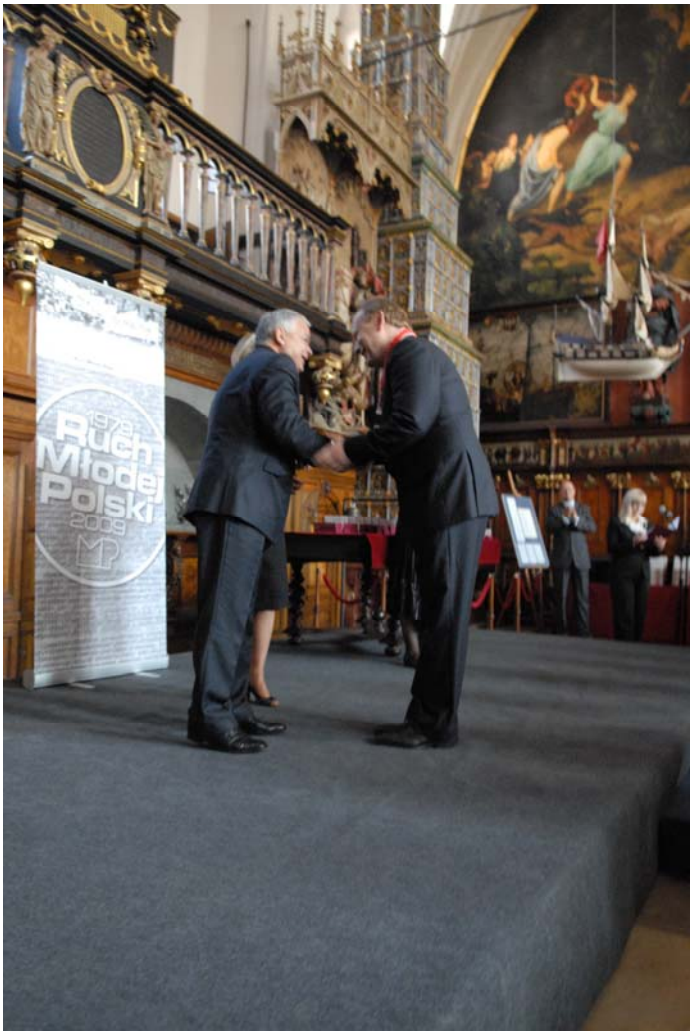
Members in the News

Andrzej Slominski has recently traveled to Poland where he received the"*Order of Polonia Restituta*" award (Order of Poland Reborn) for anti-communist and pro-democracy activity during the 1970s and early '80s. The award was established on February 4, 1921, and is one of Poland's highest Orders. Lech Kaczynski, President of the Republic of Poland, presented the award. In a communication to the PASPCR members, Andrzej Slominski noted how honored he was to receive such a prestigious and personally meaningful award. He also expressed his great pleasure at visiting with former President Walesa, a leader and activist of international stature. Walesa is a Polish politician and a former trade union and human rights activist. He co-founded Solidarity (*Solidarność*), the Soviet bloc's first independent trade union, won the Nobel Peace Prize in 1983, and served as President of Poland from 1990 to 1995.



Positions Wanted / Available

Postings for **Positions Wanted** will be open only to members of the PanAmerican Society for Pigment Cell Research or its sister societies (ASPCR, JSPCR and ESPCR). Postings for **Positions Available** will be open to all individuals and institutions so long as the position is related to pigment cell research. Please send postings to Bill Oetting at oetti001@umn.edu.

The postings will remain on the **Positions Wanted and Available** section of the PASPCR Newsletter and on the web page for 1 year, unless other arrangements are made. Please provide an expiration date for any submitted posting if less than 1 year. Final decisions will be made by the Publications Committee of the PASPCR.

Positions Available

Post-Doctoral Position

Appointment: University of Tennessee Health Science Center Department of Pathology and Laboratory Medicine, 930 Madison Avenue; Memphis, TN 38163

Project summary: A postdoctoral position is available starting September, 2009. The area of study is described in Slominski A, Wortsman J, Paus, R, Elias PM, Tobin DJ, Feingold K (2008) Skin as an endocrine organ: implications for its function. Drug Discovery Today: Dis Mech 5: e137-e144; Slominski A (2007) A nervous breakdown in the skin: Stress and the epidermal barrier. J Clin Invest 117, 3166-3169; Slominski A, Wortsman J, RC Tuckey, Paus R (2007) Differential expression of HPA axis homolog in the skin. Mol Cell Endocrinol 265-266, 143-149.
Minimum requirements: experience with mice model, skin, endocrinology and histopathology to work on the project supported by National Science Foundation entitled "UV-light regulation of skin endocrine functions: POMC system". If interested, please contact

Andrzej Slominski, MD, PhD

Professor of Pathology
Director, Dermatopathology Training Program
E-mail: aslominski@utmem.edu
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Posted: 07/09

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