N° 69 Apr 2011

ESPCR BULLETIN

PUBLISHED BY THE EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH

EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH *BULLETIN*

N° 69 Apr 2011

Editorial Office: *G. Ghanem (Editor), C. Meunier (Secretary),*
Laboratory of Oncology and Experimental Surgery (L.O.C.E.), Université Libre de Bruxelles,
Institut J. Bordet, Rue Héger-Bordet 1, B – 1000 Brussels, Belgium.
Phone: 32-2-541.32.96 E-Mail:gghanem@ulb.ac.be

CONTENT

LETTER TO THE EDITOR
DISCUSSION, REVIEW,
SHORT COMMUNICATION, ...

Minutes of the ESPCR 2010 Board of Officers Meeting, Library of the Hinxton Welcome Trust Conference Centre, UK, Saturday 4 September 2010, 10.00-12.00 am

1. Opening of the meeting: L. Larue, President, opened the meeting and welcomed the Board members: Marie-Dominique Galibert, Robert Kelsh, Rosalie Luiten, Lluis Montoliu (Treasurer and Webmaster), Alessandra Napolitano, M. Picardo (ex-officio), Miguel Seabra, Alain Taïeb (Secretary).

The president requested one minute of silence *in memoriam* of Estella Medrano, who passed away recently in a car accident.

2. Apologies for absence were received from Ghanem Ghanem, Anja Bosserhof and Jo Lambert

3. Approval of the Minutes of the 2009 Council meeting: the minutes of the two 2009 council meetings were approved and signed by the President

4. Report on follow-up of new Constitution of the Society

In the absence of G Ghanem, the following details of the registration of the ESPCR according to the Belgium law were communicated by the President:
Date of publication of the Constitution in the Belgium Official Journal (Annexe du Moniteur Belge): 11/08/2009
Address of the ESPCR: 7 rue Héger-Bordet, 1000 Bruxelles, Belgium
ESPCR AISBL VAT Registration number: BE 0817.455.226

5. President's report
The President announced the following actions/decisions:

- Approval of the promotion of the 1st Vitiligo World Congress (Milano, September 23-24, 2010) on the ESPCR Website, and presence of ESPCR logo on congress documents
- ESPCR symposium at ESDR meetings: after a large discussion, the board supported the next symposium to be hold in Barcelona, Sept 7-10 2011, before the Bordeaux IPCC to maintain the two year interval -previously Zürich (2007) and Budapest (2009). No serious impact on IPCC attendance is expected.
- The President thanked Lluis Montoliu for the efforts made to support the Journal PCMR through website newletters and advertisement.
- ESPCR has enabled some patients' support groups (e.g. albinism, vitiligo) to better communicate about their actions via the website
- The ESPCR has endorsed Eumelanet as an ESPCR special interest group (Dec 2009)
- The discussion about the ESPCR-PASPCR common regional meeting suggested by the PASPCR president-elect Greg Barsh has led to a report by an ad hoc committee (Picardo, Luiten, Lambert, Dec 2009) which is summarized below:

advantages :
1) more exchange of pigment cell research knowledge and networking between Europe and the US
2) more coverage of topics by a wider range of speakers
3) more interesting meeting, also for non members, or researchers outside the field

4) 2 in 1 (time management): no need for choosing between ESPCR or PASPCR meeting or attending two meetings.

disadvantages :

1) the risk of too much overlap with the IPCC
2) the potential political debates with other societies that feel left out
3) the overall cost will certainly be more important for the attendees
4) the young scientists will have less chance to present their work

As a consequence the ESPCR board is not in favour of supporting this initiative.

The President's report is approved by the board

6. Secretary's report

- The Secretary reported on behalf of Markus Böhm the final Meeting report of the 2009 Münster ESPCR. The meeting was a great success in terms of scientific input. The meeting was attended by 204 scientists. 64 % of the balanced budget were covered by registrations fees. The ESPCR contributed 1500 euros for the Anders lecture (plus poster prize and travel awards not included in the balance). The German Research Society contributed 12 000 euros and the rest came from industry sponsors.
- The 2010 Fritz Anders lecture nominee is H Arnheiter. An extensive discussion addressed the process of nomination of the next lecturers (from the 2012 Meeting onwards), which should begin one year before the meeting to help the organizers for the programme and allow enough time to print the medal. The award should not be restricted to genetics, and scientists outside of the pigment cell community may be nominated. The nomination process should include the board, the local organizers, but also the ESPCR membership. A memo should be prepared by the Secretary in due time to summarize these points.
- IFPCS Awards for the 2011 IPCC Bordeaux meeting (Myron Gordon Award, Seiji Memorial Lecture, Takeuchi Medal, H.S. Raper Medal). The process of nomination following the IFPCS guidelines –to be consulted on the website http://www.ifpcs.org/docs/RULESREG.pdf- is being launched and the ESPCR should be officially consulted. As the IPCC organizer the Secretary noted that it was most important to know in good time the name of the Seiji lecturer who will lecture during the opening plenary session. The proposed names for the next ESPCR award committee are A. Napolitano, R. Kelsh, M. Seabra. They are unanimously approved by the board.
- IFPCS delegates and election: the term of the officers of the IFPCS will come to an end next year at the Bordeaux IPCC. Due to the principle of rotation, the next IFPCS president should be an ESPCR member. Current ESPCR delegates are J Lambert, M Picardo, L Larue, plus A Taieb (ex officio next IPCC President) and Lluis Montoliu (Webmaster). M Picardo agreed to being appointed IFPCS president next year at the end of S Shibahara's term, in accordance with the rotation rule. As a total of 3 ESPCR delegates need to be appointed for the next IFPCS term, the acting ESPCR President and Secretary L Larue and A Taieb were designated by the ESPCR board as ESPCR representatives, together with M Picardo. L Montoliu will remain on the IFPCS board as current webmaster. The board unanimously approves these nominations.

The Secretary's report is approved by the board

7. Treasurer's report

The Treasurer reported a drop in membership in 2008, due to the inclusion only of paying members; numbers have increased steadily since.

Details of current ((31-08-2010) paying membership

146 ESPCR Members vs 134 ESPCR Members in 2009 (+9%)

- Regular Members (72%)
- Student Members (19%)
- Honorary Members (8%)
- Supporting Members (1%)

18 Members subscribed to printed PCMR issues (12%)
146 Members have access to online PCMR contents (100%) through the IFPCS web site
8 Members subscribed for 3 years of ESPCR membership (5%)
17 Members subscribed for 2 years of ESPCR membership(12%)
121 Members subscribed for 1 year of ESPCR membership (83%)

ESPCR is becoming a rather "young" society with most (66%) of its members having less than 10 years membership. 19 ESPCR members remain with their ESPCR membership since 1987 (24 years)
The following Table summarizes the current status of ESPCR finances:

==========

ESPCR Treasurer Report 2010 (from 01-12-2009 to 31-08-2010)

ESPCR AISBL Bank account at BNP-Paribas-Fortis

Balance on 31/08/10	**22.399,09 €**
INCOMES	
Funds from ESPCR previous bank account	13.746,53 €
ESPCR memberships through PAYPAL account	6.195,00 €
ESPCR memberships through Bank Wire Transfer	7.210,00 €
ESPCR memberships through cheques	555,00 €
Donations	120,00 €
PayPal Testing operations	11,50 €
Bank Interests	1,52 €
TOTAL INCOMES	**27.839,55 €**
OUTGOINGS	
7 ESPCR 2010 registration awards (2667 GBP)	-3.153,60 €
Fritz Anders Lecture (XVIth ESPCR meeting, Hinxton=1500 Euros)	-1.513,66 €
ESPCR web hosting (3 years)	-333,82 €
PAYPAL fees	-236,18 €
BNP-Paribas-Fortis Bank Fees	-111,46 €
ATOS WORDLINE Last Payment renting former credit card machine	-46,80 €
espcr.org web domain (4ARM)	-24,20 €
Reimbursement to Lluis Montoliu (IFPCS web)	-9,24 €
Reimbursements for PAYPAL Testing Operations	-11,50 €
TOTAL OUTGOINGS	**-5.440,46 €**
TOTAL INCOMES	**27.839,55 €**
TOTAL OUTGOINGS	**-5.440,46 €**
BALANCE ON 31-08-10	**22.399,09 €**

==========

Projections for the end of 2010 indicate a positive balance amounting around 16 000 euros because of IFPCS contribution. Projections for the 2011 budget indicate an increasing positive balance around 20.000 euros. The

ESPCR has accepted to cover the last minute invitation of P Enfors to the Hinxton meeting. The Paypal internet payment system for registration has saved a substantial amount of money for the Society.

The Treasurer's report is approved by the board.

8. Website report

The Webmaster summarized the use of the website in the following Table:

Summary

Reported period	Year 2009				
First visit	01 Jan 2009 - 00:06				
Last visit	31 Dec 2009 - 23:56				
	Unique visitors	Number of visits	Pages	Hits	Bandwidth
Viewed traffic *	<= 21733 Exact value not available in 'Year' view	64872 (2.98 visits/visitor)	182364 (2.81 Pages/Visit)	2618709 (40.36 Hits/Visit)	56.06 GB (906.16 KB/Visit)
Not viewed traffic *			27032	28389	9.32 MB

* Not viewed traffic includes traffic generated by robots, worms, or replies with special HTTP status codes.

Despite numerous efforts, estimates suggest that the website is receiving fewer visits overall than last year (11% for unique visitors). Of note however, ESPCR members have increased their access through the members-only pages (+11% for pages consulted).
The following features have been added/improved:

- ESPCR payments accepted through PayPal account
- Obituary page for ESPCR members that have passed away
- All previous ESPCR Bulletin issues (since 1987!) available through the web site (thanks to great efforts by Ghanem Ghanem).
- New web page for TRAVEL AWARDS
- Books advertisements (Vitiligo by A.Taïeb & M. Picardo; and The Colors of Mice by L. Lamoreux et al.) included
- Related meetings promoted
- ESPCR 2010 announcements and reminders distributed
- Expertise search engine for ESPCR members
- Color Genes Table updated regularly
- All major announcements posted at ESPCR blog and distributed through the ESPCR_list
- New web page made for the EUMELANET group

The Webmaster's report is approved by the board

9. Bulletin report

Reported by L Larue on behalf of G Ghanem:

- R Kelsh will inform all chairpersons to prepare a report of their respective sessions for publication in the Bulletin. The chairpersons will have to send their report to G Ghanem (gghanem@ulb.ac.be). Deadline is October 1st, 2010 .
- For the next meetings, the ESPCR meeting organizers will have to inform the chairpersons to prepare a report of their respective sessions for publication in the Bulletin. This will be included in the ESPCR website under "principles for ESPCR meeting organization" together with a document in preparation (L Montoliu)
- The 2010 list of members will be printed in the December issue of the Bulletin according to our new Constitution

The Bulletin report is approved by the board

10. Travel awards and poster Prize

- ESPCR travel awardees 2010 (A. Napolitano on behalf of the travel award committee Napolitano, Galibert, Bosserhoff). The following criteria were used for selection of the awardees:
    - preferably PhD students
    - a balanced consideration of the year of PhD beginning and number of publications
    - no more that one candidate per research group (in this connection it would be useful to ask the head of the group to make himself/herself a selection before application)
    - some consideration of the topic of the abstract: preferably not all people of the same field
    - age. People with a fine CV and publication list but more advanced in their research carrier were not preferred.

There were 12 applicants this year. A total amount of 3315 euros awarded to the following awardees (445/awardee)

Bonet Caroline
Campagne Cecile
Colanesi Sarah
Sarode Bhushan
Schiffner Susanne
Valluet Agathe
Widner Daniel

- ESPCR Poster prizes 2009 (R. Kelsh): a committee has been appointed including H Arnheiter (Chair), J Newton-Bishop, F Meyskens: PCMR Poster Prize - $500; ESPCR Poster Prize – PCMR Subscription; Runners-up prizes x2 – bottle of wine

11. Upcoming meetings

- The board thanked R. Kelsh for organizing the 2009 meeting. A final report is expected to be presented at the next board meeting. 41 speakers were invited. The Wellcome trust contributed £20,000.00 and other sponsors £3,752.37. According to the list provided by the Welcome Trust Conference organizer (J Beard), out of the currently-listed 180 delegates, 63 ESPCR members attended the meeting. This is about 1/3 (35%) of the delegates and about 43% of the current ESPCR membership (146 members) (Lluis Montoliu).
- IPCC 2011 Bordeaux meeting. The pre-progamme and call for abstracts draft to be discussed at IFPCS council meeting was presented by A Taïeb, who thanks the advisory board and vice-presidents for substantial help to arrange the scientific programme. The joint day programme SMR-IFPCS on melanoma is going to be finalized after the SMR Sydney meeting. The 2011 IPCC website is to be updated with the preprogramme after the 2010 ESPCR meeting. Newsletters and twitter messages will announce further steps. The industry sponsoring of IPCC is in its crucial phase, with a good promise of success. No help from ESPCR is needed at this point in time, but the ESPCR, after a board discussion, would be pleased to support up to 7 travel awards. Details should be finalized during the winter according to the IPCC planned resources. Concerning the nomination of IPCC 2011 awards and lectures, as discussed above, the ESPCR has authority and should be active in proposing names, probably also for the consultation around the newly established Fitzpatrick medal. A. Taïeb has proposed to the ad hoc committee chaired by the PCMR Editor that the Fitzpatrick award should become a lecture featured at the end of next IPCC.
- 2012-2014 meetings (L. Larue):
    - The 2012 meeting will be organized at Centre Médical Universitaire, University of Geneva, Switzerland, around 1-15th of September by B Wehrle-Haller; the proposed meeting duration is 2.5-3 days (2 nights)
    - The 2013 meeting will be organized by Miguel Seabra in Lisbon. He was warmly congratulated by the board for accepting to host the ESPCR meeting.

- For 2014 the venue for the next IPCC will be Singapore (BK Goh)

12. Honorary member nomination (L. Larue)

Stan Pavel and Jan Borovansky were proposed unanimously by the Board for Honorary membership.

13. Other businesses

The EUMELANET special interest group chaired by M d'Ischia should be allowed to recruit non ESPCR members but a fair balance is encouraged. A presentation of the EUMELANET initiative is scheduled at the ESPCR general assembly.

14. Close of the meeting

Minutes of the ESPCR 2010 General Assembly Meeting Francis Crick Auditorium, Welcome Trust Conference Centre, Hinxton, UK, Monday 6 September 2010, 13.30-14.00

1. Opening of the meeting by ESPCR President Lionel Larue

2. Approval of the Minutes of the 2009 General Assembly meeting: the minutes of the Münster 2009 GA were approved and signed by the President

3. President's report

The President announced the following actions/decisions:

- Approval of the promotion of the 1st Vitiligo World Congress (Milano, September 23-24, 2010) on the ESPCR Website, and presence of ESPCR logo on congress documents
- ESPCR symposium at ESDR meetings: after a large discussion, the board supported the next symposium to be held in Barcelona, Sept 7-10 2011, before the Bordeaux IPCC, to maintain the two year interval -previously Zürich (2007) and Budapest (2009). No serious impact on IPCC attendance is expected.
- The President thanked Lluis Montoliu for the efforts made to support the Journal PCMR through website newletters and advertisements.
- ESPCR has enabled some patients' support groups (e.g. albinism, vitiligo) to better communicate about their actions via the website
- The ESPCR has endorsed Eumelanet as an ESPCR special interest group (Dec 2009)
- The discussion about the ESPCR-PASPCR common regional meeting suggested by the PASPCR president-elect Greg Barsh has led to a report by an ad hoc committee (Picardo, Luiten, Lambert, Dec 2009) which is summarized below:

advantages :

1) more exchange of pigment cell research knowledge and networking between Europe and the US
2) more coverage of topics by a wider range of speakers
3) more interesting meeting, also for non members, or researchers outside the field
4) 2 in 1 (time management): no need for choosing between ESPCR or PASPCR meeting or attending two meetings.

disadvantages :

1) the risk of too much overlap with the IPCC
2) the potential political debates with other societies that feel left out
3) the overall cost will certainly be more important for the attendees
4) the young scientists will have less chance to present their work

As a consequence the ESPCR board is not in favour of supporting this initiative.
Discussion: Greg Barsh commented that the PASPCR board was not fully supportive either, since the sense of community at regional meeting might be altered, but that a try could still be envisaged in the future say once every 6 years without being a problem for IPCCs.

The President's report was unanimously approved by the GA

4. Secretary's report (Alain Taïeb)

- The 2010 Fritz Anders lecture nominee was H Arnheiter who gave an excellent lecture on Saturday. The process of nomination of the next lecturers (from the 2012 Meeting onwards), should begin one year before the meeting, to help the organizers for the programme and allow enough time to print the medal.

- IFPCS Awards for the 2011 IPCC Bordeaux meeting (Myron Gordon Award, Seiji Memorial Lecture, Takeuchi Medal, H.S. Raper Medal). The process of nomination following the IFPCS guidelines –to be consulted on the website http://www.ifpcs.org/docs/RULESREG.pdf- is being launched and the ESPCR should be officially consulted. The proposed names for the next ESPCR award committee are A. Napolitano, R. Kelsh, M. Seabra. They have been unanimously approved by the board.
- IFPCS delegates and election: the term of the officers of the IFPCS will come to an end next year at the Bordeaux IPCC. M Picardo agreed to being appointed IFPCS president next year at the end of S Shibahara's term, in accordance with the rotation rule. As a total of 3 ESPCR delegates need to be appointed for the next IFPCS term, the acting ESPCR President and Secretary L Larue and A Taieb were designated by the ESPCR board as ESPCR representatives, together with M Picardo. L Montoliu will remain on the IFPCS board as current webmaster. The board has approved unanimously these nominations.

The Secretary's report was approved unanimously by the General Assembly

5. Treasurer's report (Lluis Montoliu)

The Treasurer reported a drop in membership in 2008, due to the inclusion only of paying members; numbers have increased steadily since.
Details of current ((31-08-2010) paying membership
146 ESPCR Members vs 134 ESPCR Members in 2009 (+9%)

- Regular Members (72%)
- Student Members (19%)
- Honorary Members (8%)
- Supporting Members (1%)

ESPCR is becoming a rather "young" society with most (66%) of its members having less than 10 years membership. 19 ESPCR members remain with their ESPCR membership since 1987 (24 years)
The following Table summarizes the current status of ESPCR finances:

==========

ESPCR Treasurer Report 2010 (from 01-12-2009 to 31-08-2010)

ESPCR AISBL Bank account at BNP-Paribas-Fortis

Balance on 31/08/10	**22.399,09 €**
INCOMES	
Funds from ESPCR previous bank account	13.746,53 €
ESPCR memberships through PAYPAL account	6.195,00 €
ESPCR memberships through Bank Wire Transfer	7.210,00 €
ESPCR memberships through cheques	555,00 €
Donations	120,00 €
PayPal Testing operations	11,50 €
Bank Interests	1,52 €
TOTAL INCOMES	**27.839,55 €**
OUTGOINGS	
7 ESPCR 2010 registration awards (2667 GBP)	-3.153,60 €
Fritz Anders Lecture (XVIth ESPCR meeting, Hinxton=1500 Euros)	-1.513,66 €
ESPCR web hosting (3 years)	-333,82 €
PAYPAL fees	-236,18 €
BNP-Paribas-Fortis Bank Fees	-111,46 €
ATOS WORDLINE Last Payment renting former credit card machine	-46,80 €
espcr.org web domain (4ARM)	-24,20 €
Reimbursement to Lluis Montoliu (IFPCS web)	-9,24 €
Reimbursements for PAYPAL Testing Operations	-11,50 €
TOTAL OUTGOINGS	**-5.440,46 €**
TOTAL INCOMES	**27.839,55 €**
TOTAL OUTGOINGS	**-5.440,46 €**
BALANCE ON 31-08-10	**22.399,09 €**

==========

Projections for the end of 2010 indicate a positive balance amounting to around 16 000 euros because of IFPCS contribution. Projections for the 2011 budget indicate an increasing positive balance around 20.000 euros.

The Treasurer's report was approved unanimously by the General Assembly.

6. Travel awards and poster Prize

- ESPCR travel awardees 2010 (A. Napolitano on behalf of the travel award committee Napolitano, Galibert, Bosserhoff).

There were 12 applicants this year. A total amount of 3315 euros awarded to the following awardees (445/awardee)

Bonet Caroline
Campagne Cecile
Colanesi Sarah
Sarode Bhushan
Schiffner Susanne
Valluet Agathe
Widner Daniel

- ESPCR Poster prizes 2009 (R. Kelsh): a committee has been appointed including H Arnheiter (Chair), J Newton-Bishop, F Meyskens: PCMR Poster Prize - $500; ESPCR Poster Prize – PCMR Subscription; Runners-up prizes x2 – bottle of wine

7. Upcoming meetings

- The President thanked R. Kelsh for organizing the 2009 meeting.
- IPCC 2011 Bordeaux meeting (A Taïeb). The pre-progamme and call for abstract draft has been discussed at the IFPCS council meeting and presented at the opening of the ESPCR Monday morning session.
- 2012-2014 meetings (L. Larue):
    - The 2012 meeting will be organized at Centre Médical Universitaire, University of Geneva, Switzerland, around 1-15th of September by B Wehrle-Haller; the proposed meeting duration is 2.5-3 days (2 nights)
    - The 2013 meeting will be organized by Miguel Seabra in Lisbon. He was warmly congratulated by the GA for accepting to host the ESPCR meeting.
    - For 2014 the venue for the next IPCC will be Singapore (BK Goh)

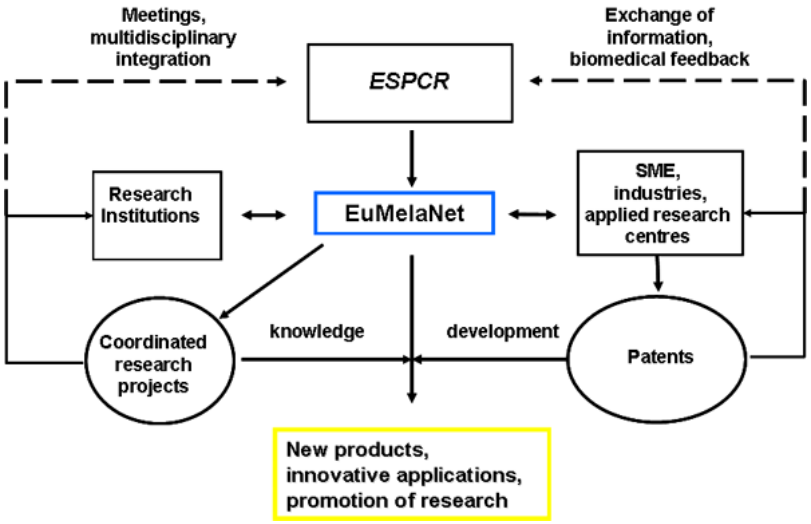
8. Honorary member nomination (L. Larue)

Stan Pavel and Jan Borovansky were proposed unanimously by the Board for Honorary membership.

9. Other business

A presentation of the EUMELANET Special ESPCR interest group was made by M D'Ischia.
The mission of EUMELANET is:
-to promote, support and coordinate research on melanins and related metabolites at multidisciplinary level within the ESPCR aims and scope;
-to bridge the gap between basic and applied research in order to 'translate' fundamental research results into applications;
-to promote practical applications of melanins and melanogenesis and to provide scientific support to companies, applied research centres and health institutions.

The following figure summarizes the goals and interactions of EUMELANET



The first project of EUMELANET is to standardise research on melanins and melanogenesis.
A consensus paper by the EuMelanet group is planned and will be discussed at Bordeaux IPCC 2011 and later published in PCMR.

10. Close of the meeting

CURRENT LITERATURE

1. Chemistry of Melanins and other Pigments

(Pr A. Napolitano)

Two interesting review papers have appeared on Pigment Cell and Melanoma Res, aimed at translating knowledge of mouse coat color pigmentation to human hair pigmentation: one by Ito and Wakamatsu addresses the role of protein mutation beyond MCR1 as well as the effects of pH and cysteine levels in melanosomes on melanogenesis control, the other by Karin Schallreuter's group focuses on the redox status of hair follicle as resulting from hydrogen peroxide homeostasis and the expression of methionine sulfoxide reductases activity.
The burst of interest on the design and exploitation of properties of melanin inspired materials continues unabated. Deposition of thin films of 5,6-dihydroxyindole melanin on indium tin oxide (ITO) substrates by costant potential electropolymerization is claimed to provide dense and conformal layers without surface defects as voids and cracks. (Kim et al. Electrochimica Acta). <100 Nm nanoparticles obtained from aerial oxidation of dopamine show excellent dispersion stability in water as well as biological media and good biocompatibility to HeLa cells after the appropriate surface modification. (Ju et al. Biomacromolecules)

As usual, a variety of new melanogenesis inhibitory substances or plant extracts have been reported, among which of particular interest the inhibitory effects of sesamol a degradation product of lignans occurring in sesame seeds on mono and diphenolase activity of tyrosinase and melanin synthesis in melanoma cells (Mahendra et al., Biochimie). A novel derivative of 3,4-dihydroxybenzamide bearing an adamantyl system on nitrogen showed good depigmenting action in cell and in vivo models (Rho et al. Arch Dermatol. Res.)

Structure, Reactivity and Properties

- Ito S, Wakamatsu K.
  Human hair melanins : what we have learned and have not learned from mouse coat color pigmentation. Pigment Cell & Melanoma Res (2011), 24(1): 63-74.

- Schallreuter KU, Salem MM A E L, Hasse S, Rokos H.
  The redox - biochemistry of human hair pigmentation. Pigment Cell & Melanoma Res (2011), 24(1): 51-62.

- Zdybel M, Chodurek E, Pilawa B.
  EPR Studies of DOPA- Melanin Complexes with Fe(III). Appl Magn Res (2011), 40(1): 113-123.

Melanin-based materials

- Bernsmann F, Ball V, Addiego F, Ponche A, Michel M, Gracio JJde Almeida Toniazzo V, Ruch D.
  Dopamine- Melanin Film Deposition Depends on the Used Oxidant and Buffer Solution. Langmuir (2011), 27(6): 2819-2825.

- Ju K-Y, Lee Y, Lee S , Park SB, Lee J-K.
  Bioinspired Polymerization of Dopamine to Generate Melanin -Like Nanoparticles Having an Excellent Free-Radical-Scavenging Property. Biomacromolecules (2011), 12(3): 625-632.

- Kim IG, Nam HJ, Ahn HJ, Jung D-Y.
  Electrochemical growth of synthetic melanin thin films by constant potential methods. Electrochimica Acta (2011), 56(7): 2954-2959.

Melanogenesis and its Modulation

- Akihisa T, Takahashi A, Kikuchi T, Takagi M, Watanabe K, Fukatsu M, Fujita Y, Banno N, Tokuda H, Yasukawa K
  The melanogenesis-inhibitory, anti-inflammatory, and chemopreventive effects of limonoids in n-hexane extract of Azadirachta indica A. Juss. (neem) seeds. J Oleo Sci (2011), 60(2): 53-59.

- Criton M, Le Mellay-Hamon V.
Dimeric cinnamoylamide derivatives as inhibitors of melanogenesis. Biol Pharm Bull (2011), 34(3): 420-5.

- Mahendra K C, Sathisha UV, Dharmesh S, Rao, A. G. Appu S, Sridevi A.
Interaction of sesamol (3,4-methylenedioxyphenol) with tyrosinase and its effect on melanin synthesis. Biochimie (2011), 93(3): 562-569.

- Ogi T, Higa M, Maruyama S.
Melanin Synthesis Inhibitors from Balanophora fungosa. J Agric Food Chem (2011), 59(4): 1109-1114.

- Oh M-J, Abdul H M, Ngadiran S, Seo Y-K, Sarmidi M R, Park CS.
Ficus deltoidea (Mas cotek) extract exerted anti-melanogenic activity by preventing tyrosinase activity in vitro and by suppressing tyrosinase gene expression in B16F1 melanoma cells. Arch Dermatol Res (2011), 303(3): 161-70.

- Rho HS, Ahn SM, Hwang JS.
Inhibitory effect of N-adamantyl-3,4-dihydroxybenzamide on melanogenesis in melan-a cells and brown guinea pigs. Arch Dermatol Res (2011), 303(3): 153-159.

Plant and fungal pigments

- Yu X, Gu Z, Shao R, Chen H, Wu X, Xu W.
Study on adsorbing chromium(VI) ions in wastewater by Aureobacidium pullulans secretion of melanin. Adv Materials Res (Zuerich, Switzerland) (2011), 156-157(Pt. 2, Advanced Manufacturing Technology): 1378-1384.

2. Biology of pigment cells and pigmentary disorders

(Dr M. Picardo)

Melanosomes are specialized organelles responsible for melanin synthesis and storage in pigment cells. In melanocytes they are trafficked away from the perinuclear area along microtubules as they mature, and are captured onto actin filaments at the cell periphery/dendrite tips where they are subsequently transferred to surrounding keratinocytes. Multiple Rab GTPases regulate different aspects of vesicle trafficking via specific effectors. Recently, transferrin (Tfn)-positive recycling endosomes (REs) have been implicated in the maturation of melanosomes. REs, and RE-associated Rabs such as Rab11, are also known to be involved in exocytic/secretory pathways in other cell types. The work by **Beaumont et al** investigates RE-associated Rabs in melanocytic cells, in particular Rab17. The authors find that Rab17 is expressed in melanocytic cells where its association with melanosomes, its function in melanosome release and its MITF-regulated expression denote this as a new pigmentation gene. Moreover, Rab17 is required for filipodia formation. Given the role of Rab17 in filopodia formation and the potent stimulatory effect of α-MSH or FSK on filopodia, the authors propose that filopodia are the site for Rab17 or RE-regulated melanosome exocytosis.

The capacity of a-melanocyte-stimulating hormone (a-MSH) to drive melanogenesis through the cyclic adenosine monophosphate/protein kinase A (cAMP / PKA) pathway is already well documented. The work by **Bellei et al**, show a novel mode of regulation for melanocyte differentiation through b-catenin phosphorylation by PKA, and demonstrates the importance of this mechanism for cAMP-induced melanogenesis. This work demonstrates that stimulation by melanocortins of melanocyte differentiation regulates b-catenin transcriptional activity independently of canonical Wnt signaling. These results highlight a previously unrecognized role of a-MSH in the regulation of Wnt signaling pathway, not only in normal melanocyte but also in melanoma cells.

There is a close and important functional association between melanocytes and keratinocytes. Melanocytes transfer mature melanosomes to neighboring keratinocytes, resulting in visible skin pigmentation and protecting the keratinocytes from the deleterious effects of ultraviolet (UV) light. Reciprocally, keratinocytes mediate melanocyte functions via several pathways, including cell-cell adhesion, cell-matrix adhesion, and paracrine signaling. Adhesion between skin cells and the surrounding matrix is regulated by various keratinocyte-produced extracellular matrix (ECM) factors, including fibronectin, laminin and collagen. Laminin-332, a component of basement membrane, is known to initiate hemidesmosome formation and support stable attachment of the epidermis to the dermis. The work by **Chung et al** demonstrate that keratinocytes play critical roles in regulating melanoma and melanocyte functions. In particular the authors show that the keratinocyte-derived ECM protein laminin-332 plays a crucial role in the adhesion, spreading and migration of melanocytes and melanoma in vitro. In contrast, keratinocyte-derived soluble factors do not essential for the adhesion of melanoma cells.

The processing of melanosomes during keratinocyte terminal differentiation and the degradative variability observed between light and dark skin remains enigmatic. **Ebanks et al.** have successfully developed a previously unreported strategy to study and elucidate the process of melanosome loss. The technique they employed offered to the knowledge a previously unreported approach to investigate how various skin types process melanosomes during keratinocytes terminal differentiation. The authors have found that keratinocytes cultures from light skin have an apparent increased rate of melanosome loss when compared with keratinocytes cultures from dark skin. This model system offers a distinct analytical methodology that may provide valuble information regarding the turnover of melanosomes in the skin and hair.

Normal cells possess a limited proliferative life span, after which they enter a state of irreversible growth arrest, called replicative senescence. Cellular senescence is characterized by a sustained growth arrest and is commonly observed in premalignant lesions but rarely in the transformed state, supporting the notion that senescence acts as a potent tumor suppressor mechanism restricting cell proliferation. The process of replicative and premature senescence in melanocytes has been already reviewed. In contrast, there is a relative dearth of information regarding the ability of melanoma cells to enter a program of senescence. The review by **Giuliano et al** mostly focuses on recent findings reporting induction of cellular senescence in melanoma cells. In particular, the authors focus their attention on recent reports indicating that senescence remains latently functional in tumor cells from melanoma and can be reactivated upon gain or loss of function of tumor suppressor or oncogenes, respectively, that have been deregulated during the process of transformation. Hence, the inactivation of c-MYC, microphthalmia-associated transcription factor (MITF), TBX2 or DEK can cause melanoma cells to senesce, as can forced expression of p16INK4A or SYK, which are generally absent in melanoma cells. As melanoma cells are highly resistant to apoptotic processes, these observations have important implications, rendering cellular senescence an attractive therapeutic strategy to limit melanoma cell proliferation.

Herraiz et al. showed that the RHC variants of the MC1R with reduced or absent signalling to cAMP, activated the ERKs as efficiently as *wild type* MC1R, in a physiological setting, both in human melanoma cells and in normal human melanocytes. They also showed that ERK activation was independent on cAMP, PKA, PKC or Ca^{++}. Instead, positive functional coupling of MC1R to the ERKs relied on the transactivation of cKIT. Moreover, their data showed that α-MSH activated the Src non-RTK in melanoma cells independently on cAMP and that Src was involved in activation of ERKs downstream of MC1R, most likely by mediating α-MSH-induced c-Kit transactivation. These findings might have important and unexpected implications for understanding of functional connections of the main signalling pathways controlling human melanocyte proliferation and differentiation. Moreover they provide new insights for the rational design of photo-protective strategies.

Proliferation and differentiation of mouse melanocytes during development is regulated by numerous genetic and epigenetic factors. Among the genetic factors, the coat colour genes are the most important. In mice, more that 300 genes

are involved in melanocyte proliferation and differentiation; about half of these have been cloned and their functions clarified. However, many unknown genes and their functions still remain to be investigated. Moreover, epigenetic factors from the surrounding tissue environment, such as keratinocytes and fibroblasts, the pituitary gland, other organs and the blood supply, as well as environmental factors such as ultraviolet radiation and ionizing radiation, are also important for the regulation of melanocytes proliferation and differentiation. The review by **Hirobe** describes and discusses in detail many studies on the genetic and epigenetic control of proliferation and differentiation of melanocytes.

Heme oxygenase is a microsomal enzyme that catalyzes the first, rate-limiting step in the degradation of heme, and plays an important role in its recycling. The enzymatic activity of Heme oxygenase results in decreased oxidative stress, an attenuated inflammatory response, and a lover rate of apoptosis. **Jin et al** detected differences in the Heme oxygenase-1 expression, in melanocytic naevi and melanomas by immunohistochemestry and in cultured normal human melanocytes and melanoma cell lines. by Western blotting, RT-PCR analysis and confocal microscopy. The results they obtained demonstrated that both primary human melanocytes and melanocytic nevi preserve the ability to produce Heme oxygenase-1 as an antioxidant, whereas melanomas lose the capacity to express this enzyme, both at cellular and tissue levels, as a result of loss of protection from oxidative stress . Further studies are warrant to determine the exact role of Heme oxygenase-1 in melanomas.

Kormos B. et al., wrote a work were they showed that melanocytes dedifferentiate in cholera toxin and PMA-free culture media. During this dedifferentiation process c-Kit and TRP-1 expressions decreases in the cells, their expression of epidermal growth factor receptor (EGFR) and nestin proteins increase, as well as their proliferative capacity. They also showed that in vitro dedifferentiation in the culture is a reversible process, both cholera toxin and PMA treatment and UVB irradiation can induce *in vitro* redifferentiation of melanocytes. The proposed culture technique provides a good model system to study mechanisms of cellular differentiation of normal human epidermal melanocytes. Further advantage of this culture is that these melanocytes are applicable for transplantation.

Melanocyte destruction in the skin of vitiligo patients has been considered to be a consequence of an autoimmune response against melanosomal proteins. However, little is known about the molecular mechanisms by which the immune system recognizes these sequestered intracellular self-proteins, which are confined in the melanosomes, and is provoked into an autoimmune response to melanocytes. The emerging view is that vitiligo melanocytes may have an intrinsic defect that makes them more susceptible to reactive oxygen species (ROS) and to overproduction of hydrogen peroxide (H2O2), which possibly induces the intracellular melanosomal antigens to be released subsequent to oxidative damage of melanocytes. A recent study demonstrated that inactivation of dopachrome tautomerase (Dct) lessens the radical-scavenging potential in Dct-deficient melanocytes and increases their vulnerability to oxidative damage. Dct is a critical enzyme in the melanogenesis pathway that isomerizes the intermediate dopachrome to 5,6-dihydroxyindole-2-carboxylic acid (DHICA) and influences the proportion of the DHICA monomer incorporated into melanin with the 5,6-dihydroxyindole (DHI) polymer, thereby generating a DHICA-rich eumelanin that confers a potent hydroxyl radical scavenging activity. In this study, **Liu et al** attempted to define the sensitivity of Dct-mutant melanocytes to oxidative stress, the immunogenicity of melanosomal proteins derived from Dct-mutant melanocytes after treatment with H2O2, as well as the protection from oxidative insults by synthetic DHICA-rich melanin. The results show that oxidative stress significantly enhances the immunogenicity of melanosomal proteins derived from Dct-mutant melanocytes and that DHICA-mediated antioxidation plays a role in the maintenance of immune hyporesponsiveness to melanosomal proteins.

The maintenance of reactive oxygen species (ROS) homeostasis is crucial for normal cell growth and survival. Several observations have also suggested the involvement of ROS in malignant transformation and tumor progression. Mitochondria are the main source of ROS in nonphagocytic cells, but other cytosolic enzymatic systems, such NADPH oxidases, xanthine oxidases, and nitric oxide synthases (NOS), can also generate superoxide. A critical aspect of NOS function is the requirement of the cofactor tetrahydrobiopterin (BH4). In its absence NOS dimerization is destabilized and NOS catalytic activity becomes “uncoupled” resulting in superoxide formation. There is no information relating NOS uncoupling and malignant transformation and tumor progression. Recently Jasiulionis’s group developed an in vitro murine melanocyte malignant transformation model, after subjecting a nontumorigenic melanocyte lineage, melan-a, to sequential cycles of anchorage impediment. During anchorage blockade, melanocytes present increased levels of superoxide, nitric oxide, and hydrogen peroxide. The aim of the study by **Melo et al** was to identify the sources of superoxide produced during melanocyte anchorage blockade and the impact of superoxide in melanocyte malignant transformation. The authors demonstrated that superoxide generation by eNOS uncoupling contributes to melanocyte malignant transformation, mediated probably by the loss of BH4 availability.

Growing evidence indicates that the MC1R and its ligand the α-MSH have other functions in the skin in addition to pigment production. Activation of the MC1R/α-MSH signalling pathway has been implicated in the regulation of both inflammation and extracellular matrix homeostasis. However, little is known about the role of MC1R/α-MSH signalling in the regulation of inflammatory and fibroproliferative responses to cutaneous injury. Although MC1R and α-MSH localization has been described in uninjuried skin, their spatial and temporal expression during cutaneous wound repair has not been investigated. **Muffley et al.** determined the localization of MC1R and α-MSH in murine excisional wounds, human acute burns and hypertrophyc scars. Changes in MC1R and α-MSH localization suggest a role in epithelisation, inflammation, and fibroproliferation during cutaneous wound repair.

The hypoxia inducible factor-1α (HIF-1α) is a pleiotropic transcription factor typically activated in response to low oxygen tension as well as other stress factors in normoxic conditions. HIF-1α is known to orchestrate a variety of vital processes mainly involved in tissue adaptation and cellular stress response that include survival and growth factor signaling,

neovascularization, glucose and energy metabolism, autophagy and apoptosis. In the epidermis HIF-1α has a vital physiological role and partecipates in crucial processes including malignant transformation and cancer progression. In this review, **Nys et al** addresse the uncovered and complex role of HIF-1α in skin carcinogenesis. In particular the authors highlight recent findings underscoring the emerging dual role of HIF-1α-regulated pathways in possibly preventing early steps of the photocarcinogenesis process or fuelling skin cancer progression.
Yang Y wrote a very comprehensive review on the structure, function and regulation of the melanocortin receptors (MCRs). MCRs belong to the seven-transmemebrane G proteins coupled receptors (GPCR). There are five MCRs subtypes, and each of the types has a different pattern of tissue expression and has its own profile regarding the relative potency of different melanocortin peptides, MCRs ligands. The majority of current ligands affects MCRs activity by binding to orthosteric site. Over the past one decade, novel opportunities for drug discovery have risen from a greater understanding of the complexity of melanocortin receptor signalling. A striking example of this is the appreciation that MCRs possess functional allosteric binding sites. Allosteric modulator ligands bind receptor domains topographically distinct from the orthosteric site, altering the biological activity of the orthosteric ligand by changing its binding affinity, functional efficacy, or both. This additional allosteric ligands offer the way for not only receptor-selective but also signalling pathway-selective therapies.

- Beaumont KA, Hamilton NA, Moores MT, Brown DL, Ohbayashi N, Cairncross O, Cook AL, Smith AG, Misaki R, Fukuda M, Taguchi T, Sturm RA, Stow JL.
  The ecycling endosome protein Rab17 regulates melanocytic filipodia formation and melanosome trafficking. Traffic Feb 3, 2011.

- Bellei B, Pitisci A, Catricalà C, Larue L, Picardo M.
  Wnt/β-catenin signaling is stimulated by α-melanocyte-stimulating hormone in melanoma and melanocyte cells: implication in cell differentiation. Pigment Cell Melanoma Res 24:309-325, 2011.

- Chung H, Suh EK, Han IO, Oh ES.
  Keratinocyte-derived laminin-332 promotes adhesion and migration in melanocytes and melanoma. J Biol Chem. Paper in press, 2011.

- Ebanks JP, Koshoffer A, Wickett RR, Schwemberger S, Babcock G, Hakozaki T, Boissy RE.
  Epidermal keratinocytes from light vs. dark skin exhibit deifferential degradation of melanosomes. J of Invest Dermatol 17: 1-8, 2011.

- Giuliano S, Ohanna M, Ballotti R, Bertolotto C.
  Advances in melanoma senescence and potential clinical application. Pigment Cell Melanoma Res 24:295-308, 2011.

- Herraiz C, Journé F, Abdel-Malek Z, Ghanem G, Jiménez-Cervantes C, García-Borrón JC.
  Signalling from the human melanocortin 1 receptor to ERK1 and ERK2 mitogen-activated protein kinases involves transactivation of cKIT. Mol Endocrinol 25:138-156, 2011.

- Hirobe T.
  How are proliferation and differentiation of melanocytes regulated ? Approved for publication in Pigment Cell Melanoma Res.

- Jin SA, Park JJ, Lee JB, Lee SC, Yun SJ.
  Decreased heme oxygenase-1 expression distinguishes human melanomas from melanocytic nevi. Pigment Cell Melanoma Res 23: 841-844, 2010.

- Kormos B, Belso N, Bebes A, Szabad G, Bacsa S, Szell M, Kemény L, Bata-Csörgo Z.
  In Vitro Dedifferentiation of melanocytes from adult epidermis. PLoS ONE 6: e17197, 2011.

- Liu XM, Zhou Q, Xu SZ, Wakamatsu K, Lei TC.
  Maintenance of immune hyporesponsiveness to melanosomal proteins by DHICA-mediated antioxidation: possible implications for autoimmune vitiligo. Free Rad Biol Med. Article in press, 2011.

- Melo FHM, Molognoni F, Morais AS, Toricelli M, Mouro MG, Higa EMS, Lopes JD, Jasiulionis MG. **Endothelial nitric oxide synthase uncoupling as a key mediator of melanocyte malignant transformation associated with sustained stress conditions**. Free Rad Biol Med. Article in press, 2011.

- Muffley LA, Zhu KQ, Engrav LH, Gibran NS, Hocking AM.

Spatial and temporal localization of the MC1R and its ligand α-MSH during cutaneous wound repair. J Histochem & Cytochem 59: 278-288, 2011.

- Nys K, Maes H, Dudek AM, Agostinis P.
Uncovering the role of hypoxia inducible factor-1α in skin carcinogenesis. Biochem Biophys Acta Article in press, 2011

- Yang Y.
Structure, function and regulation of the melanocortin receptors. European Journal of Pharmacology. Jan 3, 2011.

3. MSH, MCH, other hormones, differentiation

(Pr M. Böhm)

***POMC* gene expression by two alternative promoters**

Proopiomelanocortin (POMC) gene expression is orchestrated by several mechanisms including epigenetic regulation and transcriptional activation by two different promoters, one upstream of exon 1, the other present in intron 1. Expression of full length POMC transcripts requires expression of all 3 exons, the first one being untranslated, the second encoding the signal sequence, and the third encoding the translated POMC protein. In an interesting work on comparative endocrinology (Yoshihara *et al.,* Gen. Comp. Endocrinol. 2011; 171: 46-51), the authors investigated the peripheral POMC system in feather follicles of chicken. Of note, in chicken melanocortin-1 receptor (MC1R) mutations can cause different phenotypes of pigmentation in analogy to men. In the above paper the authors demonstrated first the presence of transcripts for POMC, the POMC-cleaving prohormone convertases PC1 and PC2, and the MC1R in feather follicles of chicken. Secondly, adrenocorticotropin immunoreactivity in chicken feathers was disclosed by immunohistology as well as by Western immunoblotting suggesting the presence of an autonomous POMC system expressed in feather follicles of chicken. Thirdly, the authors used rapid amplification of cDNA 5´end (5´RACE), 3´RACE and RT-PCR analysis to identify two classes of POMC mRNAs that encode both full-length POMC protein but have different non-coding leader exons. Interestingly, within the feather follicles these two POMC mRNAs are differently expressed at various anatomical locations. The data highlight alternative promoter usages generating different full-length POMC transcripts in vertebrates.

Wnt/beta-catenin signalling and alpha-MSH – implications in cell differentiation of melanocytes

Wnt proteins are cysteine-rich glycoproteins that regulate migration, proliferation and differentiation of neural crest cells while beta-catenin is a transcription factor that regulates the microphthalmia-associated transcription factor (MITF), a key factor orchestrating melanogenesis. In a recent paper by Bellei *et al.* (Pigm. Cell Melanoma Res. 2011; 24:309-325) the authors first investigated the impact of beta-catenin silencing on melanogenes in B16.F0 melanoma cells and normal melanocytes. Beta-catenin silencing reduced basal and alpha-melanocyte-stimulating hormone (alpha-MSH)-induced melanin synthesis as evidenced by a panel of melanogenesis-related read-outs. Interestingly, alpha-MSH induced Ser675 phosphorylation and stabilization of the beta-catenin protein, the latter presumably by PKA-mediated attenuation of glycogen synthese kinase-3beta that regulates proteolysis of beta-catenin. Moreover, cAMP, the key mediator of alpha-MSH-induced signal transduction in melanocytes, facilitated beta-catenin-dependent transactivation of several Wnt target genes, and also appeared to act directly on the promoter of MITF as shown by chromatin precipitation assays. The data highlight the existence of an important crosstalk between the alpha-MSH/cAMP and Wnt/beta-catenin pathway.

Glycosylation – a novel regulator of the functional status of the MC-1R

N-glycosylation plays in important role in proper functional state of proteins. Interestingly, little is known about the functional consequence of glycosylation of the MC1R, a key factor of coat colour regulation. Interestingly, MC1R has two N-glycosylation sites, Asn15 and Asn29, however the occupancy and functional importance of these glycosylation sequons remain unclear. Herraiz et al. (Pigm. Cell Melanoma Res. 2011; E-pub, in press) addressed this important question and found that MC1R is indeed N-glycosylated at both sites. However, while this posttranslational processing of MC1R did not appear to be relevant for high affinity agonist binding (as shown by radioligand surface binding and functional coupling studies using cAMP assays on MC1R-expressing heterologous cells) it had an impact on the availability of MC1Rs molecules on the plasma membrane. Moreover, MC1R variants were found to have different degrees of glycosylation which did not reveal a simple correlation with their functional statues or intracellular trafficking. These findings point towards a new dimension in the regulation of the functional state of the MC1R with implications not only for MC1R and pigment cells but also for other MCRs and non-melanocyte cell types expressing MCRs.

4. Photobiology

(Dr N. Smit)

Various studies published in the last months stress the fact that melanoma incidence is rising (e.g. Lim et al, Lin et al, Koster et al, Rigel DS). The dramatic increase in melanoma risk (presently, 1 in 59 in the US, Rigel) may be difficult to explain by an increase in UV(-B) exposure, only. Whereas the non-melanoma skin cancers clearly show the UVB "signature" of mutations this is not the case for melanoma. Rigel mentions several risk factors, next to sunburns due to acute sun exposure, such as (atypical) moles, immunosuppression, PUVA therapy and tanning salons. Autier et al review the epidemiological evidence that UVA may be involved in the generation of malignant melanoma and that sunbed use is the most probable cause of the melanoma epidemic with a fourfold increase in incidence. The findings of Miyamura et al that the UVA induced tanning is similar to that of UVB but does offers much less photoprotection is also not in favor of the use of UVA tanning salons. For several reasons Lim et al plead that the FDA should ban the tanning devices for minors and also Lin et al conclude that relevant counseling can lead to better sun protective behavior and reduced indoor tanning. McGee et al describe how neonatal sun exposure can influence the skin immune system in mice when they reached adulthood. They relate this to the increased incidence of melanoma after early childhood UVR exposure which could result in insufficient immune function at later age. Karlsson et al point to another important topic. The occurrence of high numbers of common melanocytic nevi is also seriously correlated with melanoma risk. They demonstrate that parental sun protection regimen can result in a reduction of the number of common melanocytic nevi. Keeping in mind, that the onset of melanocytic nevi after early childhood sunburn could be one of the intermediate events leading to melanoma, Meyskens and Yang describe some interesting observations in melanocyte cultures that produce foci after incubation with chromium and cobalt. Indeed, this kind of in vitro formation of "nevi" can be observed sometimes in melanocyte cultures. The heavy metal influence could thus be one of the additional environmental factors contributing to cutaneous melanoma. Meyskens and Yang indicate that the contribution of familial and genetic factors to cutaneous melanoma is less than 5%. Mutations in the p16(INK4A) tumor suppressor are associated with familial melanomas. Jenkins et al asked why p16 dysfunction predisposes especially to melanoma. They describe a new role for p16 as a regulator of oxidative stress which may be of higher importance in melanocytes than in keratinocytes or fibroblasts. Since p16 is rapidly upregulated after UVR and other oxidative stress induction this function of p16 may be of importance for further studies.

- **Ultraviolet radiation: a hazard to children and adolescents**. Pediatrics. 2011, 127:588-597.

- Autier P, Dore JF, Eggermont AM, Coebergh JW.
  Epidemiological evidence that UVA radiation is involved in the genesis of cutaneous melanoma. Curr.Opin.Oncol. 2011, 23:189-196.

- Balk SJ.
  Ultraviolet Radiation: A Hazard to Children and Adolescents. Pediatrics. 2011, 127:e791-e817.

- Boniol M, Cesarini P, Chignol MC, Cesarini JP, Dore JF.
  Why indoor tanning must be taxed? A proposal from La Securite Solaire, WHO collaborating centre. Presse Med. 2010, 39:1236-1237.

- Bradford PT, Goldstein AM, Tamura D, Khan SG, Ueda T, Boyle J, Oh KS, Imoto K, Inui H, Moriwaki S, Emmert S, Pike KM, Raziuddin A, Plona TM, DiGiovanna JJ, Tucker MA, Kraemer KH.
  Cancer and neurologic degeneration in xeroderma pigmentosum: long term follow-up characterises the role of DNA repair. J.Med.Genet. 2011, 48:168-176.

- Butler ST, Fosko SW.
  Increased prevalence of left-sided skin cancers. J.Am.Acad.Dermatol. 2010, 63:1006-1010.
  There were significantly more skin cancers on the left than the right side in men. This discrepancy was even more profound in malignant melanoma in situ.

- Bzhalava D, Bray F, Storm H, Dillner J.
  Risk of second cancers after the diagnosis of Merkel cell carcinoma in Scandinavia. Br.J.Cancer. 2011, 104:178-180.

- Casetti F, Miese A, Mueller ML, Simon JC, Schempp CM.
  Double Trouble from Sunburn: UVB-Induced Erythema Is Associated with a Transient Decrease in Skin Pigmentation. Skin Pharmacol.Physiol. 2011, 24:160-165.

- Cust AE, Harland M, Makalic E, Schmidt D, Dowty JG, Aitken JF, gha-Hamilton C, Armstrong BK, Barrett JH, Chan M, Chang YM, Gascoyne J, Giles GG, Holland EA, Kefford RF, Kukalizch K, Lowery J, Randerson-Moor JA, Schmid H, Taylor CF, Whitaker L, Hopper JL, Newton-Bishop JA, Mann GJ, Bishop DT, Jenkins MA.
  Melanoma risk for CDKN2A mutation carriers who are relatives of population-based case carriers in Australia and the UK. J.Med.Genet. 2011, 48:266-272.
  Conclusions Contrary to the strong association between UV radiation exposure and melanoma risk for the general population, CDKN2A mutation carriers appear to have the same cumulative risk of melanoma irrespective of the ambient UV irradiance of the region in which they live

- Dal'Forno T, Cartell A, Bakos L.
  Dermabrasion in acquired melanocytic nevi: a histopathological and immunohistochemical study. Am.J.Dermatopathol. 2011, 33:40-46.

- de Leeuw J, Assen YJ, van der BN, Bjerring P, Martino Neumann HA.
  Treatment of vitiligo with khellin liposomes, ultraviolet light and blister roof transplantation. J.Eur.Acad.Dermatol.Venereol. 2011, 25:74-81.

- DeBoyes T, Kouba D, Ozog D, Fincher E, Moy L, Iwata K, Moy R.
  Reduced number of actinic keratoses with topical application of DNA repair enzyme creams. J.Drugs Dermatol. 2010, 9:1519-1521.

- Dong Y, Wang H, Cao J, Ren J, Fan R, He X, Smith GW, Dong C.
  Nitric oxide enhances melanogenesis of alpaca skin melanocytes in vitro by activating the MITF phosphorylation. Mol.Cell Biochem. 2011.

- Easty DJ, Gray SG, O'Byrne KJ, O'Donnell D, Bennett DC.
  Receptor tyrosine kinases and their activation in melanoma. Pigment Cell Melanoma Res. 2011,10-148X.
  Complex interactions between RTKs and PTPs are implicated in the abnormal signalling driving aberrant growth and survival in malignant melanocytes, and indeed in normal melanocytic signalling including the response to ultraviolet radiation.

- Ferguson B, Konrad MH, Handoko HY, Khosrotehrani K, Beermann F, Hacker E, Soyer HP, Bosenberg M, Walker GJ.
  Differential roles of the pRb and Arf/p53 pathways in murine naevus and melanoma genesis. Pigment Cell Melanoma Res. 2010, 23:771-780.

- Franco-Lie I, Iversen T, Robsahm TE, Abdelnoor M.
  Incidence trends of melanoma of the skin compared with other localisations, in the Norwegian population, 1956-2005. Ann.Oncol. 2010.
  A wide variation in IRs and trends between the four anatomical localisations with unlike levels of UVR exposure suggests different causal pathways for melanoma

- Godden D, Brennan PA, Milne J.
  Update on melanoma: the present position. Br.J.Oral Maxillofac.Surg. 2010, 48:575-578.

- Grant WB, Moan JE, Micu E, Porojnicu AC, Juzeniene A.
  Similarities in solar ultraviolet irradiance and other environmental factors may explain much of the family link between uveal melanoma and other cancers. Fam.Cancer. 2010, 9:659-660.

- Hiramoto K.
  Increase in dopa-positive melanocytes in the mouse intestine in response to ultraviolet B rays via the eyes. Clin.Exp.Dermatol. 2011, 36:52-56.

- Hornle M, Peters N, Thayaparasingham B, Vorsmann H, Kashkar H, Kulms D.
  Caspase-3 cleaves XIAP in a positive feedback loop to sensitize melanoma cells to TRAIL-induced apoptosis. Oncogene. 2011, 30:575-587.

- Iorizzo LJ, III, Brown MD.
  Atypical fibroxanthoma: a review of the literature. Dermatol.Surg. 2011, 37:146-157.
  CONCLUSIONS People with AFX generally have had significant ultraviolet radiation exposure.

- Jenkins NC, Liu T, Cassidy P, Leachman SA, Boucher KM, Goodson AG, Samadashwily G, Grossman D.

The p16(INK4A) tumor suppressor regulates cellular oxidative stress. Oncogene. 2011, 30:265-274.
These findings suggest a potential alternate Rb-independent tumor-suppressor function of p16 as an endogenous regulator of carcinogenic intracellular oxidative stress. Compared with keratinocytes and fibroblasts, we also found increased susceptibility of melanocytes to oxidative stress in the context of p16 depletion, which may explain why the compromise of p16 predisposes to melanoma over other cancers

- Jo SJ, Kwon HH, Choi MR, Youn JI.
No evidence for increased skin cancer risk in Koreans with skin phototypes III-V treated with narrowband UVB phototherapy. Acta Derm.Venereol. 2011, 91:40-43.

- Jux B, Kadow S, Luecke S, Rannug A, Krutmann J, Esser C.
The aryl hydrocarbon receptor mediates UVB radiation-induced skin tanning. J.Invest Dermatol. 2011, 131:203-210.
Thus, the environmental signal sensor AhR links solar UVB radiation to skin pigmentation.

- Karlsson MA, Wahlgren C, Wiklund K, Rodvall Y.
Parental sun protective regimens and prevalence of common melanocytic nevi among 7-year-old children in Sweden: changes over a 5-year period. Br.J.Dermatol. 2011,10-2133.

- Kessides MC, Wheless L, Hoffman-Bolton J, Clipp S, Alani RM, Alberg AJ.
Cigarette smoking and malignant melanoma: a case-control study. J.Am.Acad.Dermatol. 2011, 64:84-90.
After matching for age, sex, race, and skin type, and further adjusting for UV exposure and number of sunburns, cigarette smoking was not statistically significantly associated with melanoma risk, but the results were consistent with previous observations of an inverse association

- Klug HL, Tooze JA, Graff-Cherry C, Anver MR, Noonan FP, Fears TR, Tucker MA, De Fabo EC, Merlino G.
Sunscreen prevention of melanoma in man and mouse. Pigment Cell Melanoma Res. 2010, 23:835-837.

- Koster B, Thorgaard C, Philip A, Clemmensen IH.
Vacations to sunny destinations, sunburn, and intention to tan: a cross-sectional study in Denmark, 2007-2009. Scand.J.Public Health. 2011, 39:64-69.

- Kutting B, Drexler H.
UV-induced skin cancer at workplace and evidence-based prevention. Int.Arch.Occup.Environ.Health. 2010, 83:843-854.

- Kvaskoff M, Bijon A, Mesrine S, Boutron-Ruault MC, Clavel-Chapelon F.
Cutaneous Melanoma and Endogenous Hormonal Factors: A Large French Prospective Study. Am.J.Epidemiol. 2011.
Results did not significantly differ according to ambient ultraviolet radiation dose and melanoma site or subtype. These findings from a large prospective cohort may suggest a reduced melanoma risk associated with decreased exposure to ovarian hormones.

- Lim HW, James WD, Rigel DS, Maloney ME, Spencer JM, Bhushan R.
Adverse effects of ultraviolet radiation from the use of indoor tanning equipment: Time to ban the tan. J.Am.Acad.Dermatol. 2011, 64:e51-e60.

- Lin JS, Eder M, Weinmann S.
Behavioral counseling to prevent skin cancer: a systematic review for the U.S. Preventive Services Task Force. Ann.Intern.Med. 2011, 154:190-201.

- Magina S, Esteves-Pinto C, Moura E, Serrao MP, Moura D, Petrosino S, Di M, V, Vieira-Coelho MA.
Inhibition of basal and ultraviolet B-induced melanogenesis by cannabinoid CB(1) receptors: a keratinocyte-dependent effect. Arch.Dermatol.Res. 2011, 303:201-210.
Our results collectively suggest that ultraviolet radiation activates paracrine CB(1)-mediated endocannabinoid signaling to negatively regulate melanin synthesis.

- Matin R.
Vitiligo in adults and children. Clin.Evid.(Online.). 2011, 2011. pii: 1717.:1717.
In this systematic review we present information relating to the effectiveness and safety of the following interventions: corticosteroids (oral and topical), oral levamisole, topical immunomodulators, topical vitamin D analogues, ultraviolet A plus psoralen (PUVA [oral or topical]), and ultraviolet B (narrowband)

- McGee HM, Malley RC, Muller HK, Woods GM.
Neonatal exposure to UVR alters skin immune system development, and suppresses immunity in adulthood. Immunol.Cell Biol. 2011.

- Meyskens FL, Yang S.
Thinking about the role (largely ignored) of heavy metals in cancer prevention: hexavalent chromium and melanoma as a case in point. Recent Results Cancer Res. 2011, 188:65-74.:65-74.

- Miyamura Y, Coelho SG, Schlenz K, Batzer J, Smuda C, Choi W, Brenner M, Passeron T, Zhang G, Kolbe L, Wolber R, Hearing VJ.
The deceptive nature of UVA tanning versus the modest protective effects of UVB tanning on human skin. Pigment Cell Melanoma Res. 2011, 24:136-147.
Thus, UVA tanning contributes essentially no photoprotection, although all types of UV-induced tanning result in DNA and cellular damage, which can eventually lead to photocarcinogenesis

- Nasser N.
UVB: susceptibility in malignant melanoma. An.Bras.Dermatol. 2010, 85:843-848.
RESULTS: Susceptibility to UVB radiation was 81.5 in the MM group and 31.2% in the control group. The risk of an UVB-susceptible individual to develop MM was 9.7 times higher than when UVB resistant. CONCLUSION: UVB susceptibility should be considered an important risk factor to the development of this type of cancer.

- Nys K, Maes H, Dudek AM, Agostinis P.
Uncovering the role of hypoxia inducible factor-1alpha in skin carcinogenesis. Biochim.Biophys.Acta. 2011, 1816:1-12.
HIF-1alpha activation by UVB exposure contributes to either repair or the removal of UVB-damaged keratinocytes by inducing apoptosis, thus revealing a tumor suppressor role for HIF-1alpha in these cells. On the other hand, the constitutive expression of HIF-1alpha evoked by the mild hypoxic state of the skin has been implicated as a positive factor in the transformation of normal melanocytes into malignant melanoma.

- Rigel DS.
Epidemiology of melanoma. Semin.Cutan.Med.Surg. 2010, 29:204-209.

- Wang L, Shirure VS, Burdick MM, Wu S.
UVB-irradiation regulates VLA-4-mediated melanoma cell adhesion to endothelial VCAM-1 under flow conditions. Mol.Carcinog. 2011, 50:58-65.

- Wang Z, Coleman DJ, Bajaj G, Liang X, Ganguli-Indra G, Indra AK.
RXRalpha ablation in epidermal keratinocytes enhances UVR-induced DNA damage, apoptosis, and proliferation of keratinocytes and melanocytes. J.Invest Dermatol. 2011, 131:177-187.
RXRalpha(ep-/-) mice represent a unique animal model in which UVR induces melanocyte proliferation/activation in both epidermis and dermis. Considered together, the results of our study suggest that RXR antagonists, together with inhibitors of cell proliferation, can be effective in preventing solar UVR-induced photocarcinogenesis.

- Yamate Y, Hiramoto K, Kasahara E, Jikumaru M, Sato EF, Inoue J, Inoue M.
Ultraviolet-A irradiation to the eye modulates intestinal mucosal functions and properties of mast cells in the mouse. Photochem.Photobiol. 2011, 87:191-198.

- Zaidi MR, Davis S, Noonan FP, Graff-Cherry C, Hawley TS, Walker RL, Feigenbaum L, Fuchs E, Lyakh L, Young HA, Hornyak TJ, Arnheiter H, Trinchieri G, Meltzer PS, De Fabo EC, Merlino G.
Interferon-gamma links ultraviolet radiation to melanomagenesis in mice. Nature. 2011, 469:548-553.

5. Neuromelanins

(Pr M. d'Ischia)

Clearance of extracellular neuromelanin from the substantia nigra in Parkinson Disease is an intriguing and important focus of research in relation to the final fate of the pigment and its possible role in exacerbating oxidative stress outside intracellular compartments. Depboylu et al. (2011) used immunohistochemistry and in situ hybridization to analyze the role of C1q in the normal and Parkinsonian substantia nigra (SNc). The interesting finding was that in Parkinson Disease microglial cells are involved in removal of cellular debris of degenerating neurons from the SNc through a C1q-mediated pathway.
Imaging of trace metals is important to understand their compartmentalization and roles in biological systems. Oin et al. (2011) review the potential of metal imaging techniques with high spatial resolution and demonstrate their application to the analysis of neuromelanin.
The association of glutathione peroxidase 4 (GPX4) to neuromelanin in dopaminergic nigral neurones and its decrease in Parkinson's disease is an interesting observation by Bellinger et al. (2001) which may provide new insights into the role of glutathione in neuromelanin synthesis.

- Bellinger FP, Bellinger MT, Seale LA, Takemoto AS, Raman AV, Miki T, Manning-Bog AB, Berry MJ, White LR, Ross GW.
  Glutathione peroxidase 4 is associated with neuromelanin in substantia nigra and dystrophic axons in putamen of Parkinson's brain. Molecular Neurodegeneration (2011), 6 8.
  Abstract: Background: Parkinson's disease is a neurodegenerative disorder characterized pathol. by the loss of nigrostriatal dopamine neurons that project from the substantia nigra in the midbrain to the putamen and caudate nuclei, leading to the clin. features of bradykinesia, rigidity, and rest tremor. Oxidative stress from oxidized dopamine and related compds. may contribute to the degeneration characteristic of this disease. Results: To investigate a possible role of phospholipid hydroperoxidase glutathione peroxidase 4 (GPX4) in protection from oxidative stress, we investigated GPX4 expression in postmortem human brain tissue from individuals with and without Parkinson's disease. In both control and Parkinson's samples, GPX4 was found in dopaminergic nigral neurons colocalized with neuromelanin. Overall GPX4 was significantly reduced in substantia nigra in Parkinson's vs. control subjects, but was increased relative to the cell d. of surviving nigral cells. In putamen, GPX4 was concd. within dystrophic dopaminergic axons in Parkinson's subjects, although overall levels of GPX4 were not significantly different compared to control putamen. Conclusions: This study demonstrates an up-regulation of GPX4 in neurons of substantia nigra and assocn. of this protein with dystrophic axons in striatum of Parkinson's brain, indicating a possible neuroprotective role. Addnl., our findings suggest this enzyme may contribute to the prodn. of neuromelanin.

- Depboylu C, Schaefer MK.-H, Arias-Carrion O, Oertel WH, Weihe E, Hoeglinger GU.
  Possible Involvement of Complement Factor C1q in the Clearance of Extracellular Neuromelanin From the Substantia Nigra in Parkinson Disease. Journal of Neuropathology & Experimental Neurology (2011), 70(2), 125-132.
  Abstract: Activation of the complement system promotes the removal of pathogens and tissue damage products from the brain and may also be involved in neuronal cell death in neurodegenerative diseases. Here, we analyzed the expression of C1q, the initial recognition subcomponent of the classic complement cascade, in the substantia nigra pars compacta (SNc) in Parkinson disease (PD) and control cases using immunohistochem. and in situ hybridization. Microglia were detd. to be the only cells that expressed C1q in the SNc and other brain areas. In the SNc of PD cases, there was increased deposition of extracellular neuromelanin in the parenchyma, resulting from degeneration of dopaminergic neurons. Neuromelanin granules and blebs of degenerated neurons seemed to be opsonized by C1q and phagocytosed by C1q-pos. microglia and macrophages in the parenchyma and in the perivascular spaces. Neuromelanin-laden C1q-pos. cells were also attached to the luminal surfaces of blood vessels in the SNc in PD. Thus, we present evidence suggesting that microglia are capable of phagocytosing and clearing cellular debris of degenerating neurons from the SNc through a C1q-mediated pathway in PD.

- Qin Z, Caruso JA, Lai B, Matusch A, Becker JS.
  Trace metal imaging with high spatial resolution: applications in biomedicine. Metallomics (2011), 3(1), 28-37.
  Abstract: New generations of anal. techniques for imaging of metals are pushing hitherto boundaries of spatial resoln. and quant. anal. in biol. Because of this, the application of these imaging techniques described herein to the study of the organization and dynamics of metal cations and metal-contg. biomols. in biol. cell and tissue is becoming an important issue in biomedical research. In the current review, three common metal imaging techniques in biomedical research are introduced, including synchrotron X-ray fluorescence (SXRF) microscopy, secondary ion mass spectrometry (SIMS), and laser ablation inductively coupled plasma mass spectrometry (LA-ICP-MS). These are exemplified by a demonstration of the dopamine-Fe complexes, by assessment of boron distribution in a boron neutron capture therapy cell model, by mapping Cu and Zn in human brain cancer and a rat brain tumor model, and by the anal. of metal topog.

within neuromelanin. These studies have provided solid evidence that demonstrates that the sensitivity, spatial resoln., specificity, and quantification ability of metal imaging techniques is suitable and highly desirable for biomedical research. Moreover, these novel studies on the nanometer scale (e.g., of individual single cells or cell organelles) will lead to a better understanding of metal processes in cells and tissues.

6. Genetics, molecular and developmental biology

(Dr. Lluís Montoliu)

- Aruta C, Giordano F, De Marzo A, Comitato A, Raposo G, Nandrot EF, Marigo V.
In vitro differentiation of retinal pigment epithelium from adult retinal stem cells. Pigment Cell Melanoma Res. 2011 Feb;24(1):233-40.
Abstract: One of the limitations in molecular and functional studies of the retinal pigment epithelium (RPE) has been the lack of an in vitro system retaining all the features of in vivo RPE cells. Retinal pigment epithelium cell lines do not show characteristics typical of a functional RPE, such as pigmentation and expression of specific markers. The present study was aimed at the development of culture conditions to differentiate, in vitro, retinal stem cells (RSC), derived from the adult ciliary body, into a functional RPE. Retinal stem cells were purified from murine eyes, grown as pigmented neurospheres and induced to differentiate into RPE on an extracellular matrix substrate using specific culture conditions. After 7-15 days of culture, pigmented cells with an epithelial morphology showed a polarized organization and a capacity for phagocytosis. We detected different stages of melanogenesis in cells at 7 days of differentiation, whereas RPE at 15 days contained only mature melanosomes. These data suggest that our protocol to differentiate RPE in vitro can provide a useful model for molecular and functional studies.

- Bellei B, Pitisci A, Catricalà C, Larue L, Picardo M.
Wnt/β-catenin signaling is stimulated by α-melanocyte-stimulating hormone in melanoma and melanocyte cells: implication in cell differentiation. Pigment Cell Melanoma Res. 2011 Apr;24(2):309-25.
Abstract: Wnt/β-catenin signaling plays important roles in many developmental processes including neural crest-derived melanocyte development and migration. However, the effective contribution of Wnt/β-catenin pathway in melanogenesis in adult human melanocytes has not been fully elucidated. Here, we report that in melanoma cells and in normal human melanocytes, melanogenesis stimulation by α-melanocyte-stimulating hormone (α-MSH) induces phosphorylation of β-catenin-Ser675 and stabilization of β-catenin protein. Activation of protein kinase A by α-MSH attenuates glycogen synthase kinase-3β, which regulates ubiquitin-dependent degradation of β-catenin, suggesting a coordinated mechanism of β-catenin activity stimulation. Consistent with increased nuclear β-catenin, cyclic adenosine monophosphate (cAMP) elevation facilitates β-catenin-dependent transactivation of many Wnt target genes. Moreover, chromatin immunoprecipitation assays demonstrated an increased association of β-catenin with the proximal promoter of microphthalmia-associated transcription factor, the master regulator of pigmentation. These results demonstrate the existence of cross talk between the cAMP and Wnt pathways in melanocytes, suggesting that β-catenin could play a key role in the physiological regulation of epidermal melanogenesis.

- Bharti K, Miller SS, Arnheiter H.
The new paradigm: retinal pigment epithelium cells generated from embryonic or induced pluripotent stem cells. Pigment Cell Melanoma Res. 2011 Feb;24(1):21-34.

- Chaki M, Sengupta M, Mondal M, Bhattacharya A, Mallick S, Bhadra R; Indian Genome Variation Consortium, Ray K.
Molecular and functional studies of tyrosinase variants among Indian oculocutaneous albinism type 1 patients. J Invest Dermatol. 2011 Jan;131(1):260-2.

- Gargiulo A, Testa F, Rossi S, Di Iorio V, Fecarotta S, de Berardinis T, Iovine A, Magli A, Signorini S, Fazzi E, Galantuomo MS, Fossarello M, Montefusco S, Ciccodicola A, Neri A, Macaluso C, Simonelli F, Surace EM.
Molecular and clinical characterization of albinism in a large cohort of italian patients. Invest Ophthalmol Vis Sci. 2011 Mar 14;52(3):1281-9.

- Gunnarsson U, Kerje S, Bed'hom B, Sahlqvist AS, Ekwall O, Tixier-Boichard M, Kämpe O, Andersson L.
The Dark brown plumage color in chickens is caused by an 8.3-kb deletion upstream of SOX10. Pigment Cell Melanoma Res. 2011 Apr;24(2):268-74.

- Hirobe T, Ito S, Wakamatsu K.
The mouse pink-eyed dilution allele of the P-gene greatly inhibits eumelanin but not pheomelanin synthesis. Pigment Cell Melanoma Res. 2011 Feb;24(1):241-6.

- Hoyle DJ, Rodriguez-Fernandez IA, Dell'angelica EC.
Functional interactions between OCA2 and the protein complexes BLOC-1, BLOC-2, and AP-3 inferred from epistatic analyses of mouse coat pigmentation. Pigment Cell Melanoma Res. 2011 Apr;24(2):275-81.

- Johnson SL, Nguyen AN, Lister JA.

mitfa is required at multiple stages of melanocyte differentiation but not to establish the melanocyte stem cell. Dev Biol. 2011 Feb 15;350(2):405-13

- Liang H, Fekete DM, Andrisani OM.
CtBP2 downregulation during neural crest specification induces expression of Mitf and REST, resulting in melanocyte differentiation and sympathoadrenal lineage suppression. Mol Cell Biol. 2011 Mar;31(5):955-70.

- Li Y, Zhu X, Yang L, Li J, Lian Z, Li N, Deng X.
Expression and network analysis of genes related to melanocyte development in the Silky Fowl and White Leghorn embryos. Mol Biol Rep. 2011 Feb;38(2):1433-41.

- Manceau M, Domingues VS, Mallarino R, Hoekstra HE.
The developmental role of Agouti in color pattern evolution. Science. 2011 Feb 25;331(6020):1062-5
Abstract: Animal color patterns can affect fitness in the wild; however, little is known about the mechanisms that control their formation and subsequent evolution. We took advantage of two locally camouflaged populations of Peromyscus mice to show that the negative regulator of adult pigmentation, Agouti, also plays a key developmental role in color pattern evolution. Genetic and functional analyses showed that ventral-specific embryonic expression of Agouti establishes a prepattern by delaying the terminal differentiation of ventral melanocytes. Moreover, a skin-specific increase in both the level and spatial domain of Agouti expression prevents melanocyte maturation in a regionalized manner, resulting in a novel and adaptive color pattern. Thus, natural selection favors late-acting, tissue-specific changes in embryonic Agouti expression to produce large changes in adult color pattern.

- Metz HC, Manceau M, Hoekstra HE.
Turing patterns: how the fish got its spots. Pigment Cell Melanoma Res. 2011 Feb;24(1):12-4.

- Ohta S, Imaizumi Y, Okada Y, Akamatsu W, Kuwahara R, Ohyama M, Amagai M, Matsuzaki Y, Yamanaka S, Okano H, Kawakami Y.
Generation of human melanocytes from induced pluripotent stem cells. PLoS One. 2011 Jan 13;6(1):e16182.
Abstract: Epidermal melanocytes play an important role in protecting the skin from UV rays, and their functional impairment results in pigment disorders. Additionally, melanomas are considered to arise from mutations that accumulate in melanocyte stem cells. The mechanisms underlying melanocyte differentiation and the defining characteristics of melanocyte stem cells in humans are, however, largely unknown. In the present study, we set out to generate melanocytes from human iPS cells in vitro, leading to a preliminary investigation of the mechanisms of human melanocyte differentiation. We generated iPS cell lines from human dermal fibroblasts using the Yamanaka factors (SOX2, OCT3/4, and KLF4, with or without c-MYC). These iPS cell lines were subsequently used to form embryoid bodies (EBs) and then differentiated into melanocytes via culture supplementation with Wnt3a, SCF, and ET-3. Seven weeks after inducing differentiation, pigmented cells expressing melanocyte markers such as MITF, tyrosinase, SILV, and TYRP1, were detected. Melanosomes were identified in these pigmented cells by electron microscopy, and global gene expression profiling of the pigmented cells showed a high similarity to that of human primary foreskin-derived melanocytes, suggesting the successful generation of melanocytes from iPS cells. This in vitro differentiation system should prove useful for understanding human melanocyte biology and revealing the mechanism of various pigment cell disorders, including melanoma.

- Rouleau M, Saxena V, Rodrigue A, Paquet ER, Gagnon A, Hendzel MJ, Masson JY, Ekker M, Poirier GG.
A key role for poly(ADP-ribose) polymerase 3 in ectodermal specification and neural crest development. PLoS One. 2011 Jan 17;6(1):e15834.

- Schouwey K, Aydin IT, Radtke F, Beermann F.
RBP-Jκ-dependent Notch signaling enhances retinal pigment epithelial cell proliferation in transgenic mice. Oncogene. 2011 Jan 20;30(3):313-22.

- Shah M, Bhoumik A, Goel V, Dewing A, Breitwieser W, Kluger H, Krajewski S, Krajewska M, Dehart J, Lau E, Kallenberg DM, Jeong H, Eroshkin A, Bennett DC, Chin L, Bosenberg M, Jones N, Ronai ZA.
A role for ATF2 in regulating MITF and melanoma development. PLoS Genet. 2010 Dec 23;6(12):e1001258.

- Sommer L.
Generation of melanocytes from neural crest cells. Pigment Cell Melanoma Res. 2011 Feb 10.

- Thomas JL, Vihtelic TS, Dendekker AD, Willer G, Luo X, Murphy TR, Gregg RG, Hyde DR, Thummel R.
The loss of vacuolar protein sorting 11 (vps11) causes retinal pathogenesis in a vertebrate model of syndromic albinism. Invest Ophthalmol Vis Sci. 2011 Feb 17

- Trantow CM, Cuffy TL, Fingert JH, Kuehn MH, Anderson MG.
Microarray analysis of iris gene expression in mice with mutations influencing pigmentation. Invest Ophthalmol Vis Sci. 2011 Jan 5;52(1):237-48.

- Woods SL, Bishop JM.
A new transgenic mouse line for tetracycline inducible transgene expression in mature melanocytes and the melanocyte stem cells using the Dopachrome tautomerase promoter. Transgenic Res. 2011 Apr;20(2):421-8.

- Zaidi MR, Hornyak TJ, Merlino G.
A genetically engineered mouse model with inducible GFP expression in melanocytes. Pigment Cell Melanoma Res. 2011Apr;24(2):393-4.

7. Tyrosinase, TRPs, other enzymes

(Pr. J.C. Garcia-Borron)

- Enomoto A, Yoshihisa Y, Yamakoshi T, Ur Rehman M, Norisugi O, Hara H, Matsunaga K, Makino T, Nishihira J, Shimizu T.
  UV-B radiation induces macrophage migration inhibitory factor-mediated melanogenesis through activation of protease-activated receptor-2 and stem cell factor in keratinocytes. Am J Pathol. 2011 Feb;178(2):679-87.
  UV radiation indirectly regulates melanogenesis in melanocytes through a paracrine regulatory mechanism involving keratinocytes. Protease-activated receptor (PAR)-2 activation induces melanosome transfer by increasing phagocytosis of melanosomes by keratinocytes. This study demonstrated that macrophage migration inhibitory factor (MIF) stimulated PAR-2 expression in human keratinocytes. In addition, we showed that MIF stimulated stem cell factor (SCF) release in keratinocytes; however, MIF had no effect on the release of endothelin-1 or prostaglandin E2 in keratinocytes. In addition, MIF had no direct effect on melanin and tyrosinase synthesis in cultured human melanocytes. The effect of MIF on melanogenesis was also examined using a three-dimensional reconstituted human epidermal culture model, which is a novel, commercially available, cultured human epidermis containing functional melanocytes. Migration inhibitory factor induced an increase in melanin content in the epidermis after a 9-day culture period. Moreover, melanin synthesis induced by UV-B stimulation was significantly down-regulated by anti-MIF antibody treatment. An in vivo study showed that the back skin of MIF transgenic mice had a higher melanin content than that of wild-type mice after 12 weeks of UV-B exposure. Therefore, MIF-mediated melanogenesis occurs mainly through the activation of PAR-2 and SCF expression in keratinocytes after exposure to UV-B radiation.

- García-Molina F, Muñoz-Muñoz JL, Martínez-Ortiz F, García-Ruíz PA, Tudela J, García-Cánovas F, Rodríguez-López JN.
  Tetrahydrofolic Acid is a potent suicide substrate of mushroom tyrosinase. J Agric Food Chem. 2011 Feb 23;59(4):1383-91.
  The coenzyme tetrahydrofolic acid is the most rapid suicide substrate of tyrosinase that has been characterized to date. A kinetic study of the suicide inactivation process provides the kinetic constants that characterize it: λ(max), the maximum apparent inactivation constant; r, the partition ratio or the number of turnovers made by one enzyme molecule before inactivation; and k(cat) and K(m), the catalytic and Michaelis constants, respectively. From these values, it is possible to establish the ratio λ(max)/K(m), which represents the potency of the inactivation process. Besides acting as a suicide substrate of tyrosinase, tetrahydrofolic acid reduces o-quinones generated by the enzyme in its action on substrates, such as l-tyrosine and l-DOPA (o-dopaquinone), thus inhibiting enzymatic browning.

- Ghanem G, Fabrice J.
  Tyrosinase related protein 1 (TYRP1/gp75) in human cutaneous melanoma. Mol Oncol. 2011 Feb 3.
  Melanoma prognosis is based on specific pathological features at the primary lesion. In metastatic patients, the extent of lymph node involvement is also an important prognosis indicator. Many progression markers both in tissues and serum, including circulating tumor cells, have been studied and new molecular markers are awaited from high-throughput screenings to discriminate between clinical stages and predict disease progression. The present review focuses on human tyrosinase related protein 1 also known as gp75 glycoprotein (Tyrp1/gp75), a melanosomal protein involved in the pigmentary machinery of the melanocyte and often used as differentiation marker, with a special emphasis on its emerging roles in the malignant melanocyte and melanoma progression.

- Ha YM, Kim JA, Park YJ, Park D, Kim JM, Chung KW, Lee EK, Park JY, Lee JY, Lee HJ, Yoon JH, Moon HR, Chung HY.
  Analogs of 5-(substituted benzylidene)hydantoin as inhibitors of tyrosinase and melanin formation. Biochim Biophys Acta. 2011 Mar 18.
  BACKGROUND: Many tyrosinase inhibitors find application in cosmetics and pharmaceutical products for the prevention of the overproduction of melanin in the epidermis. A series of 5-(substituted benzylidene)hydantoin derivatives 2a-2k were prepared, and their inhibitory activities toward tyrosinase and melanin formation were evaluated.
  METHODS: The structures of the compounds were established using (1)H and (13)C NMR spectroscopy and mass spectral analyses. All the synthesized compounds were evaluated for their mushroom tyrosinase inhibition activity.
  RESULTS: The best results were obtained for compound 2e which possessed hydroxyl group at R(2) and methoxy group at R(3), respectively. We predicted the tertiary structure of tyrosinase, simulated its docking with compound 2e and confirmed that this compound interacts strongly with mushroom tyrosinase residues as a competitive tyrosinase inhibitor. In addition, we found that 2e inhibited melanin production and tyrosinase activity in B16 cells.
  CONCLUSIONS: Compound 2e could be considered as a promising candidate for preclinical drug development in skin hyperpigmentation applications.
  GENERAL SIGNIFICANCE: This study will enhance understanding of the mechanism of tyrosinase inhibition and will contribute to the development of effective drugs for use hyperpigmentation.

- Hida T, Sohma H, Kokai Y, Kawakami A, Hirosaki K, Okura M, Tosa N, Yamashita T, Jimbow K.
  Rab7 is a critical mediator in vesicular transport of tyrosinase-related protein 1 in melanocytes. J Dermatol. 2010 Sep 20. doi: 10.1111/j.1346-8138.2010.01004.x.
  How melanosomal proteins such as enzymic proteins (tyrosinase and tyrosinase-related proteins, Tyrps) and structural protein (gp100) are transported from Golgi to melanosomal compartments is not yet fully understood. A number of small GTPases have been found to be associated with melanosomes and we have identified one of them, Rab7, a regulator of vesicular transport, organelle motility, phospholipid signaling and cytosolic degradative machinery, as being involved in the transport of Tyrp1 from Golgi to stage I melanosomes. This study further characterizes the role of Rab7 as a regulator of differential sorting of melanosomal proteins in this process. Murine melanocytes were transiently transfected with a plasmid encoding either wild-type (Rab7WT), constitutively active (Rab7Q67L) or dominant-negative (Rab7N125I and Rab7T22N) Rab7. Through immunocytostaining and confocal laser scanning microscopy, we quantitatively compared the bio-distribution of melanosomal proteins between Rab7WT-expressing cells and mutant Rab7-expressing cells. We also characterized their differential elimination from melanosomal compartments by Rab7 by utilizing a proteasome inhibitor, MG132. Our findings indicate that Rab7 plays an important role in differential sorting of tyrosinase, Tyrp1 and gp100 in early melanogenesis cascade, and that it is more specifically involved with Tyrp1 than tyrosinase and gp100 in the trafficking from Golgi to melanosomes and the specific exit from the degradative process.

- Hirobe T, Ito S, Wakamatsu K.
  The mouse pink-eyed dilution allele of the P-gene greatly inhibits eumelanin but not pheomelanin synthesis. Pigment Cell Melanoma Res. 2011 Feb;24(1):241-6.
  The mouse pink-eyed dilution (p) locus is known to control eumelanin synthesis, melanosome morphology, and tyrosinase activity in melanocytes. However, it has not been fully determined whether the mutant allele, p affects pheomelanin synthesis. Effects of the p allele on eumelanin and phemelanin synthesis were investigated by chemical analysis of dorsal hairs of 5-week-old mice obtained from the F(2) generations (black, pink-eyed black, recessive yellow, pink-eyed recessive yellow, agouti, and pink-eyed agouti) between C57BL/10JHir (B10)-congenic pink-eyed black mice (B10-p/p) and recessive yellow (B10-Mc1r(e)/Mc1r(e)) or agouti (B10-A/A) mice. The eumelanin content was dramatically (>20-fold) decreased in pink-eyed black and pink-eyed agouti mice, whereas the pheomelanin content did not decrease in pink-eyed black, pink-eyed recessive yellow, or pink-eyed agouti mice compared to the corresponding P/- mice. These results suggest that the pink-eyed dilution allele greatly inhibits eumelanin synthesis, but not pheomelanin synthesis.

- Kawamura-Konishi Y, Maekawa S, Tsuji M, Goto H.
  C-terminal processing of tyrosinase is responsible for activation of Pholiota microspora proenzyme. Appl Microbiol Biotechnol. 2011 Apr;90(1):227-34.
  Tyrosinase is expressed as a 67-kDa protein in Pholiota microspora (synonym Pholiota nameko), whereas the same enzyme purified from fruiting bodies of P. microspora is a 42-kDa protein that is cleaved with a C-terminal 25-kDa polypeptide from the 67-kDa protein. To confirm the role of C-terminal processing in enzyme activity, we expressed a recombinant 67-kDa tyrosinase in Escherichia coli cells. To obtain a soluble protein, the recombinant tyrosinase was expressed as a thioredoxin fusion protein with an enterokinase-cleavable site. Enterokinase digestion of the fusion protein produced a recombinant 67-kDa tyrosinase that did not have any catalytic activity. However, chymotrypsin digestion of the fusion protein produced a recombinant 44-kDa tyrosinase that was catalytically active and had a 25-kDa cleaved C-terminal. Kinetic parameters of the 44-kDa tyrosinase were similar to those of the 42-kDa tyrosinase purified from the fruiting bodies. These results suggest that tyrosinase is expressed in P. microspora as a latent 67-kDa proenzyme and is converted to the mature active 42-kDa enzyme by proteolytic processing of the C-terminal

- Kedlaya R, Kandala G, Liu TF, Maddodi N, Devi S, Setaluri V.
  Interactions between GIPC-APPL and GIPC-TRP1 regulate melanosomal protein trafficking and melanogenesis in human melanocytes. Arch Biochem Biophys. 2011 Apr 15;508(2):227-33.
  By virtue of the presence of multiple protein-protein interaction and signaling domains, PDZ proteins play important roles in assembling protein complexes that participate in diverse cell biological processes. GIPC is a versatile PDZ protein that binds a variety of target proteins in different cell types. In previous studies we showed that, in epidermal melanocytes, GIPC interacts with newly synthesized melanosomal protein TRP1 in the Golgi region and proposed that this interaction may facilitate intracellular trafficking of TRP1. However, since GIPC contains a single PDZ domain and no other known protein interaction motifs, it is not known how GIPC-TRP1 interaction affects melanosome biogenesis and/or melanin pigmentation. Here, we show that in human primary melanocytes GIPC interacts with AKT-binding protein APPL (adaptor protein containing pleckstrin homology, leucine zipper and phosphotyrosine binding domains), which readily co-precipitates with newly synthesized TRP1. Knockdown of either GIPC or APPL inhibits melanogenesis by decreasing tyrosinase protein levels and enzyme activity. In melanocytes, APPL exists in a complex with GIPC and phospho-AKT. Inhibition of AKT phosphorylation using a PI3-kinase inhibitor abolishes this interaction and results in retardation TRP1 in the Golgi. These data suggest that interactions between TRP1-GIPC and GIPC-APPL-AKT provide a potential link between melanogenesis and PI3 kinase signaling.

- Lee JE, Kim SY, Jeong YM, Yun HY, Baek KJ, Kwon NS, Park KC, Kim DS.
The regulatory mechanism of melanogenesis by FTY720, a sphingolipid analogue. Exp Dermatol. 2011 Mar;20(3):237-41.
We previously reported that sphingosine-1-phosphate (S1P) decreases melanin synthesis via extracellular signal-regulated protein kinase (ERK) activation and microphthalmia-associated transcription factor (MITF) degradation. Although FTY720 is an S1P structural analogue, the effects of FTY720 on melanogenesis are not completely understood. Thus, we investigated the influence of FTY720 on melanin synthesis in a spontaneously immortalized mouse melanocyte cell line (Mel-Ab). FTY720 inhibited melanin synthesis in a concentration-dependent manner. Further, FTY720 has a different signal transduction mechanism to regulate melanogenesis from the S1P-induced signalling pathway. Our results showed that FTY720 down-regulated MITF and tyrosinase expression without ERK activation. MITF, the master regulator of pigmentation, is a target for the Wnt signalling pathway, including glycogen synthase kinase 3β (GSK3β) and β-catenin. Thus, the influence of FTY720 on GSK3β and β-catenin was further investigated. Decreased MITF and tyrosinase were associated with a reduction of β-catenin protein and mRNA levels. Decreased β-catenin expression by FTY720 may down-regulate expression of MITF, which finally reduces melanin synthesis.

- Morpurgo G, Babudri N, Fioretti B, Franciolini F, Catacuzzeno L.
Synthetic aromatic compounds interfering with melanogenesis are responsible of the rising trend of malignant melanoma incidence. Med Hypotheses. 2011 Mar;76(3):374-7.
The hypotheses is forwarded that the introduction in the environment of high concentrations of phenols and other aromatic compounds (AC) is one, perhaps the main cause of the continuously rising trend of malignant melanoma (MM) incidence. Two, non-mutually exclusive, possibilities could explain how AC may induce MM: (1) AC may act as inhibitors or alternative substrates of tyrosinase, the enzyme synthesizing melanin, thus impairing the melanocyte photoprotection. (2) AC may impair, directly or indirectly, the activity or synthesis of the melanocorticotropin receptor (MC1R), which photoprotects melanocytes from the UV rays (UVR) by stimulating the DNA repair system. Particularly suspected are sunscreens, as they contain high concentrations of a large variety of AC, three of which are known to be tyrosinase inhibitors. AC that may interfere with tyrosinase are also present in a large variety of medicines used orally or as creams, and in many industrial products with which man is frequently in contact.

- Mu Oz-Mu Oz JL, Garcia-Molina F, Arribas E, Garcia-Ru Z PA, Tudela J, Garcia-C Novas F, Rodr Guez-L Pez JN.
Suicide inactivation of tyrosinase in its action on tetrahydropterines. J Enzyme Inhib Med Chem. 2011 Feb 8.
Tetrahydrobiopterin (BH(4)), methyl-tetrahydropterin (MBH(4)) and dimethyl-tetrahydropterin (DMBH(4)) are oxidized by tyrosinase in a process during which the suicide inactivation of tyrosinase may occur. From the kinetic study of this process, [Formula: see text] (apparent maximum constant for the suicide inactivation), [Formula: see text] (Michaelis constant for the substrate) and r (number of turnovers that the enzyme makes before the inactivation) can be obtained. From the results obtained, it can be deduced that the velocity of the inactivation governed by ([Formula: see text]) and the potency of the same ([Formula: see text]) follow the order: BH(4) > MBH(4) > DMBH(4).

- Nakajima H, Wakabayashi Y, Wakamatsu K, Imokawa G.
An extract of Melia toosendan attenuates endothelin-1-stimulated pigmentation in human epidermal equivalents through the interruption of PKC activity within melanocytes.
Arch Dermatol Res. 2011 Mar 29.
To elucidate the effects of redox balance regulation on epidermal pigmentation, we used an antioxidant-rich extract of the herb Melia toosendan (dried mature fruits) to assess its effect on endothelin-1 (EDN1)-stimulated pigmentation in human epidermal equivalents and analyzed its biological mechanism of action. Addition of the Melia toosendan extract elicited a marked depigmenting effect on EDN1-stimulated pigmentation after 14 days of treatment, which was accompanied by a significant decrease in eumelanin content. Real-time RT-PCR and Western blotting revealed that the EDN1-stimulated expression of melanocyte-specific proteins (including tyrosinase) was significantly suppressed at the gene and protein levels by the extract. Signaling analysis with specific inhibitors and immunoblots revealed that in melanoma cells treated with the extract, there was a marked deficiency in the EDN1-stimulated phosphorylation of Raf-1, MEK, ERK, MITF and CREB. Since all those proteins are downstream phosphorylation targets of PKC activity, these findings indicate that the Melia toosendan extract attenuates the EDN1-stimulated pigmentation by preferentially inhibiting PKC activity within melanocytes.

- Rolff M, Schottenheim J, Decker H, Tuczek F**.**
Copper-O(2) reactivity of tyrosinase models towards external monophenolic substrates: molecular mechanism and comparison with the enzyme. Chem Soc Rev. 2011 Mar 17.
The critical review describes the known dicopper systems mediating the aromatic hydroxylation of monophenolic substrates. Such systems are of interest as structural and functional models of the type 3 copper enzyme tyrosinase, which catalyzes the ortho-hydroxylation of tyrosine to DOPA and the subsequent two-electron oxidation to dopaquinone. Small-molecule systems involving μ-ηÂ²:ηÂ² peroxo, bis-μ-oxo and trans-μ-1,2 peroxo dicopper cores are considered separately. These tyrosinase models are contrasted to copper-dioxygen systems inducing radical reactions, and the different mechanistic pathways are discussed. In addition to considering the stoichiometric conversion of

phenolic substrates, the available catalytic systems are described. The second part of the review deals with tyrosinase. After an introduction on the occurrence and function of tyrosinases, several aspects of the chemical reactivity of this class of enzymes are described. The analogies between the small-molecule and the enzymatic system are considered, and the implications for the reaction pathway of tyrosinase are discussed.

- Sáez-Ayala M, Sánchez-Del-Campo L, Montenegro MF, Chazarra S, Tárraga A, Cabezas-Herrera J, Rodríguez-López JN.
  Comparison of a pair of synthetic tea-catechin-derived epimers: synthesis, antifolate activity, and tyrosinase-mediated activation in melanoma. ChemMedChem. 2011 Mar 7;6(3):440-9.
  Despite bioavailability issues, tea catechins have emerged as promising chemopreventive agents because of their efficacy in various animal models. We synthesized two catechin-derived compounds, 3-O-(3,4,5-trimethoxybenzoyl)-(-)-catechin (TMCG) and 3-O-(3,4,5-trimethoxybenzoyl)-(-)-epicatechin (TMECG), in an attempt to improve the stability and cellular absorption of tea polyphenols. The antiproliferative and pro-apoptotic activities of both compounds were analyzed with various cancer cell systems, and TMCG, which was easily synthesized in excellent yield, was more active than TMECG in both melanoma and non-melanoma cell lines. TMCG was also a better inhibitor of dihydrofolate reductase and was more efficiently oxidized by tyrosinase, potentially explaining the difference in activity between these epimers.

- Tamura K, Ohbayashi N, Ishibashi K, Fukuda M.
  Structure-Function Analysis of VPS9-Ankyrin-repeat Protein (Varp) in the Trafficking of Tyrosinase-related Protein 1 in Melanocytes. J Biol Chem. 2011 Mar 4;286(9):7507-21.
  Because Varp (VPS9-ankyrin-repeat protein)/Ankrd27 specifically binds two small GTPases, Rab32 and Rab38, which redundantly regulate the trafficking of melanogenic enzymes in mammalian epidermal melanocytes, it has recently been implicated in the regulation of trafficking of a melanogenic enzyme tyrosinase-related protein 1 (Tyrp1) to melanosomes. However, the functional interaction between Rab32/38 and Varp and the involvement of the VPS9 domain (i.e. Rab21-GEF domain) in Tyrp1 trafficking have never been elucidated. In this study, we succeeded in identifying critical residues of Rab32/38 and Varp that are critical for the formation of the Rab32/38·Varp complex by performing Ala-based site-directed mutagenesis, and we discovered that a conserved Val residue in the switch II region of Rab32(Val-92) and Rab38(Val-78) is required for Varp binding activity and that its point mutant, Rab38(V78A), does not support Tyrp1 trafficking in Rab32/38-deficient melanocytes. We also identified two critical residues for Rab32/38 binding in the Varp ANKR1 domain and demonstrated that their point mutants, Varp(Q509A) and Varp(Y550A), do not support peripheral melanosomal distribution of Tyrp1 in Varp-deficient cells. Interestingly, the VPS9 domain point mutants, Varp(D310A) and Varp(Y350A), did support Tyrp1 trafficking in Varp-deficient cells, and knockdown of Rab21 had no effect on Tyrp1 distribution. We also found evidence for the functional interaction between a vesicle SNARE VAMP7/TI-VAMP and Varp in Tyrp1 trafficking. These results collectively indicated that both the Rab32/38 binding activity and VAMP7 binding activity of Varp are essential for trafficking of Tyrp1 in melanocytes but that activation of Rab21 by the VPS9 domain is not necessary for Tyrp1 trafficking.

8. Melanosomes

(Pr J. Borovansky)

A charming review full of colour illustrations both for chronic melanosome admirers and newcomers was written by *Delevoye et al.*

The review of *Ghanem and Fabrice* focuses on the human tyrosinase related protein 1 also known as gp75 glycoprotein (Tyrp1/gp75), a melanosomal protein involved in the pigmentary machinery of the melanocyte and often used as a differentiation marker, with a special emphasis on its emerging roles in the malignant melanocyte and melanoma progression.

In a review devoted to the use of the photodynamic therapy /PDT/ in melanoma, *Davids & Kleemann* noticed that pigmented melanomas were much less susceptible to hypericin-PDT than the unpigmented, amelanotic ones. They suggest a model of PDT destruction of melanoma cells. In pigmented melanomas melanosome melanin can neutralize the PDT-derived ROS which leads to cell survival.

Melanosome biogenesis ; proteins involved in it

Hoyle et al suggested functional links between the OCA2 potein and BLOC-1, BLOC-2 and AP3 complexes involved in the biogenesis of melanosomes.

Leonhardt et al addressed the question whether Pmel17 is cleaved into fibrillogenic fragments only in melanosomes or earlier. They demonstrate that the processing of Pmel17 occurs at an early time point prior to plasma membrane exposure, *i.e.* during secretion and that it does not require an entry of the protein into the endocytic system. They conclude that the multistep processing of Pmel17 begins with an early cleavage which primes the protein for a later functional processing.

Lung lamellar bodies, in which surfactant is stored prior to its secretion into the alveolar airspaces, belong among specialized secretory lysosomal related organelles. *Risdale et al* upon proteomic analysis demonstrated that the lamellar bodies shared 37.8% of its proteins with the melanosome but only 9.9% with lamellar bodies from the skin.

McGlinchey et al. report that the repeat domains (RPT) of mouse and zebrafish, as well as a small splice variant of human Pmel17, all form amyloid specifically at mildly acidic pH (pH ~5.0). Protease digestion, mass per unit length measurements, and solid-state NMR experiments suggest that the amyloid of the mouse RPT has an in-register parallel β-sheet architecture with two RPT molecules per layer, similar to the amyloid of the Aβ peptide. Although there is no sequence conservation between the human and zebrafish RPT, the amyloid formation at an acidic pH is conserved.

Melanosome composition and the exploitation of melanosomal constituents

Energy-filtered Analytical Electron Microscopy was used to image the ultrastructure and determine quantitatively the chemical composition of rat melanosomes of the choroid and the retinal pigment epithelium. For the first time, the effect of staining in elemental analysis of melanosomes was investigated. Detection limits and accuracies of the applied methods were determined.

Van den Boorn et al. report a new promising mechanism of inducing robust anti-melanoma immunity by the vitiligo-inducing compound monobenzone. Monobenzone is able to increase melanocyte and melanoma cell immunogenicity by forming quinone-haptens to the tyrosinase protein and by inducing the release of tyrosinase- and melanoma antigen recognized by T cells-1 (MART-1)-containing CD63+ exosomes following melanosome oxidative stress induction. Monobenzone further augments the processing and shedding of melanocyte-differentiation antigens by inducing melanosome autophagy and enhanced tyrosinase ubiquitination, ultimately activating dendritic cells, which induced cytotoxic human melanoma-reactive T cells. These T cells effectively eradicated melanoma in vivo.

Melanosomes in melanocytes under experimental and pathological situations

Ohta et al generated human melanocytes from induced pluripotent stem cells that had been derived from dermal fibroblasts. Eight weeks after differentiation the expression of markers characteristic of the melanocyte lineage was apparent and the cells contained ovoid melanosomes.

When zebrafish were maintained at 17°C, the pigmentation of their pigment stripes was reduced compared with zebrafish at 26.5°C. In cold zebrafish, gene expression levels of the tyrosinase and dopachrome tautomerase, were down-regulated, suggesting that either a down-regulation of the melanin synthesis occurred or the number of melanophores decreased. Both a regular and electron microscopic observation of zebrafish skin showed that the number of melanophores decreased,

whereas aggregation of melanosomes was not changed. *Kulkeaw et al* concluded that the cold exposure down-regulated adult zebrafish pigmentation through decreasing the number of melanophores.

In lesions of progressive macular hypomelanosis /PMH/ the melanin content was reported *by Wu et al* to be decreased compared with the normal skin. S100, TRP-1 and tyrosinase immunostaining showed no differences between the two regions. An EM study revealed a large reduction of mature melanosomes in the PMH lesions: there were many clusters of membrane bound groups of stage II-IV melanosomes. No degradation of melanosomes was demonstrated in the lysosomes of the PMH lesions.

Melanosomes and keratinocytes

Post-transfer modification of pigmented melanosomes provides an attractive and distinct avenue of modulating skin pigmentation. The processing of melanosomes during keratinocyte terminal differentiation and the degradative variability observed between light and dark skin was studied by *Ebanks et al*.: In a a model system they investigated the loss of fluorescently labelled and isolated melanosomes by cultured human KCs. The extent of melanosome loss has been qualitatively assessed using TEM and indirect immunofluorescence with confocal microscopy, and quantitatively assessed using flow cytometry analysis. Melanosomes were incorporated into the cytoplasm of both light and dark keratinocytes (LKCs and DKCs) and trafficked to a perinuclear region. Over a 48-hour time frame, LKCs appeared to lose melanosomes more efficiently than DKCs.

Soy-based products containing serine protease inhibitors may represent a new therapeutic option for dermatological treatment of hyperpigmentation. *Leyden & Wallo* demonstrated that soy-derived serine protease inhibitors affect skin pigmentation by inhibiting protease-activated receptor-2-mediated phagocytosis of melanosomes by keratinocytes.

Using known filopodial markers (MyoX/Cdc42) and the filopodial disrupter, low-dose cytochalasin-B, Singh et al demonstrate a requirement for filopodia in melanosome transfer from melanocytes to keratinocytes and also, unexpectedly, between keratinocytes. They have proposed a new model for the regulation of pigmentation in human skin cells under both constitutive and facultative (post-UVR) conditions, which they call the "filopodial-phagocytosis model."

Other topics concerning melanosomes

The first attempt to identify the anatomical basis of glossiness in feathers has been made by *Maia et al.* Both theoretical and empirical data suggested that it is produced by a simple arrangement of an extremely thin keratin cortex (110-180nm should produce the greatest amount of gloss) over a quasi-ordered layer of melanin granules in barbules. The contribution of melanin layer to glossines was negligible because the size of melanosomes exceeded the 115nm limit.

Xu and Xie studied the function of α- and β-adrenoceptors of zebrafish melanophores. Both α1- and α2-adrenoceptors induced melanosome aggregation in adult zebrafish.

- Biesemeier A, Schraermeyer U, Eibl O.
  Quantitative chemical analysis of ocular melanosomes in stained and non-stained tissues. Micron 2011 Jan 25. [Epub ahead of print]

- Davids LM, Kleemann B.
  Combating melanoma: The use of photodynamic therapy as a novel, adjuvant therapeutic tool. Cancer Treatment Rev. 2010:doi.1016/j.ctrv.2010.11.007

- Delevoye C, Giordano F, van Niel G, Raposo G.
  Biogenesis of melanosomes - The chessboard of pigmentation. /In French/. Med Sci (Paris). 27(2):153-162, 2011.

- Ebanks JP, Koshoffer A, Wickett RR, Schwemberger S, Babcock G, Hakozaki T, Boissy RE.
  Epidermal Keratinocytes from Light vs. Dark Skin Exhibit Differential Degradation of Melanosomes. Journal of Investigative Dermatology , (17 February 2011) doi:10.1038/jid.2011.22

- Ghanem G, Fabrice J.
  Tyrosinase related protein 1 (TYRP1/gp75) in human cutaneous melanoma. Mol Oncol. 2011 Feb 3. [Epub ahead of print]

- Hoyle DJ, Rodriguez-Fernandez IA, Dell'angelica EC.
  Functional interactions between OCA2 and the protein complexes BLOC-1, BLOC-2, and AP-3 inferred from epistatic analyses of mouse coat pigmentation. Pigment Cell Melanoma Res. 24(2):275-281, 2011.

- Kulkeaw K, Ishitani T, Kanemaru T, Ivanovski O, Nakagawa M, Mizuochi C, Horio Y, Sugiyama D.
Cold exposure down-regulates zebrafish pigmentation. Genes Cells. 2011 [Epub ahead of print].

- Leonhardt RM, Vigneron N, Rahner C, Cresswell P.
Proprotein convertase process Pmel17 during secretion. J Biol Chem jbc M110.168088, in press, 2011.

- Leyden J, Wallo W.
The mechanism of action and clinical benefits of soy for the treatment of hyperpigmentation.
Int J Dermatol. 2011 Feb 20. doi: 10.1111/j.1365-4632.2010.04765.x.

- Maia R, D´Alba, L, Shawkey MD.
What makes a feather shine? A nanostructural basis for glossy black colours in feathers. Proc. R. Soc. B doi:10.1098/rspb. 2010, 1637.

- McGlinchey RP, Shewmaker F, Hu KN, McPhie P, Tycko R, Wickner RB.
Repeat Domains of Melanosome Matrix Protein Pmel17 Orthologs Form Amyloid Fibrils at the Acidic Melanosomal pH. J Biol Chem. 286(10):8385-8393, 2011.

- Ohta S, Imaizumi Y, Okada Y, Akamatsu W, Kuwahara R, Ohyama M, Amagai M, Matsuzaki Y, Yamanaka S, Okano H, Kawakami Y.
Generation of human melanocytes from induced pluripotent stem cells. PLos ONE 6(1), e16182, e16182

- Risdale R, Na CL, Xu Y, Kenneth D. Greis KD, Weaver T.
Comparative Proteomic Analysis of Lung Lamellar Bodies and Lysosome-Related Organelles. PLOS ONE 6(1) Article Number: e16482 Published: JAN 26 2011

- Singh, S. K., Kurfurst, R., Nizard, C., Schnebert, S., Perrier, E., Tobin, D. J.
Melanin transfer in human skin cells is mediated by filopodia-a model for homotypic and heterotypic lysosome-related organelle transfer. FASEB J. 24: 3756-3769, 2010..

- van den Boorn JG, Picavet DI, van Swieten PF, van Veen HA, Konijnenberg D, van Veelen PA, van Capel T, de Jong EC, Reits EA, Drijfhout, JW Bos JD, Melief CJM, Luiten RM.
Skin-Depigmenting Agent Monobenzone Induces Potent T-Cell Autoimmunity toward Pigmented Cells by Tyrosinase Haptenation and Melanosome Autophagy. J. Invest Derm. (17 February 2011) | doi:10.1038/jid.2011.16

- Wu XG, Xu AE, Song XZ, Zheng JH, Wang P, Shen H.
Clinical, pathologic and ultrastructural studies of progressive macular hypomelanosis. Int J Dermatol 49(10): 1127-1132, 2010.

- Xu J, Xie F.
α- and β-Adrenoceptors of zebrafish in melanosome movement: A comparative study between embryo and adult melanophores. Biochem Biophys Res Com 11(2): 250-255, 2011.

9. Melanoma experimental, cell culture

(Dr R. Morandini)

Cell senescence is more and more studied in cell culture as a key to understand the indefinitely proliferation of cancer cell and particularly melanoma. Soo *et al*. from the lab of D. Bennett proposed a revised genetic model of melanoma progression. In this model primary melanoma are proposed to be in a peri-crisis than immortal and are assumed to have escaped normal p16/RB-based senescence. Furthermore activation of telomerase is proposed as a late event conferring immortality to the cell line.
Kormos *et al*. describes a new culture technique using a cholera toxin and PMA-free medium (Mel-mix) for obtaining pure melanocytes cultures from human adult epidermis. In addition culture of these melanocytes with human serum as the only growth factor in Mel-mix medium can be suitable for autologous cell transplantation. This medium can serve as a model system to study melanocyte proliferation/differentiation, and melanoma development.
Ohta et al. have published an interesting study about the generation of human melanocytes from Induced Pluripotent Stem Cells (IPS) with the use of "Yamanaka factors" (SOX2, OCT3/4, and KLF4, with or without c-MYC) that critically regulate the developmental signaling network. After addition of Wnt3a, SCF, and ET-3 the cells were differentiated into melanocytes.

A. Signal transduction and cell culture

- Blackiston D, Adams DS, Lemire JM, Lobikin M, Levin M.
  Transmembrane potential of GlyCl-expressing instructor cells induces a neoplastic-like conversion of melanocytes via a serotonergic pathway. Dis Model Mech. 2011 Jan;4(1):67-85.

- Burgess BL, Rao NP, Eskin A, Nelson SF, McCannel TA.
  Characterization of three cell lines derived from fine needle biopsy of choroidal melanoma with metastatic outcome. Mol Vis. 2011 Feb 25;17:607-15.

- Czajkowski R.
  BRAF, HRAS, KRAS, NRAS and CDKN2A genes analysis in cultured melanocytes used for vitiligo treatment. Int J Dermatol. 2011 Feb;50(2):180-3.

- Giricz O, Lauer JL, Fields GB.
  Variability in melanoma metalloproteinase expression profiling. J Biomol Tech. 2010 Dec;21(4):194-204.

- Hu DN, Chen M, Zhang DY, Ye F, McCormick SA, Chan CC.
  Interleukin-1{beta} increases baseline expression and secretion of interleukin-6 by human uveal melanocytes in vitro via p38 MAPK/NF-{kappa}B pathway. Invest Ophthalmol Vis Sci. 2011 Mar 11.

- Kapoor A, Goldberg MS, Cumberland LK, Ratnakumar K, Segura MF, Emanuel PO, Menendez S, Vardabasso C, Leroy G, Vidal CI, Polsky D, Osman I, Garcia BA, Hernando E, Bernstein E.
  The histone variant macroH2A suppresses melanoma progression through regulation of CDK8. Nature. 2010 Dec 23;468(7327):1105-9.

- Kormos B, Belső N, Bebes A, Szabad G, Bacsa S, Széll M, Kemény L, Bata-Csörgő Z.
  In Vitro Dedifferentiation of Melanocytes from Adult Epidermis. PLoS One. 2011 Feb 23;6(2):e17197.

- Kumar R, Parsad D, Kanwar AJ, Kaul D.
  Altered levels of Ets-1 transcription factor and metalloproteinases in melanocytes from vitiligo patients. Br J Dermatol. 2011 Mar 24. doi: 10.1111/j.1365-2133.2011.10324

- Levati L, Ruffini F, Muzi A, Umezawa K, Graziani G, D'Atri S, Lacal PM.
  Placenta growth factor induces melanoma resistance to temozolomide through a mechanism that involves the activation of the transcription factor NF-κB. Int J Oncol. 2011 Jan;38(1):241-7.

- Ohta S, Imaizumi Y, Okada Y, Akamatsu W, Kuwahara R, Ohyama M, Amagai M, Matsuzaki Y, Yamanaka S, Okano H, Kawakami Y.
  Generation of human melanocytes from induced pluripotent stem cells. PLoS One. 2011 Jan 13;6(1):e16182.

- Payton F, Bose R, Alworth WL, Kumar AP, Ghosh R.

4-Methylcatechol-induced oxidative stress induces intrinsic apoptotic pathway in metastatic melanoma cells. Biochem Pharmacol. 2011 Mar 22.

- Steele L, Errington F, Prestwich R, Ilett E, Harrington K, Pandha H, Coffey M, Selby P, Vile R, Melcher A.
Pro-inflammatory cytokine/chemokine production by reovirus treated melanoma cells is PKR/NF-κB mediated and supports innate and adaptive anti-tumour immune priming. Mol Cancer. 2011 Feb 21;10:20.

- Stock C, Jungmann O, Seidler DG.
Decorin and chondroitin-6 sulfate inhibit B16V melanoma cell migration and invasion by cellular acidification. J Cell Physiol. 2010 Dec 28.

- Väisänen A, Kuvaja P, Kallioinen M, Turpeenniemi-Hujanen T.
A prognostic index in skin melanoma through the combination of matrix metalloproteinase-2, Ki67, and p53. Hum Pathol. 2011 Feb 18.

B. Melanin and cell culture

- Beaumont KA, Wong SS, Ainger SA, Liu YY, Patel MP, Millhauser GL, Smith JJ, Alewood PF, Leonard JH, Sturm RA.
Melanocortin MC(1) receptor in human genetics and model systems. Eur J Pharmacol. 2011 Jan 1.

- Enomoto A, Yoshihisa Y, Yamakoshi T, Ur Rehman M, Norisugi O, Hara H, Matsunaga K, Makino T, Nishihira J, Shimizu T.
UV-B radiation induces macrophage migration inhibitory factor-mediated melanogenesis through activation of protease-activated receptor-2 and stem cell factor in keratinocytes. Am J Pathol. 2011 Feb;178(2):679-87.

- Magina S, Esteves-Pinto C, Moura E, Serrão MP, Moura D, Petrosino S, Di Marzo V, Vieira-Coelho MA.
Inhibition of basal and ultraviolet B-induced melanogenesis by cannabinoid CB(1) receptors: a keratinocyte-dependent effect. Arch Dermatol Res. 2011 Apr;303(3):201-10.

C. 3D cell culture and/or skin reconstitution

- Antonicelli F, Lorin J, Kurdykowski S, Gangloff SC, Le Naour R, Sallenave JM, Hornebeck W, Grange F, Bernard P.
CXCL10 reduces melanoma proliferation and invasiveness in vitro and in vivo. Br J Dermatol. 2010 Dec 14.

- Bao W, Chen M, Zhao X, Kumar R, Spinnler C, Thullberg M, Issaeva N, Selivanova G, Strömblad S.
PRIMA-1Met/APR-246 induces wild-type p53-dependent suppression of malignant melanoma tumor growth in 3D culture and in vivo. Cell Cycle. 2011 Jan 15;10(2):301-7. Epub 2011 Jan 15.

- Liu F, Luo XS, Shen HY, Dong JS, Yang J.
Using human hair follicle-derived keratinocytes and melanocytes for constructing pigmented tissue-engineered skin. Skin Res Technol. 2011 Feb 21. doi: 10.1111/j.1600-0846.2011.00510.x.

- Thurber AE, Douglas G, Sturm EC, Zabierowski SE, Smit DJ, Ramakrishnan SN, Hacker E, Leonard JH, Herlyn M, Sturm RA.
Inverse expression states of the BRN2 and MITF transcription factors in melanoma spheres and tumour xenografts regulate the NOTCH pathway. Oncogene. 2011 Feb 28.

D. Other tools and cell culture

- Eves PC, Baran M, Bullett NA, Way L, Haddow D, Neil SM.
Establishing a Transport Protocol for the Delivery of Melanocytes and Keratinocytes for the Treatment of Vitiligo. Tissue Eng Part C Methods. 2010 Dec 7.

- Liu H, Ong SE, Badu-Nkansah K, Schindler J, White FM, Hynes RO.
CUB-domain-containing protein 1 (CDCP1) activates Src to promote melanoma metastasis. Proc Natl Acad Sci U S A. 2011 Jan 25;108(4):1379-84. Epub 2011 Jan 10. PubMed PMID: 21220330;

- Ma X, Piao S, Wang DW, McAfee QW, Nathanson KL, Lum JJ, Li LZ, Amaravadi R.
Measurements of tumor cell autophagy predict invasiveness, resistance to chemotherapy, and survival in melanoma. Clin Cancer Res. 2011 Feb 15.

- Onoue K, Kusubashi H, Sato Y, Wakitani S, Takagi M.
Quantitative correlation between production rate of melanoma inhibitory activity and aggrecan gene expression level during differentiation from mesenchymal stem cells to chondrocytes and redifferentiation of chondrocytes. J Biosci Bioeng. 2011 Jan 27.

- Soo JK, Mackenzie Ross AD, Kallenberg DM, Milagre C, Heung Chong W, Chow J, Hill L, Hoare S, Collinson RS, Hossain M, Nicol Keith W, Marais R, Bennett DC.
Malignancy without immortality? Evidence for cellular immortalization as a late event in melanoma progression. Pigment Cell Melanoma Res. 2011 Mar 21. doi:10.1111/j.1755-148X.2011.00850.

- Stine MJ, Wang CJ, Moriarty WF, Ryu B, Cheong R, Westra WH, Levchenko A, Alani RM.
Integration of Genotypic and Phenotypic Screening Reveals Molecular Mediators of Melanoma-Stromal Interaction. Cancer Res. 2011 Feb 15.

- Trapp V, Parmakhtiar B, Papazian V, Willmott L, Fruehauf JP.
Anti-angiogenic effects of resveratrol mediated by decreased VEGF and increased TSP1 expression in melanoma-endothelial cell co-culture. Angiogenesis. 2010 Dec;13(4):305-15.

- Wang Z, Coleman DJ, Bajaj G, Liang X, Ganguli-Indra G, Indra AK.
RXRα ablation in epidermal keratinocytes enhances UVR-induced DNA damage, apoptosis, and proliferation of keratinocytes and melanocytes. J Invest Dermatol. 2011 Jan;131(1):177-87.

E. Melanoma Experimental

- Ataera H, Hyde E, Price KM, Stoitzner P, Ronchese F.
Murine Melanoma-Infiltrating Dendritic Cells Are Defective in Antigen Presenting Function Regardless of the Presence of CD4CD25 Regulatory T Cells. PLoS One. 2011 Mar 3;6(3):e17515.

- Dudley ME, Gross CA, Langhan MM, Garcia MR, Sherry RM, Yang JC, Phan GQ, Kammula US, Hughes MS, Citrin DE, Restifo NP, Wunderlich JR, Prieto PA, Hong JJ, Langan RC, Zlott DA, Morton KE, White DE, Laurencot CM, Rosenberg SA.
CD8+ enriched "young" tumor infiltrating lymphocytes can mediate regression of metastatic melanoma. Clin Cancer Res. 2010 Dec 15;16(24):6122-31. Epub 2010 Jul 28. PubMed PMID: 20668005;

- Garcia-Uribe A, Smith EB, Zou J, Duvic M, Prieto V, Wang LV.
In-vivo characterization of optical properties of pigmented skin lesions including melanoma using oblique incidence diffuse reflectance spectrometry. J Biomed Opt. 2011 Mar-Apr;16(2):020501. PubMed PMID: 21361657

- Meyskens FL, Yang S.
Thinking about the role (largely ignored) of heavy metals in cancer prevention: hexavalent chromium and melanoma as a case in point. Recent Results Cancer Res. 2011;188:65-74.

- Mikesh LM, Kumar M, Erdag G, Hogan KT, Molhoek KR, Mayo MW, Slingluff CL Jr.
Evaluation of molecular markers of mesenchymal phenotype in melanoma. Melanoma Res. 2010 Dec;20(6):485-95.

- Miller AK, Dusing R, Meggison A, Aires D.
Regression of internal melanoma metastases following application of topical imiquimod to overlying skin. J Drugs Dermatol. 2011 Mar 1;10(3):302-5.

- de Ridder GG, Gonzalez-Gronow M, Ray R, Pizzo SV.
Autoantibodies against cell surface GRP78 promote tumor growth in a murine model of melanoma. Melanoma Res. 2010 Dec 15.

- Tseng JR, Stuart D, Aardalen K, Kaplan A, Aziz N, Hughes NP, Gambhir SS.
Use of DNA Microarray and Small Animal Positron Emission Tomography in Preclinical Drug Evaluation of RAF265, a Novel B-Raf/VEGFR-2 Inhibitor. Neoplasia. 2011 Mar;13(3):266-75. PubMed PMID: 21390189.

ANNOUNCEMENTS & RELATED ACTIVITIES

Calendar of events

Calendar of Events

2011 Large Congenital Melanocytic Nevi / Neurocutaneous Melanocytosis
May 6–7, Tübingen, Germany
Contact: E-mail: hans-martin.haefner@med.uni-tuebingen.de
Web: www.hautklinik-tuebingen.de/fortbildungen/index.htm

2011 7th EADO Congress European Association of Dermato-Oncology
June, 20-23 Nantes, France
Contact: Web: http://www.eado2011.com/

2011 41st Annual ESDR Meeting
September, 7-10 Barcelona, Spain
Contact: Web: www.esdr.org

2011 Perspectives in Melanoma XV
September, 16-17 New York, USA
Chairs: JM Kirkwood and AMM Eggermont
Contact: Web: imedex.com/AppWeb/announcements/a260-01.asp

2011 XXIth IPCC
September, 21-24, Bordeaux, France
Contact: Pr Alain TAÏEB
Web: www.ipcc2011.org

2011 20th European Academy of Dermatology and Venereology Congress (EADV)
October 20-24, Lisbon, Portugal
Contact: Web: http://eadvlisbon2011.org/event/eadv-2011/

2012 XVIIth Meeting of the ESPCR
September, Geneva, Switzerland
Contact: Dr Bernhard WEHRLE-HALLER

2012 42nd Annual ESDR Meeting

September 19-22, Venice, Italy
Contact: Web: www.esdr.org

2013 International Investigative Dermatology

May 8-11, Edinburgh, Scotland
Contact: Web: www.esdr.org

2013 8th World Congress of Melanoma

July 18–20, Hamburg, Germany
Contact: 8th World Congress of Melanoma
E-mail: congress@worldmelanoma2013.com
Web: www.worldmelanoma2013.com