N° 60 Apr 2008

E S P C R B U L L E T I N

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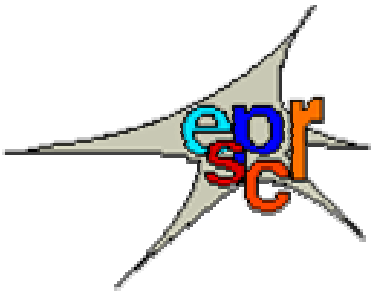

EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH

BULLETIN

N° 60 - Apr 2008

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DISCUSSION, REVIEW,
SHORT COMMUNICATION, ...

Letter from ESPCR President

Dear Friends,

This is the first 2008 Issue and I wish you a great and fruitful year.

I would like to welcome all new members and to thank all those who, continuing supporting the ESPCR with their membership, contribute in keeping our Society active and productive.
The Society is healthy and its popularity is growing year after year, receiving recognitions from the scientific world for the research work carried on and for our valuable members.
It was very nice seeing you all in Bari for our Annual meeting. The conference was success, with a very high scientific standard and with the participation of outstanding colleagues.

The XXth IPCC will take place in may this year and for the first time together with the Vth International Melanoma Research Congress. The willingness of Pigmentary and Melanoma Societies to develop and reinforce their link, has also taken to changing the title of Pigment Cell Research to *Pigment Cell & Melanoma Research*, which means a greater involvement of the Journal in Melanoma researches, but the ESPCR must remain committed to supporting and promoting the journal.

With regard to PCMR, I would like to thank Colin Goding who is going to finish his mandate as Editor-in-Chief of the Journal. He has done an excellent work, contributing to maintain and develop the high standard of the Journal. The Society has also decided to offer one year free subscription to 2007 New ESPCR Students Members and to Non-Members authors/reviewers most cited in PCMR; this will contribute in expanding the popularity of PCMR and of the Society.

I am also glad to inform you that the ESPCR Special Interest Group on Vitiligo (VETF) is developing valuable projects and partnership, and it will organize a Workshop on Vitiligo within the next IPCC meeting in Sapporo.
I take the chance to remind that, within the ESPCR, the organization of small interest groups focused on specific topics is welcome, as it underlines the Society's commitment to develop the cooperation and the active participation of their members, also contributing to spread the name of the Society internationally.

A great challenge will be the XXIst IPCC which will be held in Europe in 2011. Bordeaux and Florence are the possible locations and shortly will be taken a decision to chose one.
With regard to future events, considering the great success of the ESPCR Satellite Symposium at the last ESDR meeting in Zurich, I am in contact with the Scientific Committee of the 2009 ESDR Meeting in Budapest to repeat the experience, and this will surely expand the International interest in the Society. Finally, I would just like to remind you that the 2009 ESPCR meeting will be organized in Münster.

Last but not least, let me thank Dr Lionel Larue and Prof Jo Lambert, ESPCR Secretary and Treasurer respectively, who have been excellent and dedicated in assisting the Society.

I hope to see the most of you in Sapporo

Best wishes
Mauro Picardo

MINUTES OF THE ESPCR COUNCIL MEETING

Sunday October 14th 2007, 12:00
Bari, Sheraton Hotel

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1. Opening of the Meeting
2. Apologies for absence
3. Minutes of the 2006 of the 1st and 2nd Council Meetings in Barcelona
4. President's Report on the status of the Society
5. Secretary's Report and matters arising
6. Treasurer's Report
7. Honorary and supporting members
8. ESPCR Bulletin and Web site report
9. ESPCR travel award committee report and related matters
10. Matters concerning the IFPCS
11. Matters concerning PCR – PCMR
12. Matters concerning the Bari meeting
13. Venues for forthcoming IFPCS and ESPCR Meetings
14. Any other business
15. Close of the Meeting

1. Opening of the Meeting

M. Picardo, President of ESPCR, opened the meeting.

The president welcomed the Council members: Anja Bosserhoff, Jose Carlos Garcia-Borron, Colin Goding, Ghanem Ghanem, Lionel Larue, Lluis Montoliu, Alessandra Napolitano, and Alain Taieb.

The president also welcomed the following invited personalities: Zalfa Abdel-Malek as President of IFPCS. Rosa Cicero as organizer of the 2007 Bari meeting, and Markus Böhm as organizer of the 2009 Münster meeting.

2. Apologies for absence

Apologies for absence were received from J. Lambert, M. Seabra and F. Beermann. The Council accepted them.

3. Minutes of the 2006 of the 1st and 2nd Council Meetings in Barcelona

The Minutes of the 1st and 2nd Council Meetings in Bari were approved without amendments and signed by the President.

4. President's Report

Status of the Society
The legal status of the Society was discussed. As of today, the ESPCR is not legally registered, because the original register in Italy is no longer valid.

The main decisions taken and voted unanimously were the following:

1) The ESPCR society will be moved to Brussels (Belgium).
2) The ESPCR society new status will be registered officially as an International non-profitable association.
3) The ESPCR will have a stable address. This address will be the one of an ESPCR member.
4) The ESPCR bank account will be in Belgium.

The new status will have to be in French and Flemish (Belgium law). They will be officially translated in English. The new status will be written first in English by Ghanem Ghanem (our current ESPCR Belgium contact). This status will be transmitted by the secretary to the members of the council for amendments. Discussion by email will go on until full agreement. Status will then officially be deposited by Ghanem Ghanem. The new constitution and status of ESPCR will be sent to all ESPCR members.
The establishment of the new status of the society should cost 2,000 euros. Thereafter it should cost 2,000 euros per year. Potential financial problem may raise due to this overcost. The current real income is about 6000-7000 euros per year, it means that about 30% of our income will be spent without any direct benefit for the Society. In the future we may think of increasing the member subscriptions (JCGB) or find sponsor for the Fritz Anders lecture (ZAM).
The bank will be the Forty's bank. It should cost 30 euros/year.

ESPCR workshop at the Zürich ESDR 2007 meeting
An ESPCR workshop was organized during the ESDR meeting in Zürich. The topic was based on UV and four lectures were given (Goding, Böhm, Galibert and Bellei). The talks were excellent. Unfortunately, the allocated room was too small. ESDR members and councils very well appreciated this ESPCR workshop. This experience will be renewed next year in Kyoto.
A topic has to be chosen and speakers designated.

5. Secretary's Report and matters arising

a) Meeting reports
- 2006 ESPCR Meeting report: The reports were sent to the secretary. After proper formatting the reports, it was send to Ghanem Ghanem (Web master – Bulletin of ESPCR).
- 2007 ESPCR Meeting report: The chairmen and chairwomen were asked to provide a report of their session for the bulletin. Due date November 15th, 2007.

b) Awards for 2008 IPCC
Myron Gordon Award: the ESPCR Council proposed three names. An internal council election has to be performed to design the ESPCR candidate. The final decision will be communicated by the secretary in due time to the IFPCS President, to be forwarded to the IFPCS Awards Committee.
Seiji Memorial Lecturer: the ESPCR Council proposed three names. An internal council election has to be performed to design the ESPCR candidates. The final decision will be communicated by the secretary in due time to the IFPCS President, to be forwarded to the IFPCS Awards Committee.
Takeuchi Medal: the ESPCR Council proposed three names. An internal council election has to be performed to design the ESPCR candidates. The final decision will be proposed by the secretary in due time to the JSPCR Awards Committee.
H.S. Raper Medal: Three names will be proposed by the ESPCR Council to the ESPCR award committee (Hans Rorsmann, as President of the committee, Alessandra Napolitano and Lionel Larue).

c) Officer elections
The officer election will occur in 2008 and the new officers will start their mission in 2009 after the Münster meeting.

d) Council elections

No new election occurred in 2007. The next election will be performed in 2008.

The ESPCR Council members remain Anja Bosserhoff, Jose Carlos Garcia-Borron as ex officio, Colin Goding, Ghanem Ghanem as non-voting permanent (Web site), Jo Lambert as Treasurer, Lionel Larue as Secretary, Lluis Montoliu, Alessandra Napolitano, Mauro Picardo as President, Miguel Seabra and Alain Taieb

The Council approved the report, and the President thanked the secretary for his work.

6. Treasurer's Report

Lionel Larue in the name of Jo Lambert performed the treasurer report.

- Statistics

The number of members in the ESPCR Web site list is 202. However, the actual number of members is 111 (8 honorary members, 88 regular members, 15 student members). We have 34 new members (6 students and 28 regulars).

This means that we decrease the number of members (111 for 122). We observe a high turn over of student but also regular members.

- Finances

The finances are good over the year. For the 2007-year, we have a positive balance of 2,353 euros. On the account, we have a general positive balance of 7,500 euros.

The following report of incomes and outgoings (in Euros) during this 2007-year was reported.

Financial report 2007 – ESPCR	in EURO
Number of members on 10/2007	111
Members who paid subscription up to 10/2006:	111
Regular members	88
Student members	15
Honorary members	8
View on new members in 2007:	34
Regular members	28
Student members	6
Income 10/2006-10/2007	
Member subscriptions 2007	6,605
Pigment Cell Research subscriptions	4,605
Donations by members	70
Total income	11,280 EURO
Outgoings 10/2006-10/2007 (1 USD = 0.72 EURO)	

International Federation of Pigment Cell Societies	
Member dues for 2007:	
88 x 28 USD = 2464 USD	(1,774.00)
Bank charges Centea	(215.80)
ESPCR Travel Awards at Bari meeting	(1,500.00)
Fritz Anders Lecture	(1,500.00)
Pigment Cell Research Subscriptions:	
41 x 128 USD = 4736 USD	(3,410.00)
Credit card machine (running budget)	(527.20)
Total outgoings	(8927.00) EURO

Balance on 08 October 2007 2353 EURO

This is an approximate amount, pending minor adjustments due to bank charges and exchange rates.

PS: The account balance on October, 2007 – after payment of all costs will be on approximately 7500 EURO = amount that was saved the last years

Member statistics

	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Members				106	113	121	99	121	122	111
Regular				97	99	106	89	91	92	88
Student				9	9	15	10	22	22	15
Honorary				6	6	8	8	8	8	8
New members	16	18	18	18	19	15	20	36	38	34
Regular				14	13	10	16	22	26	28
Student				4	6	5	4	14	12	6
Resignations					6	4	13			
Out people					12	7	12			

The Council approved the report, and the President thanked Jo Lambert for her work.

7. Honorary and supporting members

Two new honorary members were nominated: Roger Bowers and Yvon Gauthier.

A new category of members was created: Supporting member. A supporting member is a member bringing its full support in a non-scientific manner. The council meeting after proposal of one nominates the supporting member. Two new supporting members were nominated: Maxime Whitton and Alida de Pase.

8. ESPCR Bulletin and Web site report

The ESPCR Web Master G. Ghanem and Lluis Montoluis reported this.
- Web site: G. Ghanem reported that the Web site has been regularly updated and improved. L. Montoliu reported the creation of a new address for the web site: www.espcr.org

- Email addresses. Lluis Montoliu reported the creation of a series of email addresses to communicate between various members of the society: members@espcr.org, council_list@espcr.org, treasurer@espcr.org, secretary@espcr.org, president@espcr.org.
- ESPCR list: Everything is going smoothly
- Bulletin: Everything is going smoothly
The Council approved the report, and the President thanked G. Ghanem and Lluis Montoliu for their work.

9. ESPCR travel award committee report and related matters

L. Larue reported for F. Beermann to inform on the activity of the Visiting Scientist and Travel Awards Committee (composed of Beermann, Larue and Smit).
- Visiting scientist award. No grant was available from IFPCS. The information concerning the visiting scientist award will be removed from the ESPCR web site.
- Three applications of good quality from PhD students were received for the deadline of June 1st 2007. This deadline was set due to the general rules (8 weeks before end of early registration, i.e. July 31st for Bari). The deadline was extended to June 15th and finally to July1st, without any further application arriving. This is in contrast to the past years where we had always more than 10 applicants. One thousand five hundred euros was allocated for the travel awards this year. The three awardees [Laurence Denat (Orsay, France), Agatha Kokot (Münster, Germany), Karine Schouwey (Lausanne, Suisse)] received 500 Euro.
The travel awards will be advertised in the Bulletin.
The travel awards committee will have the same composition until 2009.
The Council approved the report, and the President thanked the member of the travel award committee.

10. Matters concerning the IFPCS

A new situation will link IFPCS and the publisher of the journal of IFPCS.
Two executive editors are now appointed one for the Pigment Cell side (Shosuke Ito) and one for the Melanoma side (Ze'ev Ronai). Editorial boards of the melanoma and Pigment cell side were created.
The Editor-in-Chief (Colin Goding) remains in function.
The contract between IFPCS and Blackwell will be signed in the last 2007 trimester.
The ESPCR President thanked Zalfa Abdel-Malek and Jose-Carlos Garcia-Borron.

11. Matters concerning PCR - PCMR

The impact factor (IF) of PCR for 2007 is 3.2. On January 1st, PCR will change its name to PCMR (Pigment Cell and Melanoma Research). The calculation of the IF for PCMR will be based on the result of PCR for the new first years of existence.
A committee was designated to choose the new Editor-in-chief. It is composed of Colin Goding (actual Editor-in-Chief), Shosuke Ito and Ze'ev Ronai (two executive editors), Zalfa Abdel-Malek (IFPCS President), Vince Hearing, Dot Bennett, David Fisher, Meenhard Herlyn and Jürgen Becker. In agreement with the publisher, the name of the new Editor-in-Chief will be announced in Sapporo in 2008.
ESPCR has 30 free subscriptions for PCR/PCMR. The goal of these subscriptions is to develop our Society and to use the journal as a mirror of our activities. The priority of the beneficial members was discussed. (i) Persons writing a review for PCR/PCMR which is not an ESPCR member, (ii) Persons publishing an interesting article in any journal, the other priorities were kept.
The ESPCR President thanked Colin Goding.

12. Matters concerning the Bari meeting

171 persons registered to the 2007 ESPCR meeting. The budget is even. The last two ESPCR meetings had more attendees 252 in 2006 (the highest number of attendees) and 210 in 2004 (the second number of attendees). We hope the low number of attendees is just an accident.
The entire board thanked Rosa Cicero for her work.

13. Venues for forthcoming IFPCS and ESPCR Meetings

The venue of the IPCC Meeting, 2008, will be held in Sapporo, Japan, organized by K. Jimbow.
The venue of the 2009 XVth ESPCR Meeting is Münster, organized by Markus Böhm. It will be from the 20-23th of September 2009.
For 2010, a possibility was considered. Organizer: Robert Kelsh, Location: Bath, UK. This issue has now being solved before the Sapporo meeting.
For 2011, ESPCR has to organize IFPCS meeting. Two serious options were considered, one in Firenze (Italy) and the other one in Bordeaux (France). The council committee will take a final decision during the last trimester of 2007 according financial information coming from the University of Firenze.
For 2012, an option for Rennes (France) was considered.

14. Any other business

None

15. Close of the Meeting

With no other matters to discuss, the meeting was closed by Mauro Picardo.

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MINUTES OF THE ESPCR
GENERAL ASSEMBLY MEETING

Tuesday October 16th 2007, 18:45
Bari, Sheraton Hotel

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1. Opening of the Meeting

M. Picardo, President of ESPCR, who welcomed all ESPCR members, opened the meeting

2. Minutes of the 2006 of the ESPCR general assembly in Barcelona

The Minutes of the General assembly Meeting in Barcelona were published in December 2006 ESPCR bulletin, issue number 56. The Minutes of the ESPCR General Assembly in Barcelona were unanimously approved.

3. President's Report

Status of the Society
It was reported that (1) The ESPCR society new status will be registered officially as an International non-profitable association. (2) The ESPCR society already has a stable address in Brussels (Belgium), so the society will be registered in Belgium. (3) The ESPCR bank account will be in Belgium at the Forty Bank.

ESPCR workshop at the Zürich ESDR 2007 meeting
An ESPCR workshop was organized during the ESDR meeting in Zürich. The topic was based on UV and four lectures were given (Goding, Böhm, Galibert and Bellei). The talks were excellent. Unfortunately, the allocated room was too small. ESDR members and councils very well appreciated this ESPCR workshop. This experience will be renewed at the 2009 ESDR Meeting in Budapest.

4. Secretary's Report

a) Meeting reports
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b) Awards for 2008 IPCC

A series of nomination by the council meeting will be performed for the Myron Gordon Award, the Seiji Memorial Lecturer, the Takeuchi Medal and the H.S. Raper Medal. The ESPCR award committee (Rorsmann, Napolitano and Larue) will designate the awardees among the names given by the different Societies.

c) Officer elections

The officer election will occur in 2008 and the new officers will start their mission in 2009 after the Münster meeting.

d) Council elections

No new election occurred in 2007. The next election will be performed in 2008.

The ESPCR Council members remain Anja Bosserhoff, Jose Carlos Garcia-Borron as ex officio, Colin Goding, Ghanem Ghanem as non-voting permanent (Web site), Jo Lambert as Treasurer, Lionel Larue as Secretary, Lluis Montoliu, Alessandra Napolitano, Mauro Picardo as President, Miguel Seabra and Alain Taieb.

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- Email addresses. Lluis Montoliu reported the creation of a series of email addresses to communicate between various members of the society.
- ESPCR list: Everything is going smoothly
- Bulletin: Everything is going smoothly
Lluis Montoliu also reported about the possibility of having a Secure address for fees' payment with credit card through the Society web site. This Council approved and Lluis Montoliu will dela with this.

9. Venues for forthcoming IFPCS and ESPCR Meetings

The venue of the IPCC Meeting, 2008, will be held in Sapporo, Japan, organized by K. Jimbow.
The venue of the 2009 XVth ESPCR Meeting is Münster, organized by Markus Böhm. It will be from the 20-23th of September 2009.
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For 2011, ESPCR has to organize IFPCS meeting. Two serious options were considered, one in Firenze (Italy) and the other one in Bordeaux (France). The council committee will take a final decision during the last trimester of 2007 according financial information coming from the University of Firenze. It was proposed by Dot Bennett that IPCC and SMR meetings occur at the same time at the same place. Mauro Picardo will contact the President of SMR to ask if SMR would like to have a joint meeting and he will check if the location of the venue may deal an extra 400 persons.
For 2012, an option for Rennes (France) was considered.

10. Any other business

Organize other work task beside the vitiligo task work.

11. Close of the Meeting

With no other matters to discuss, Mauro Picardo closed the meeting at 19:45.

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CURRENT LITERATURE

1. Chemistry of Melanins and other Pigments

(Pr A. Napolitano)

Preparation of melanin-like materials with high solubility in organic solvents was obtained by oxidative polymerization of lipophilic analogues of the melanin precursor 5,6-dihydroxyindole-2-carboxylic acid. The solubility properties of these materials allowed to follow the polymerization process by spectroscopic techniques such as UV, fluorescence and NMR, confirming the involvement of the 4 and 7 position of the indole nucleus in the polymer formation. (Lawrie *et al Photochem. Photobiol.* 2008) Most interestingly, the UV spectrum of such soluble materials looked very similar to that of natural melanins.

A cooperative study of the Simon's and Sarna's groups on a synthetic pheomelanin from dopa and cysteine (Ye *et al. Photochem. Photobiol.* 2008) provided a further insight into this still poorly characterized pigment. The electron paramagnetic resonance oximetry measurements showed a peak of oxygen uptake between 338 and 323 nm, with a local enhancement around 370 nm. Pump-probe absorption spectroscopy revealed that UVA light photoexcitation generates a transient absorption peak in the visible and UV regions. However careful comparison of the maximum of the action spectrum derived from the transient data, the emission excitation spectrum and the action spectrum for photoconsumption revealed significant differences suggesting the presence of different molecular species with similar chromophores.

The search for efficient skin depigmenting agents is growing to an impressive pace. Many of the active extracts and formulations reported in this period derive from Chinese traditional medicine, thus the active principles remain in most cases to be identified. Among these, extracts from Bamboo (Song *et al*, *Yakhak Hoechi* , 2007) from Radix Polygoni multiflori, (Guan *et al. J. Enz. Inh. Med. Chem*, 2008), and from Nigella glandulifera Freyn (Nguyen *et al J Microbiol Biotechnol.*, 2007). The tyrosinase inhibitory activity of the prenylated flavonoid found in the ethanolic extracts of Sophora flavescens was further investigated and kurarinol , kuraridinol, and trifolirhizin were found to be more potent than the reference depigmenting agent kojic acid. (Hyun *et al Biol Pharm Bull.*, 2008)

Among the innovative methodologies for melanin analysis in biological samples is the use of EPR for non-invasive in vivo mapping of melanomas. (Vanea *et al NMR Biomed.,* 2008)

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Bee venom stimulates human melanocyte proliferation, melanogenesis, dendricity and migration. Exp Mol Med. 39(5):603-13, 2007.

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2. Biology of pigment cells and pigmentary disorders

(Dr M. Picardo)

Cutaneous pigmentation is the major photoprotective mechanism against the carcinogenic and aging effects of UV, then it is important to elucidate how epidermal melanocytes respond to UV. α-MSH hormone is a key physiological regulator of human pigmentation, through its binding to the melanocortin receptor type I (MC1R) on melanocytes and the activation of the cAMP pathway. The review by **Abdel-Malek *et al*** summarized the effects of melanocortins on UV response of human melanocytes. Activation of functional MC1R by α-MSH results in the stimulation of melanogenesis and in the inhibition of UV-induced apoptosis. Moreover, melanocortins reduce oxidative stress, enhance repair of UV-induced DNA damage, independently of pigmentation, and restore genomic stability. The authors also reported the use of potent melanocortin analogs able to stimulate melanogenesis and to mimic α-MSH in enhancing nucleotide excision repair and in inhibiting hydrogen peroxide generation and apoptosis in UV-irradiated human melanocytes. The strategy of developing potent α-MSH analogs is expected to be effective in melanoma prevention, particularly in individuals who express *MC1R* genotypes that reduce but not abolish MC1R function or mutations in other melanoma susceptibility genes, such as p16.

A good deal of information has been gathered on the commonest genetic and epigenetic alterations found in human sporadic melanoma. **Bennett** proposes an exhaustive review on our current understanding of the key clonally heritable changes required to convert a normal melanocytes to a VGP or invasive melanoma cell. All the commonest affected genes encoded regulatory components implicated in the control of cell proliferation, apoptosis, and cell behaviour or cell senescence. Together, the data support a model in which, genesis of melanoma, requires changes that induce clonal expansion, overcome melanocyte senescence and suppress apoptosis. The patterns and molecular mechanisms that come out could help to select the most critical therapeutic targets and diagnostic markers.

The melanogenic process takes place in melanocytes within lysosomes-related vesicles named melanosomes which are transported to the dendrite tips and transferred to surrounding keratinocytes to ensure hair and skin pigmentation. In humans, α-MSH is a key physiological regulator of melanocyte differentiation and skin pigmentation through its binding to the melanocortin receptor type I and the activation of the cAMP pathway. In melanocytes the effects of cAMP on melanin synthesis are mediated by Microphthalmia associated transcription factor (MITF) that is the master gene of melanocyte development, differentiation and survival. Until now MITF has been demonstrated to control the expression of tyrosinase, tyrosinase-related protein 1 and dopachrome tautomerase, the enzymes essential for melanin production. In this report, **Chiaverini *et al*** demonstrated that MITF also regulates the peripheral distribution of melanosomes to the dendrites tips via the control of Rab27 expression. The authors identified *RAB27A* as a new MITF target gene and showed that MITF directly binds to the Rab27 promoter thereby increasing its activity. Moreover, re-expression of Rab27, in MITF depleted cells, restores the peripheral melanosome transport. Taken together, these results demonstrated the involvement of MITF in the actin-dependent melanosome transport which is, with melanin synthesis, another key parameter of melanocyte differentiation and skin pigmentation.

Cutaneous melanoma is often resistant to chemo- and radiotherapy. Recently, it has been found that activating transcription factor 2 (ATF-2) is responsible, at least in part, for this resistance. Retinoids (RA) have been shown to inhibit proliferation and to induce differentiation in a variety of cancer cell lines and tumor xenografts. Moreover, some mouse and human melanoma cell lines are sensitive to the growth inhibitory and pro-differentiating effects of RA. **Huang *et al*** demonstrated that ATF-2 is expressed at higher level in B16 melanoma cells when compared with an immortalized but non-malignant mouse melanocyte cell line. In addition, a much greater amount of phosphorylated ATF-2 protein (active) was found in B16 cells, compared with the non-malignant ones. Furthermore, the authors reported that RA treatment of B16 cells decreased ATF-2 phosphorylation, likely through the inhibition of p38 MAP kinase activation and that the inhibition of ATF-2 phosphorylation correlated with the ability of RA to sensitize the B16 melanoma cells to the growth inhibitory activity of the cancer chemotherapeutic agent taxol.

Cutaneous melanoma is one of the most aggressive tumours and displays remarkable resistance to all conventional cancer therapies. The review by **Lopez-Bergami et al.** deals with the major signalling pathways currently known to be deregulated in melanoma, that affect growth control, metabolism, motility and the ability to escape cell death programs, with an implication to its development and progression. Among these, there are Ras, B-Raf, MEK, PTEN, PI3Ks and AKT constitutively activated in a significant number of tumours. The knowledge of molecular basis of this pathology offers a unique opportunity for targeting drug development.

Tyrosinase-related protein 2 (TRP-2) plays a key role in regulating eu-melanin synthesis, moreover this protein is able to counteract oxidative stress and consequently to improve the resistance to anti-tumour drugs, such as cisplatin, carboblatin and metatrexate. TRP-2 expression was shown to be uncoupled to that of Tyrosinase (Tyr) and Tyrosinase-related protein 1 (TRP-1) and to dramatically decline in senescent melanocytes, whereas Tyr and TRP-1 levels remained unaltered. **Michard et al.** investigated TRP-2 contribution against oxidative stress in two different melanoma cell lines. The authors showed for the first time that TRP-2 expression was beneficial to the cell lines exposed to oxidative stress. Among the benefits related to its expression, the authors described an increase in GSH level, a reduction in DNA damage and a diminution in overall sensitivity to H_2O_2 and paraquat. They concluded that, because of oxidative stress is strictly connected to ageing and age-associated diseases, TRP-2 expression *in vivo* may therefore provide melanocytes with beneficial protective effects against these events.

Induction of antioxidant and/or phase 2 detoxifying enzymes is a major cellular strategy aiming at increasing the protection against harmful reactive oxygen species generated either by endogenous metabolism or by environmental stress. Several studies have demonstrated that a specific transcription factor, nuclear factor erythroid 2-related factor 2 (Nrf2), is involved in the regulation of the basal expression as well as in the induction of these enzymes. While the roles of Nrf2 and phase 2 genes in chemoprevention of carcinogenesis have been well described, only few studies have dealt with their role in human skin cells. **Marrot *et al*** investigated the effects of some chemical inducers of Nrf2 pathway, as well as solar UV or UVA alone on the phase 2 detoxifying enzymes in NHK and NHK. They observed that expression of most of phase 2 genes studied was significantly modulated, but there were clear differences between NHK and NHM. This was the first study comparing phase 2 gene modulation in NHK and NHM and the results presented suggested that Nrf2 is involved in pathways of the human skin adaptation to environmental stress.

Catalase is an homotetrameric enzyme catalysing the disproportionation of hydrogen peroxide to molecular oxygen and water. For full activity this enzyme functions as a homotetrameric structure with the monomer having no activity. To maintain fully active catalase, NADPH must form a stable complex in its specific binding domain of each subunit. In the past **Schallreuter et al.** had demonstrated that vitiligo patients have low catalase levels/activities in both their lesional and non-lesional epidermis, and that lesional skin accumulated H_2O_2 at mM concentrations. Along with this line, it was also suspected that catalase in patients with vitiligo possesses an increased sensitivity to this reactive oxygen species, and indeed single nucleotide polymorphisms was documented in the catalase gene of these patients. In a recent work, based on 3D structure of human catalase monomer, the same research group has modelled the influence of three selected single nucleotide polymorphisms on the enzyme active site, on the NADPH- as well as the tetramerization-binding domains. Obtained results have shown that these genetic polymorphisms severely alter catalase, both structurally and functionally, making it more susceptible to the deleterious effects of free radicals.

Melanomagenesis and progression are commonly described as de-differentiation processes of transformed, mature melanocytes, enabling the stepwise metamorphosis from nevus to radial growth phase and vertical growth phase melanoma and, lastly, to disseminated disease. Strikingly, the majority of melanomas emerge in normal appearing skin or in unexpected sites along the neural crest migratory route, not in displastic nevi. Based on these observations and recent findings of melanoma heterogeneity and plasticity, an alternative hypothesis has been put forth in light of the cancer stem cell concept, suggesting mutated melanocyte stem cells or immature progenitor cells present in skin as precursors to melanoma. In accord to this latter hypothesis **Schatton and Frank** propose an exhaustive review, supporting, on this basis, the high degree of therapy resistance, invasiveness and neoplastic progression of the tumour. The authors conclude asserting that the identification and molecular characterization of melanoma stem cell subsets (MMSC) could lead to the development of improved biomarkers for diagnosis, disease staging and clinical management of melanoma. Moreover, if MMSC populations are indeed associated with chemo-resistance and malignant progression in human patients, specific targeting of MMSC via a molecular marker could provide more potent and selective means for melanoma therapy.

Tyrosinase is the first and rate-limiting enzyme in the synthesis of melanin responsible for colouring hair, skin and eyes. Mutation of tyrosinase often decreases melanin production resulting in albinism, but the effects are not always understood at molecular level. The structural basis of tyrosinase catalysis and loss of function in albinism is only partially understood. However, based on the first, recently published structure of tyrosinase, the influence of some mutations in mammalian tyrosinase can now be interpreted at molecular level using homology modelled structures. To test this methodology, **Schweikardt et al.** have generated tyrosinase mutants with the potential to impair the enzymatic activity by interfering with the packing of amino acid side chain located at the active site, and they have interpreted the behaviour of the mutant enzymes on the basis of homology modelled structure. The authors also used the modelled structure to analyse the molecular basis of loss of function in two known natural albino mutations. The ability of the model to account for the properties of both the artificial and natural mutants supports its accuracy and its general use for analysis of the structural and functional effects of active site mutations.

Solar ultraviolet radiation (UVR) is a major environmental risk for the skin, and UVB has been proposed to be a main factor for melanoma development. In response to sunlight exposure, the skin has adapted a number of innate resistance mechanisms. Among them, the stress proteins are known playing a role in the protection of cells from a host of external stresses, including UV irradiation. The role of HSP27 (one member of the heat shock protein family) in protecting the skin has been widely investigated in keratinocytes, but a little work has been done to investigate its role in melanocytes. **Shi *et al*** demonstrated for the first time that HSP27 is expressed in normal human skin melanocytes and in cultured non-malignant melanocytes. Moreover, they showed that UVB irradiation with a physiological dose resulted in HSP27 phosphorylation through reactive oxygen species (ROS)/p38 MAP kinase pathway and in an intracellular translocation of HSP27 from the cytoplasm to the nucleus. Understanding the regulation of HSP27 in melanocytes by UVB may ultimately provide clues as to its protective functions in these cells.

In mammals the Melanocortin-1 receptor (MC1R) plays a pivotal role in the photo-protection against ultraviolet radiation and this effect goes beyond its ability to driving melanogenesis and melanin types. The paper **by Smith et al.** shows for the first time that MC1R signalling in B16 mouse melanoma cells and primary human melanocytes rapidly and transiently, induces the transcription of the NR4A sub-family of orphan receptors and that some RHC variants are unable to promote its induction in response to a potent MC1R agonist. Using siRNA mediated attenuation of NR4A1 and NR4A2 expression in melanocytes, the same authors observed that the ability to remove cyclobutane pyrimidine dimmers following ultraviolet irradiation appeared to be impaired in the context of MC1R signalling. These results identify the NR4A receptor family as potential mediators of MC1R co-ordinated DNA damage response to UV exposure in melanocytic cells.

Dimerization of the Melanocortin-1 receptor (MC1R) was demonstrated in the past by co-immunoprecipitation studies. The mechanisms of G-protein coupled receptors dimerization are often incompletely understood, but may involve: (a) coiled-coil interactions between the C-terminal domains, (b) covalent intersubunit disulfide bonding, and (c) the swapping of large receptor domains to yield functional units that comprise structural elements from each partner. The paper by **Zanna et al.** has analysed the contribution of these three types of inter-subunit interactions to MC1R dimerization and it demonstrated that this tridimensional organization involves the formation of four disulfide bonds and non-covalent interactions, probably of domain swap type. The authors conclude that dimeric structure of the receptor should be taken into account for better interpretation of structure –function data and for accurate design of pharmacological active ligands.

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3. MSH, MCH, other hormones, differentiation

(Pr M. Böhm)

POMC, α-MSH and MC-1Rs – what's new?

MC1R signalling, NR4A gene expression and DNA damage

In a recent paper by Smith *et al.,* new downstream targets of the melanocortin-1 receptor (MC1R) were identified which may shed more light into the protective effect of the wild-type MC1R against DNA damage and melanoma development. Using B16 murine melanoma cells the authors demonstrated that treatment with NDP-α-melanocyte-stimulating hormone (NDP-α-MSH) at nanomolar doses transiently induces mRNA expression of the NR4A1-3 genes (Nurr77, Nurr1 and NOR-1). This effect of NDP-α-MSH was associated with increased NR4A promoter activity. Interestingly, normal human melanocytes harbouring homozygous RHC variant MC1R alleles exhibited impaired induction of NR4A genes upon stimulation with NDP-α-MSH. Moreover, silencing the NDP-α-MSH-induced upregulation of NR4A1 or NR4A2 by siRNA led to enhanced amounts of cyclopyrimidine dimers as assessed by immunofluorescence studies of normal human melanocytes exposed to UVB and NDP-α-MSH.

- Smith AG, Luk N, Newton RA, Roberts DW, Sturm RA, Muscat GE.
  Melanocortin-1 receptor signalling markedly induces the expression of the NR4A nuclear receptor subgroup in melanocytic cells. J Biol Chem 2008, in press.

Mechanism of MC1R dimerization

Many G protein coupled receptors exist as homo- and heterodimers and ongoing work by the group of J. C. García-Borrón has convincingly shown hat MC1R also undergoes constitutive dimerization. In the most recent paper of the above group, Zanna *et al.* transfected wild-type MC1R and distinct deleted mutants into HEK293 cells followed by electrophoretic pattern analysis, surface binding studies of iodinated NDP-α-MSH and immunofluorescence to investigate whether MC1R dimerization involves coiled-coil interaction, covalent intersubunit disulfide bonding or swapping of large receptor domains to yield functional domains. When cells were transfected with MC1R expression constructs lacking the 7th transmembrane fragment and the cytosolic C-terminal extension, oligomerization appeared normal excluding coiled-coil interaction as the basis of dimerization. Using MC1R expression constructs with specific Cys residues mutated to Ala it could be demonstrated that only the disulfide involving Cys35 was identified as being essential for traffic of the receptor to the membrane. However, when several Cys residues of the extracellular side of wild-type MC1R were simultaneously mutated to Ala (quadruple Cys35-267-273-275Ala) the electrophoretic pattern became monomeric. Interestingly, in cells coexpressing the quadruple Cys35-267-273-275Ala MC1R mutant and wild-type MC1R dimerization was again detected suggesting domain swapping.

- Zanna PT, Sánchez-Laorden BL, Pérez-Oliva AB, Turpín MC, Herraiz C, Jiménez-Cervantes C, García-Borrón JC.
  Mechanism of dimerization of the human melanocortin 1 receptor. Biochem Biophys Res Commun. 368: 211-216, 2008.

More evidence for disruption of the POMC system in vitiligo

Precursor proteases such as prohormone convertase (PC) 1/3 and 2 are well known for the endoproteolytic capacity to process proopiomelanocortin (POMC) to α-MSH and related peptides. However, there may be more players in the game of POMC processing within the epidermis. Spencer and coworkers investigated in particular the potential role of furin, a ubiquitously expressed member of the PC family, in the pathogenesis of vitiligo. They showed that immunoreactivity for furin is decreased in the epidermis (as well as in melanocytes) of patients with vitiligo (n=10). Furin expression at RNA and protein level could also be detected in normal human melanocytes and keratinocytes in vitro. Based on the fact that epidermal concentration of hydrogen peroxide is dramatically increased in patients with vitiligo, it was then tested if decreased epidermal furin immunoreactivity would normalize upon treatment with pseudokatalase and UVB. Consistent with the normalization of decreased furin immunoreactivity after treatment of vitiligo patients with the above regimen, in vitro oxidation of the enzyme with hydrogen peroxide resulted in a loss of one Ca^{2+} binding site, an observation further supported by computer simulation. The data suggest that the POMC processing machinery via excessive amounts of hydrogen peroxide is altered within the epidermis in patients with vitiligo.

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4. Photobiology

(Dr N. Smit)

Production of melanin from bacterial strains and its protective properties is the topic of papers by Geng et al and Wan et al, all from the same group. The melanin produced by Pseudomonas maltophilia as described by Geng et al is a water soluble melanin and similar to the synthetic melanin produced by Sigma. The bacterial melanin was shown to scavenge ROS generated by UVA and to protect (plasmid) DNA from UVB (JBBM). Also in a cellular system ROS scavenging by the bacterial melanin was demonstrated and higher viability and reduced apoptosis in (XP)fibroblasts was found for cells treated with melanin. A different microbial strain WS produced more and slightly different melanin (Wan et al). This melanin was more effective in the protection of a bioinsecticide that is normally very sensitive to inactivation by solar radiation. As described by the authors melanin synthesis in bacteria is mostly dependent on tyrosinase or laccase activity. Addition of L-tyrosine to the agar of the bacterial plates results in the formation of visible pigmented colonies. The advantage of the bacterial produced melanin above a chemically or tyrosinase produced (synthetic) melanin is not fully clear from the papers although it is apparent that the different bacteria produce different amount and types of melanin.
In the paper by Lin et al the process of melanization after solar simulated UV irradiation is connected to the restoration of the epidermal barrier function (as measured by normalization of the transepidermal water loss. The study is suggested to be useful as baseline information on changes occurring after photodamage in Asian skin.
The paper by Besaratinia et al nicely demonstrates that in fibroblasts irradiated with UVB, UVA or simulated sunlight, the resulting oxidized purines in the DNA are removed much faster than cyclobutane pyrimidine dimers (CPDs), both in the genome overall and also more specifically in the cII transgene. Also it can be seen that UVB induced 6-4photoproducts are removed more rapidly from the overall genome than the CPDs. The average mutation frequency in the cIItransgene is about 25 fold higher for UVB than for UVA. This may be demonstrative for the non-melanoma tumors with UVB signature mutations seen in e.g. TP53. However, different kinetics in repair of the UVB DNA lesions has been known for long and much faster repair is seen for 6-4PP compared to CPDs. Obviously, the oxidative UVA induced oxidized ppurines are also removed very efficiently. The paper thus indicates that it is more likely that UVB induced lesions are responsible for Mutations but the question still remains whether in vivo conditions may occur (in the pigment cells and especially atypical nevi) where (oxidative) DNA lesions may be strongly elevated that may be responsible for mutagenesis. In the paper by Biesemeier et al aged human RPE cells containing melanin and lipofuscin granules showed higher prooxidative than antioxidative capacity compared to non-pigmented cells when they were irradiated by UVA. As a result the pigmented cells were less viable and showed more apoptosis. Newton et al demonstrate some effects of NDP-MSH in melanocytes with wild type MC1R and some red hair colour variants. The RHC cells do not show the increased transcription of MITF, c-Fos and SLC45A2 that is found in WT cells after stimulation with NDP-MSH. Also p38 signaling was found to be regulated by MC1R and the effect was strongly enhanced by UVB irradiation. Although also in RHC variants the combined effect of UVB and MSH on p38 activation was observed it was less than that in the WT cells. The p38 MAP kinase was also indicated to play a role in the HSP27 phosphorylation in UVB irradiated melanocytes next to reactive oxygen species (Shi et al). Both antioxidant treatment and an inhibitor of p38 MAP kinase prevented HSP27 phosphorylation (demonstrated by IEF and immunoblotting).

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CONCLUSION: This study shows that in the skin of Korean subjects, changes in skin barrier function and delayed melanization do occur even in exposure to a suberythemogenic dose of SSUV. Also, given the fact that restoration of barrier function occurs as the process of melanization begins, melanization is considered to be a useful predictive indicator of the restoration of the skin barrier function after sunburn.

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Human melanocytes expressing MC1R variant alleles show impaired activation of multiple signaling pathways. Peptides. 28:2387-2396, 2007.

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Does imiquimod histologically rejuvenate ultraviolet radiation-damaged skin? Dermatol.Surg. 33:1419-1428, 2007.

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Isolation of a novel strain of Aeromonas media producing high levels of DOPA-melanin and assessment of the photoprotective role of the melanin in bioinsecticide applications. J.Appl.Microbiol. 103:2533-2541, 2007.
SIGNIFICANCE AND IMPACT OF THE STUDY: Our study suggests that the melanin produced by our newly isolated A. media strain has the potential to be used as a general photoprotective agent for bioinsecticides

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5. Neuromelanins

(Pr M. d'Ischia)

In this issue we will focus on a paper by Gerlach et al. (2008) addressing a current gap in research on Parkinson's disease, namely the lack of a reliable marker. The paper addresses the various possible types of markers and their value not only for the early detection of the disease but also for evaluating therapeutic approaches and their outcome. Unfortunately, the identification and exploitation of such markers does not seem to be just behind the door. Several difficulties account for these "unmet needs", including the slow course of the disease and its unknown etiopathogenesis. The possibility of relying on neuromelanin and its metabolic products as a rational basis to develop practical markers for the early diagnosis of the disease would be a most attractive research goal, but this requires a more in-depth understanding of the biochemical dysfunctions underlying accumulation of the pigment and selective demise of pigmented neurones.

- Gerlach, Manfred; Hendrich, Albrecht; Hueber, Roland; Jost, Wolfgang; Winkler, Juergen; Woitalla, Dirk; Riederer, Peter.
  Early Detection of Parkinson's Disease: Unmet Needs. Neurodegenerative Diseases 5(3-4):137-139, 2008.
  Abstract: A biomarker (biol. marker) is a characteristic that is objectively measured and evaluated as an indicator of normal biol. processes, pathogenetic processes or pharmacol. responses to a therapeutic intervention. Expectations are high for the development of biomarkers since they make it possible to achieve a significant improvement in the diagnosis and classification of diseases like Parkinson's disease. As a surrogate marker for clin. studies, a biomarker can also be used to det. the efficacy of novel therapeutic interventions, such as neuroprotective strategies, and for monitoring the progress of the disease. Imaging techniques (18F-DOPA PET, 123I-□-CIT SPECT, MIBG scintigraphy, functional imaging), clin. tests (e.g. hyposmia, microg., hyperechogenicity, apomorphine test), biochem. markers (e.g. □-synuclein and neuromelanin antibodies, oxidative and mitochondrial markers) and genetic tests for hereditary forms (PARK1 to PARK11) are evaluated for their suitability.

- Shamoto-Nagai, M., Maruyama, W., Hashizume, Y., Yoshida, M., Osawa, T., Riederer, P., Naoi, M.
  In parkinsonian substantia nigra, □ -synuclein is modified by acrolein, a lipid-peroxidation product, and accumulates in the dopamine neurons with inhibition of proteasome activity. Journal of Neural Transmission. 114(12):1559-1567, 2007. **Abstract :** □-Synuclein (□SYN) plays a central role in the neural degeneration of Parkinson's disease (PD) through its conformational change. In PD, □SYN, released from the membrane, accumulates in the cytoplasm and forms Lewy body. However, the mechanism behind the translocation and conformational change of □SYN leading to the cell death has not been well elucidated. This paper reports that in the dopamine neurons of the substantia nigra contg. neuromelanin from PD patients, □SYN was modified with acrolein (ACR), an aldehyde product of lipid peroxidn. Histopathol. observation confirmed the co-localization of protein immunoreactive to anti-□SYN and ACR antibody. By Western blot analyses of samples pptd. with either anti-□SYN or anti-ACR antibody, increase in ACR-modified □SYN was confirmed in PD brain. Modification of recombinant □SYN by ACR enhanced its oligomerization, and at higher ACR concns. □SYN was fragmented and polymd. forming a smear pattern in SDS-PAGE. ACR reduced 20S proteasome activity through the direct modification of the proteasome proteins and the prodn. of polymd. ACR-modified proteins, which inhibited proteasome activity in vitro. These results suggest that ACR may initiate vicious cycle of modification and aggregation of proteins, including □SYN, and impaired proteolysis system, to cause neuronal death in PD.

6. Genetics, molecular and developmental biology

(Dr F. Beermann)

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The Melanocortin 1 Receptor and the UV Response of Human Melanocytes - A Shift in Paradigm. Photochem Photobiol 84: 501-508, 2008.

- Alizadeh A, Fitch KR, Niswender CM, McKnight GS, Barsh GS.
Melanocyte-lineage expression of Cre recombinase using Mitf regulatory elements. Pigment Cell Melanoma Res 21: 63-69, 2008.
Summary: This manuscript describes a novel Cre-transgenic line for melanocyte-specific gene targeting, using a Cre expressed from a *Mitf* BAC (bacterial artificial chromosome). This *Mitf::Cre* line was used to delete a subunit of protein kinase A (Prkca) in mice in vivo. Resulting mice exhibited a darker coat color than controls, due to a shift from pheomelanin to eumelanin synthesis.

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Complex signatures of selection for the melanogenic loci TYR, TYRP1 and DCT in humans. BMC Evol Biol 8: 74, 2008.

- Bemis LT, Chen R, Amato CM, Classen EH, Robinson SE, Coffey DG, Erickson PF, Shellman YG, Robinson WA.
MicroRNA-137 targets microphthalmia-associated transcription factor in melanoma cell lines. Cancer Res 68: 1362-1368, 2008.
Shortened abstract: In these studies, we have identified microRNA-137 (miR-137) as a regulator of MITF expression. The genomic locus of miR-137 at chromosome 1p22 places it in a region of the human genome previously determined to harbor an allele for melanoma susceptibility. Here, we show that expression of mature miR-137 in melanoma cell lines down-regulates MITF expression. Further, we have identified a 15-bp variable nucleotide tandem repeat located just 5' to the pre-miR-137 sequence, which alters the processing and function of miR-137 in melanoma cell lines.

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Alternative promoter use in eye development: the complex role and regulation of the transcription factor MITF. Development 135: 1169-1178, 2008.
Abstract: During vertebrate eye development, the transcription factor MITF plays central roles in neuroepithelial domain specification and differentiation of the retinal pigment epithelium. MITF is not a single protein but represents a family of isoforms generated from a common gene by alternative promoter/exon use. To address the question of the role and regulation of these isoforms, we first determined their expression patterns in developing mouse eyes and analyzed the role of some of them in genetic models. We found that two isoforms, A- and J-Mitf, are present throughout development in both retina and pigment epithelium, whereas H-Mitf is detected preferentially and D-Mitf exclusively in the pigment epithelium. We further found that a genomic deletion encompassing the promoter/exon regions of H-, D- and B-Mitf leads to novel mRNA isoforms and proteins translated from internal start sites. These novel proteins lack the normal, isoform-specific N-terminal sequences and are unable to support the development of the pigment epithelium, but are capable of inducing pigmentation in the ciliary margin and the iris. Moreover, in mutants of the retinal Mitf regulator Chx10 (Vsx2), reduced cell proliferation and abnormal pigmentation of the retina are associated with a preferential upregulation of H- and D-Mitf. This retinal phenotype is corrected when H- and D-Mitf are missing in double Mitf/Chx10 mutants. The results suggest that Mitf regulation in the developing eye is isoform-selective, both temporally and spatially, and that some isoforms, including H- and D-Mitf, are more crucial than others in effecting normal retina and pigment epithelium development.

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An unstable targeted allele of the mouse Mitf gene with a high somatic and germline reversion rate. Genetics 178: 259-272, 2008.
Abstract: The mouse Mitf gene encodes a transcription factor that is regulated by serine phosphorylation and is critical for the development of melanin-containing pigment cells. To test the role of phosphorylation at a particular serine, S73 in exon 2 of Mitf, we used a standard targeting strategy in mouse embryonic stem cells to change the corresponding codon into one encoding an alanine. By chance, we generated an allele in which 85,222 bp of wild-type Mitf sequence are duplicated and inserted into an otherwise correctly targeted Mitf gene. Depending on the presence or absence of a neomycin resistance cassette, this genomic rearrangement leads to animals with a white coat with or without pigmented spots or a gray coat with obligatory white and black spots. Several independent, genetically stable germline revertants that lacked the duplicated wild-type sequence but retained the targeted codon were then derived. These animals were normally pigmented, indicating that the serine-to-alanine mutation is not deleterious to melanocyte development. The fact that mosaic coat reversions occur in all mice lacking the neo-cassette and that approximately 1% of these transmit a

reverted allele to their offspring places this mutation among those with the highest spontaneous reversion rates in mammals.

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Association of polymorphic sites in the OCA2 gene with eye colour using the tree scanning method. Ann Hum Genet 72: 184-192, 2008.

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Microphthalmia associated transcription factor (MITF) regulates rab27A gene expression and controls melanosomes transport. J Biol Chem, 2008.

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Impact of Homozygosity of R151C Variant of MC1r in Human Hair Follicle Melanocytes. J Invest Dermatol, 2007

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The proliferating field of neural crest stem cells. Dev Dyn 236: 3242-3254, 2007.

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Pigmentation in Black-boned sheep (Ovis aries): association with polymorphism of the MC1R gene. Mol Biol Rep, 200.7

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Neurofibromin as a regulator of melanocyte development and differentiation. J Cell Sci 121: 167-177, 2008.
Abstract: Patients with the genetic disease type I neurofibromatosis (NF1) exhibit characteristic pigmentary lesions associated with loss of a single allele of NF1, encoding the 260 kDa protein neurofibromin. To understand the basis for these pigmentary problems, the properties of melanocytes haploinsufficient for the murine gene Nf1 were studied using Nf1(+/-) knockout mice. We demonstrate that neurofibromin regulates the Kit-Mitf signaling axis in vivo during melanocyte development. Primary Nf1(+/-) melanocytes were purified by FACS to measure melanogenic gene expression. We found that Nf1(+/-) melanocytes exhibit higher levels of melanogenic gene expression than their wild-type counterparts. Both prior to and following Kit stimulation, Nf1(+/-) melanocytes also exhibit increased activation of the MAP kinase pathway compared with primary cells. The melanogenic response of primary melanocytes to Mek inhibition is consistent with the changes observed with Nf1 haploinsufficiency; however, these changes differ from those observed with their immortalized counterparts. The observation that reduction of neurofibromin, either from haploinsufficiency in the case of primary melanocytes or from neurofibromin knockdown in the case of melan-a cells, enhances melanogenic gene expression suggests that neurofibromin plays a dominant role to MEK activity in controlling melanogenic gene expression in murine melanocyte

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Rescue From Oculocutaneous Albinism Type 4 Using Medaka slc45a2 cDNA Driven by Its Own Promoter. Genetics 178: 761-769, 2008.
Shortened abstract: Patients and vertebrate mutants with oculocutaneous albinism type 4 (OCA4) have mutations in the solute carrier family 45 member 2 (slc45a2) gene. However, there is no empirical evidence for this gene-phenotype relationship. There is a unique OCA4 mutant in medaka (b) that exhibits albinism only in the skin, but the mechanism underlying this phenotype is also unknown. In this study, we rescued medaka OCA4 phenotypes, in both the eyes and the skin, by micro-injection of an slc45a2-containing genomic fragment or slc45a2 cDNA driven by its own 0.9-kb promoter.

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Altered expression of the iron transporter Nramp1 (Slc11a1) during fetal development of the retinal pigment epithelium in microphthalmia-associated transcription factor Mitf(mi) and Mitf(vitiligo) mouse mutants. Exp Eye Res 86: 419-433, 2008.

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SLC24A5 Encodes a trans-Golgi Network Protein with Potassium-dependent Sodium-Calcium Exchange Activity That Regulates Human Epidermal Melanogenesis. J Biol Chem 283: 5486-5495, 2008.

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Expression patterns of MITF during human cutaneous embryogenesis: evidence for bulge epithelial expression and persistence of dermal melanoblasts. J Cutan Pathol, 2008.

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Allelic Heterogeneity at the Equine KIT Locus in Dominant White (W) Horses. PLoS Genet 3: e195, 2007.

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Characterization of the porcine KIT ligand gene: expression analysis, genomic structure, polymorphism detection and association with coat colour traits. Anim Genet, 2008.

- Hutton SM, Spritz RA.
A comprehensive genetic study of autosomal recessive ocular albinism in caucasian patients. Invest Ophthalmol Vis Sci 49: 868-872, 2008.

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colgate/hdac1 Repression of foxd3 expression is required to permit mitfa-dependent melanogenesis. Dev Biol 313: 568-583, 2008.
Shortened abstract: The zebrafish mutant colgate (col)/histone deacetylase1 (hdac1) has reduced numbers, delayed differentiation and decreased migration of neural crest-derived melanophores and their precursors. In hdac1(col) mutants normal numbers of premigratory neural crest cells are induced. Later, while there is only a slight reduction in the number of neural crest cells in hdac1(col) mutants, there is a severe reduction in the number of mitfa-positive melanoblasts suggesting that hdac1 is required for melanoblast specification. Concomitantly, there is a significant increase in and prolonged expression of foxd3 in neural crest cells in hdac1(col) mutants. We found that partially reducing Foxd3 expression in hdac1(col) mutants rescues mitfa expression and the melanophore defects in hdac1(col) mutants. Furthermore, we demonstrate the ability of Foxd3 to physically interact at the mitfa promoter. Because mitfa is required for melanoblast specification and development, our results suggest that hdac1 is normally required to suppress neural crest foxd3 expression thus de-repressing mitfa resulting in melanogenesis by a subset of neural crest-derived cells.

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Isolation and characterization of Kit-independent melanocyte precursors induced in the skin of Steel factor transgenic mice. Dev Growth Differ 50: 63-69, 2008.

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A novel mutation in a Turkish patient with Hermansky-Pudlak syndrome type 5. Eur J Haematol 80: 356-360, 2008.

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Both Notch1 and Notch2 contribute to the regulation of melanocyte homeostasis. Pigment Cell Melanoma Res 21: 70-78, 2008.
Summary: Using heterozygous mutant mice for Notch1 and Notch2 they confirm data from others obtained using conditional knockout mice (Schouwey et al., Developmental Dynamics 2007;236:282-9), showing that deletion of Notch1 and Notch2 in the melanocyte lineage leads to hair graying and affects melanocyte populations in bulge and bulb. In addition, these data suggest an interaction of Notch and c-kit signalling in the melanocyte lineage.

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Inducible expression of cre recombinase in the retinal pigmented epithelium. Invest Ophthalmol Vis Sci 49: 1248-1253, 2008.
Commentary: A novel transgenic approach for conditional gene activation/knockout in the RPE. Transgenic mice carrying the human vitelliform macular dystrophy-2 (VMD2) promoter (P(VMD2))-directed reverse tetracycline-dependent transactivator (rtTA) and the tetracycline-responsive element (TRE)-directed cre were generated.
See also the paper on a *Tyrp1::Cre* transgenic line (Mori et al., Invest Ophthalmol Vis Sci. 2002 43:1384-8).

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Analysis of RAB27A gene in Griscelli syndrome type 2: novel mutations including a deletion hotspot. J Clin Immunol, 2008.

- Miller CT, Beleza S, Pollen AA, Schluter D, Kittles RA, Shriver MD, Kingsley DM.
cis-Regulatory changes in Kit ligand expression and parallel evolution of pigmentation in sticklebacks and humans. Cell 131: 1179-1189, 2007.

This paper has been subject of a commentary in the same issue of Cell:
Boughman JW.
Sticklebacks and humans walk hand in fin to lighter skin. Cell 131: 1041-1043, 2007.
In this issue, Miller et al. (2007) show that evolution makes repeated use of the same genes to produce light pigmentation in animals as divergent as stickleback fish and humans. This study indicates that analyzing parallel evolution at the genetic level could help to answer a number of outstanding questions in evolutionary genetics.

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Network topology determines dynamics of the mammalian MAPK1,2 signaling network: bifan motif regulation of C-Raf and B-Raf isoforms by FGFR and MC1R. Faseb J, 2008.

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Characterization of Japanese Quail yellow as a genomic geletion upstream of the avian homolog of the mammalian ASIP (agouti) gene. Genetics 178: 777-786, 2008.

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Key basic helix-loop-helix transcription factor genes Hes1 and Ngn2 are regulated by Pax3 during mouse embryonic development. Dev Biol, 2008.

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Cancer stem cells and human malignant melanoma. Pigment Cell Melanoma Res 21: 39-55, 2008.

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Genes affecting coat colour and pattern in domestic dogs: a review. Anim Genet 38: 539-549, 2007.

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A single SNP in an evolutionary conserved region within intron 86 of the HERC2 gene determines human blue-brown eye color. Am J Hum Genet 82: 424-431, 2008.
Conclusion from abstract: We conclude that the conserved region around rs12913832 represents a regulatory region controlling constitutive expression of OCA2 and that the C allele at rs12913832 leads to decreased expression of OCA2, particularly within iris melanocytes, which we postulate to be the ultimate cause of blue eye color.

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Oncogenic BRAF induces senescence and apoptosis through pathways mediated by the secreted protein IGFBP7. Cell 132: 363-374, 2008.
This paper has been subject of a commentary in the same issue of Cell:
Chien Y, Lowe SW, **Secreting tumor suppression**. Cell 132: 339-341, 2008.
Cellular senescence limits the proliferative capacity of damaged cells and thereby acts as an intrinsic mechanism of tumor suppression. In this issue, Wajapeyee et al. (2008) identify insulin growth factor binding protein 7 (IGFBP7) as a

secreted factor that mediates senescence induced by oncogenic BRAF in normal melanocytes. In addition, IGFBP7 triggers apoptosis in cells that have progressed to melanoma, suggesting a new approach for melanoma treatment.

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EphA2 is an essential mediator of UV radiation-induced apoptosis. Cancer Res 68: 1691-1696, 2008.

7. Tyrosinase, TRPs, other enzymes

(Pr. J.C. Garcia-Borron)

NOT AVAILABLE

8. Melanosomes

(Pr J. Borovansky)

Review articles. *Izumi* summarized the current knowledge of the roles of the Rab27 effector family proteins in regulated exocytic pathways based on physiologically relevant studies. *Kaplan et al* paid a special attention to the function of CHS1/LYST/Beige protein involved in either the vesicle fusion or fission. (The CHS1/LYST gene was identified just 10 years ago). They also discussed the advances in understanding of the clinical aspects of the Chediak-Higashi syndrome. *Schmutz & Berryere* characterized the genes affecting the coat colour and pattern in domestic dogs. Although the melanosomes are not the direct subject of the review, many gene products do have a relationship to the melanosome ultrastructure and properties.

Melanosome biogenesis and transport. *Marks* commented on a finding of *Chow et al* (*Nature 448: 68-72, 2007*). They identified the gene FIG4(Fig4) to be mutated in the Charcot-Marie-Tooth disease in humans and in the „pale tremor" mouse. The gene encodes an inositol phospholipid phosphatase that most likely regulates the biogenesis of melanosomes and neurosecretory granules. The invagination of both the PMel17 and MART-1 and the retrograde transport from melanosomes to endosomes might require a normal function of FIG4(Fig4). The silver homologue (SILV) gene plays a major role in the melanosome development. *Kawakami et al* demonstrated a regulatory effect of Rab7 on the melanosome matrix protein maturation. In MMAC human melanoma cells the wild type Rab 7 and its dominant-active mutant (Rab7 Q67L) (but not the dominant-negative form Rab7 T22N) were colocalized in the perinuclear region with the Stage I melanosomes containing pg100/Pmel17 protein. siRNA-mediated Rab7 knockdown inhibited the gp100/Pmel 17 maturation. *Kawasaki et al* analyzed the effects of the Mitf transcription factor on Xenopus melanophores in vitro: The Mitf was involved in both the melanophore dendricity and the melanosome dispersion. *Kuehn & Weikard* provide evidence for a ubiquitous transcription of bovine SILV gene not restricted only to the pigment cells and demonstrate a striking variety of alternative splice sites. They propose that the SILV might have functions other than the melanosome development.
In melanophores, the Rab32 was shown by *Park et al* to act as a melanosome-specific protein A kinase-anchoring protein that is essential for regulation of melanosome transport.

Optical and histochemical properties of melanosomes. *Binzoni et al.* show that the optical/biological information contained in a typical spectral image mainly reflects the properties of a small conic-like volume of tissue situated vertically under each individual pixel. The objects appearing on a spectral image reasonably reproduce the correct geometrical shape and size of underlying inclusions of tissue up to the depth of 2-3mm. As for melanosomes, interpretation is not easy: skin melanin content depends on 2 intimately interconnected factors: the skin concentration /fraction of melanosomes and the melanin content of melanosomes. The free melanin is expected not to have the same optical properties such as the cluster of pigment molecules inside melanosomes.(*See also Meglinski IV, Matcher SJ/Physiological Measurement 23(4): 741-753, 2002).* The first attempt to evaluate the contribution of melanin and haemosiderin to the skin pigmentation in a chronic venous insufficiency by histochemical means was reported by *Caggiati et al*: Melanin and haemosiderin participate in the different developmental phases of the skin changes. The hypermelanization is due to the enhanced melanogenesis, however an increase in the melanocyte population was not observed. The occurrence of haemosiderin indicates the progression of the skin damage towards lipodermatosclerosis.

Melanosomes ultrastructure in various tissues and under various situations.
According to *Franzen et al.* melanosomes of the fungus *Fonsecaea pedrosoi* possess a fibrillar matrix, similar to that found in the mammalian and amphibian melanosomes, functioning as a support site for melanin deposition. Melanin is transported inside the melanosome towards the cell wall where it is deposited in concentric layers. X-ray microanalysis of melanosomes revealed the presence of calcium, iron and phosphorus. *(See also Franzen AJ et al./ FEMS Microbiol Lett 17: 395-402, 1999).*

Light, ultrastructural, immunochemical and chemical studies of the first case of the urinary bladder melanosis in the red-spotted cow was performed by *Russo et al.* Pigment-containing cells were found in the submucosa and lamina propria but – unlike in the humans - not in the urothelium.The cells, positive for the S-100 and HMB-45, contained mostly the stage IV melanosomes of remarkable pleomorphism and size variability, but no aberrant melanosomes were observed. A chemical analysis demonstrated the presence of eumelanin. Melanosome complexes were noted in melanocytes, melanophages, endothelial cells, pericytes and some mast cells.

Relyveld et al compared the distribution and the size of melanosomes between lesional and non-lesional skin areas in 8 patients with the progressive macular hypomelanosis in an effort to get an insight into the pathogenesis of the disease. Hypopigmentation seems to be the result both of the production of smaller, less melanized melanosomes and of the change of the melanosomal distribution in keratinocytes.

Our limited knowledge of the ultrastructural characteristics of avian neoplastic melanocytes was enhanced by *Irizarry-Rovira et al.* Malignant melanoma cells in zebra finch, negative for S100 and MelanA (features so far typical of avian melanoma cells), were variably pigmented and mildly pleomorphic. They contained variable numbers of oval-to-round aberrant fibrillar melanosomes with membrane defects in various stages of melanization.

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9. Melanoma experimental, cell culture

(Dr R. Morandini)

About cell culture:
Lin (Cancer Res., 2008) describes a comprehensive genomic analysis of several (101) melanoma short-term cultures and cell lines. The authors show that cultured melanoma cells encompass the spectrum of significant genomic alterations present in primary tumors. Furthemore integrating gene expression data, and suggest novel candidate effector genes linked to recurrent copy gains and losses, including both phosphatase and tensin homologue (PTEN)-dependent and PTEN-independent tumor suppressor mechanisms associated with chromosome 10 deletions. The cell culture models reflective of in vivo tumor genetic diversity offer an attractive avenue to identify molecular features that modify the efficacy of therapeutic agents. In melanoma, the MAP kinase pathway is commonly activated by BRAF or NRAS oncogene point mutations, and BRAF(V600E) mutation is associated with sensitivity to RAF or MEK inhibition. The data suggest that in some contexts, NRAS or FGFR1 mutations may also confer sensitivity to MAP kinase pathway inhibition, but that high p-ERK may correlate with insensitivity to these inhibitors.
A two parts paper by Hatina (2008), explains that cell culture models are a very valuable experimental system. The degree of tumorigenic transformation can be precisely defined. Tumor cell lines display similar functional hierarchy as tumors or tissues in vivo and can, consequently, provide a crucial source of minor cell subsets, like tumor stem cells. Progression series of clonally related cell lines offer the opportunity to follow the process of sequential acquisition of transformation-related traits up to the development of properties with direct clinical equivalents, like tumorigenicity and metastatic competence.
Nevertheless, there are several limitations to the use of the classical monolayer cell culture and the results obtained by means of it. Newer developments in cell culture methodology seek approaches to mimic the in vivo situation in the cell culture as closely as possible. Remarkable variety of such approaches can be noticed, ranging from relative simple three-dimensional conditions of culturing pure cell lines on collagen gels or in form of multicell tumor spheroids. More complex forms try to combine multiple cell types in a single co-culture, e.g. of tumour cells and stromal fibroblasts.
In conclusion Lin shows that, a cultured melanoma collection can reflect the diversity of genomic aberrations observed in primary melanomas and then should facilitate the characterization of critical and "druggable" effectors linked to key molecular lesions in this malignancy. Furthermore, Hatina explains newer developments in cell culture methodology close to mimic the in vivo situation.

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ANNOUNCEMENTS & RELATED ACTIVITIES

Calendar of events

2008 Dermatologia Globale

April 23-26, Genoa, Italy

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Tel.: +39 02 36 57 07 00
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2008 20th International Pigment Cell Conference (IPCC)

conjoined with

Vth International Melanoma Research Congress

May 7–12 Sapporo, Japan

Contact: Secretariat Office
Toshiharu YAMASHITA (Sapporo Medical University, Japan)
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E-mail: ipcc-imrc2008@sapmed.ac.jp
Web site: www.e-convention.org/ipcc-imrc2008

2008 International Investigative Dermatology (Joint Meeting of the ESDR, SID and JSID)

May 14-17 , Kyoto, Japan

Contact: The International Investigative Dermatology 2008 Secretariat
c/o The Convention
Tel: +81-3-3423-4180
Fax: +81-3-3423-4108
E-mail: iid08@the-convention.co.jp
Web site: www.iid2008.org

2008 9th Congress of the European Society for Pediatric Dermatology

May 15-17, Athens, Greece

Contact: Ms. Penelope Mitrogianni
Tel: +30 210 725 7693 Fax: +30 210 725 7532
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Web site: www.espd2008.com

2008 5th EADV Spring Symposium

May 22-25, Istanbul, Turkey

Contact: Professor Mehmet Ali Gürer
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2008 ICATMM-EADO MEETING 2008

The 7th International Conference of Adjuvant Therapy on Malignant Melanoma and the 4th European Association of Dermato-Oncology Congress

19-21 June 2008, Palais du Pharo - Marseille, France

Contact: Congress Office:
ICATMM-EADO 2008
MCI - 24 Rue Chauchat
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2008 17th Annual Congress of the European Academy of Dermatology Venereology

September 17-21, Paris, France

Contact: EADV PARIS 2008 CONGRESS OFFICE:
EADV 2008 MCI - 24, rue Chauchat
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E-mail: www.eadvparis2008.com

2008 5th European Meeting on SOLAR CHEMISTRY AND PHOTOCATALYSIS: ENVIRONMENTAL APPLICATIONS

October 4-8, Palermo, Italy

Contact: Secretariat e-mail: spea5@yahoo.it
Web site: www.spea5.altervista.org

2009 6th EADV Spring Symposium

April 23 – 26, Bucharest, Romania

2009 Annual Meeting for the Society for Investigative Dermatology

May 6-9, Montreal, Quebec, Canada

Contact: Web site: www.sidnet.org

2009 39th Annual ESDR Meeting

September 9-12, Budapest, Hungary

2009 XVth Meeting of the ESPCR

September 20-23, Münster, Germany

Contact: Pr Markus Böhm
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2009 18th EADV Congress

October 7-11, Berlin, Germany

2010 40th Annual ESDR Meeting

September 8-11, Helsinski, Finland

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NEW MEMBERS

The ESPCR is delighted to welcome the following colleagues to membership and hope they will play a full and active part in the Society

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Unfortunately, as you probably know, Professor Dr John Martin Wood died on February 5th 2008. This is a great loss for those who knew him and for all the scientific community, my deepest sympathy goes to his family and to his wife Karin Schallreuter. To commemorate Professor Wood in the current bulletin you will find a Memorial written by one of his students. Mauro Picardo

In memoriam Professor John M Wood
1938-2008

John Martin Wood was born on the 22nd of March 1938 in Huddersfield, UK and lost the battle against cancer on February 5th 2008. A multitalented young man, he was an accomplished artist, a professional cricketer and a talented footballer, playing for his local team "Huddersfield Town". However, above all, he will be remembered as an outstanding scientist. His early career in science took him from his native Yorkshire to America. Completing his PhD at the University of Leeds, UK, in 1964, he moved to the chemistry department of the University of Illinois, USA, to follow his interest in transition metals in biology, researching the structure and function of B12 enzymes, dioxygenases and metabolic cycles for toxic elements. He became associate professor at the age of 32 and shortly after a sabbatical year as a Guggenheim fellow in Oxford he was promoted to full professor of biochemistry at the University of Illinois. His expertise then took him to Minnesota, becoming the first director of the Gray-Freshwater Biological Institute and professor of biochemistry at the University of Minnesota. Here, John Wood lead substantial research into the environmental conversion of inorganic metal compounds, the biological synthesis and bio-accumulation of alkyl-lead compounds in food chains, and chemical studies with free and bound Vitamin B12. He was heavily involved in unravelling the mechanism behind Minamata disease. His research on methyl mercury resulted in three Nobel-prize nominations. Yielding 9 publications in Science and 2 in Nature, amongst others, John Wood served 2 years on the editorial board of Science.

However, in the late 1980's following a life-changing encounter with his future wife Professor Karin U Schallreuter, John Wood changed his area of research to the field of dermatology and both began a successful partnership lasting over 20 years. With his passion for understanding and teaching the pure fundamentals of chemistry, John Wood became an important contributor to the field of dermatology with emphasis on the biochemistry of epidermal pigmentation, oxidative stress and epidermal free radical defence. This has become especially important with regards to the depigmentation disease vitiligo, but also other disorders. Together with his wife and with funding from Stiefel Inc, he moved back to England to the University of Bradford as professor for medical biochemistry in 1992. Publishing over 70 original papers in this field, John Wood has had a huge impact in advancing the understanding of the principal biochemical problems in dermatology.

In addition, not only has he contributed significantly to science with his research, he has also been immensely important as an outstanding teacher to countless undergraduate and post-graduate students in Illinois, Minnesota and the UK. He took great pride in imparting his knowledge to his students and he had a gifted ability to teach science in a way that was passionate, exciting and interesting. His own passion for science was evident to all of his students and colleagues and this was combined with a great humorous personality and love for life. His humour endeared him to many, ranging from young patients with vitiligo to his university students, and to colleagues within the scientific community.

He will be sorely missed by all who got to know him and none more so than his wife, his 4 children and his beloved 8 grandchildren.

"Politicians come and go but scientists are here forever" a quote from Professor John M. Wood in April 2006 should be motivation to all of us.