N° 39 - April 2001

ESPCR BULLETIN

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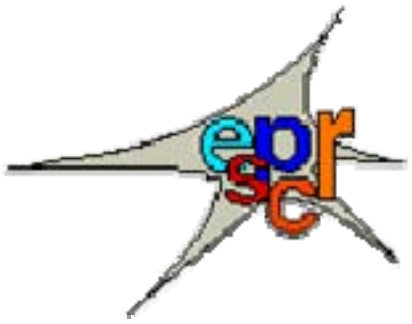

EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH *BULLETIN*

N° 39 - April 2001

Editorial Office: *G. Ghanem (Editor), C. Meunier, R. Morandini (Production Team), 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 Fax: 32-2-534.95.50 E-Mail:gghanem@ulb.ac.be

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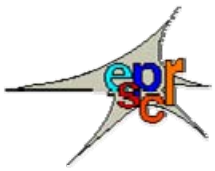

LETTER TO THE EDITOR
DISCUSSION, REVIEW,
SHORT COMMUNICATION, ...

GENERAL ASSEMBLY

9TH MEETING OF THE EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH

ULM, GERMANY
27 September - 1 October 2000

Agendas were distributed to all who attended the General Assembly (28 in total).

1. The Assembly was opened by Professor Stan Pavel.

2. Professor Mac Neil read the **Secretary's Report for 1999/2000**. Features of this report for 2000 were a meeting of the ESPCR Officers held on 10 January in London to make amendments to the Constitution. Following this, members were balloted on their support for the Constitution, also their support for the Institution of a Fritz Anders Memorial Lecture.

   Also, at this meeting, changes were made to the ESPCR Membership subscription. The decision was taken to pay membership fees in Euros and also to report on the membership database of the ESPCR Website, the year when fees were last paid (recorded after members' names). Professor Mac Neil reported that there was still a discrepancy between the number of members recorded on the Treasurer's database (203 in June 2000) and the number of members recorded on Professor Ghanem's database (176). Professor Mac Neil commented that while this was an improvement on the situation a year ago, there was still room for further improvement.

   With respect to election of the new Officers for the Society (President, Secretary and Treasurer), a call for nominees went out to all ESPCR members in July 2000. By the end of July, the Society had two nominees for each of the positions of President, Secretary and Treasurer. A postal ballot was conducted and the results of this ballot led to the election of Professor Dorothy Bennett as President, Professor José García-Borrón as Secretary and Dr. Lionel Larue as Treasurer.

   Finally, at the suggestion of the Editor of Pigment Cell Research, contributors to the journal who were not members of the ESPCR were contacted by letter bringing the benefits of joining the Society to their attention (110 such contributors). This mailshot took place in August 2000.

3. The Secretary (Professor Sheila Mac Neil) then read the Minutes from the last General Assembly held in Prague 1998. These Minutes were approved by the General Assembly.

4. The Treasurer (Professor Ralf Peter) presented the Treasurer's Report for 1999/2000. Some pertinent details of that report were as follows:

No. of Members:	203
New Members in 1999:	13
New Members in 2000:	8

Members Cancelled in Total in 1999/2000:	63
Members Paid in 1999:	132
Members Paid in 2000:	107

The financial balance for 2000 is slightly more than for 1998 and 1999. There were no questions related to the Financial Report for 1999/2000 and this was approved by the Membership.

5. Professor Ghanem then gave a brief report on the ESPCR Bulletin Website. He reported that there were no problems with the running of the Website and no increase in costs. He reported that, at Professor Wiete Westerhof's suggestion, the Website would now publish abstracts from Ph.D. theses from members' laboratories concerning pigmentation research.

   With respect to the running of the Bulletin, he reported that a new section on Developmental Biology had been suggested by Friedrich Beermann who would undertake to write this section. Professor Ghanem also reported that at the first Council Meeting, the suggestion had been put forward by him that contributors to the Bulletin should, in addition to receiving a free subscription to Pigment Cell Research, also be offered free registration at the ESPCR meetings for their work in compiling literature reports for the Bulletin. This was supported by the Council.

   Professor Mac Neil then commented that two other matters had been discussed in the Council Meeting concerning the Website and Bulletin: the first was the issue of how much information concerning members' contact details should be openly available on the Website and the second was whether the contents of the Bulletin should be available for members only (via a password) or be on the open Website.

   Professor Mac Neil said that these were matters that could be considered by the new Council Members and did not require an immediate decision.

   Professor Dorothy Bennett added a comment, that one good solution would be to have two membership lists: one open access to all which contained very brief contact details and not e-mail addresses and another fuller membership list available via password only which would contain not only full contact details for the members but also a few lines describing their key research interests.

6. Professor Pavel then commented on the venues for the next ESPCR meetings. In 2001, the 10th ESPCR Meeting is to be held in Rome and the Chairman of the Local Organising Committee is Professor Mauro Picardo. In 2002, the next International Federation Pigment Cell Society Meeting will be in Scheveningen (The Hague) and Professor Pavel is the Chairman of the Local Organising Committee.

   For 2003 and 2004, we do not have venues at present and Professor Pavel urged those attending the General Assembly to consider possible venues. At this stage, Professor Garcia-Borron is to discuss with his colleagues whether Murcia might be a venue for 2003.

   For 2005, the provisonal venue for the next International Federation of Pigment Cell Society Meeting will be in the USA with Professor Vince Hearing as Chairman of the Local Organising Committee.

7. Professor Pavel then reported on the changes to the statues for continuing the ESPCR beyond 2000. He reported that it had been necessary in the original Constitution to make it time limited such that it would cease to exist beyond December 2000. Accordingly, the Constitution was amended with respect to this and a few other minor changes were made at this time at a meeting

held in London in January 2000 attended by the Officers of the Society and Professor Patrick Riley whose advice was invaluable in this respect. Following this meeting, the revised Constitution was then posted to all ESPCR members and placed on the Website and a ballot was undertaken requesting support for the continuation of the Society beyond December 2000. Professor Pavel reported that we had more than 50% support for continuing the Society and he had put it to the General Assembly that this be approved by the Assembly. The motion to continue the Society was approved by the Assembly.

8. Under Any Other Business, the Treasurer (Professor Peter) raised a number of related issues concerning what percentage of the ESPCR budget should be committed at any one time to:

(a) supporting the ESPCR conference running
(b) travel awards
(c) the Fritz Anders Memorial Lecture (which was supported by the Society for running on an annual basis from 2000 onwards)
(d) the Society's contribution to the IFPCS

Professor Pavel pointed out that the latter (the IFPCS contribution) was fixed at 20% of our income but that, in practice, when an International Meeting was held in Europe then a percentage of this income was returned to the European Society.

There was discussion of the fact that part of the budget should support the running of meetings possibly to the extent of 10 - 15% of our budget. Similarly, support for travel awards to enable young scientists or scientists from countries where access to travel funds is difficult to attend the meetings should also be supported - the percentages discussed ranged from 10 - 20% of our budget.

Professor Peter pointed out that, in practice, these matters were generally left to the discretion of the Treasurer but that he would wish the Assembly to support a motion that, at any one time, that no more than 50% in total of the annual budget should be committed to these outgoings. This motion was supported by the General Assembly.

9. The next issue raised was that of registering the Society in London and of moving the bank account. At present, it is not clear whether the Society needs to be formally registered but the feeling of the Council Members and of the Assembly was that it was wise to look into this and, if necessary, register it in London. It was agreed to contact Professor Riley for advice on this issue.

With respect to transferring the Society's bank account, this currently is in Germany. The incoming Treasurer (Dr. Lionel Larue) is based in Paris but there seemed to be a good argument for also basing the bank account in London as successive Treasurers may be in any European country. Professor Pavel reported that Professor Riley had advised that it was possible to have an account based in London with monies paid in from other countries that this was probably handled more readily if one used a large bank with branches in a number of European countries. Professor Pavel requested that the new Officers of the Society look into this as a matter of some urgency so that the new account could be set up and, once this was set up, then Professor Peter would close the existing account.

Another issue that was raised by Dr. Helene Hill was that of bank transfers from the USA - she suggested that it would be, in many cases, more convenient to pay cash at the time of the meeting when travelling to European meetings. Professor Peter pointed out that it would be necessary to open a cash account for this by the Local Meeting Organiser but that this would, in practice, be easy to manage. There was broad agreement that this was worth exploring.

Professor Peter pointed out that with respect to closure of accounts, there would be need for signature transfers at a Consulate Office.

SMN/SLMA
5 October 2000

MINUTES OF THE ESPCR COUNCIL MEETING OF THE 9TH ANNUAL ESPCR MEETING

ULM, GERMANY
27 September - 1 October 2000

1. Opening of Meeting
The meeting was opened and Council members welcomed by Professor Stan Pavel.

2. Apologies
Apologies for absence were received from Professor Martin Peter.

3. Minutes of the 1999 ESPCR Council Meeting in Nagoya
These Minutes, previously circulated, were approved and then signed by Professor Pavel.

4. Secretary's Report

This was delivered by Professor Sheila Mac Neil. Professor Mac Neil reported that the main events of the preceding 12 months had included a meeting of the ESPCR Officers in London (10 January 2000) concerning the Constitution of the Society - see item 11 beneath. Also, at this meeting, a decision was taken to undertake a ballot to see whether the Society would support the institution of a Fritz Anders Memorial Lecture to commemorate Professor Anders. The decision to pay membership fees in Euros was taken by the Officers of the Society at the meeting in January and discussions were held concerning the running of the Treasurer's database and that of the database managed by Professor Ghanem on the website. In October 1999, the Treasurer's list had 227 names whereas the list managed by Professor Ghanem on the website had 153 members. By September 2000, the Treasurer's list had 203 names and that managed by Professor Ghanem had 176. Thus, the discrepancy between these databases has improved significantly but there is still significant room for improvement. Some of the differences between these databases will relate to the issue of new members who have not yet paid their fees and are not yet recorded on Professor Ghanem's database. However, this is unlikely to be as many as 27 members.

Other items which concerned the Secretary over the last year were a ballot for new ESPCR Officers and recruitment of new members. With respect to the ballot, it was necessary to hold elections for the President, Secretary and Treasurer of the Society. Professor Mac Neil sent a call for nominees out to all ESPCR members in July 2000. A request was also made to the membership to look into the feasibility of conducting the ballot by e-mail - unfortunately only around 30 members replied by e-mail stating their willingness to conduct the ballot in this way. Accordingly, the ballot was conducted by post. There were two nominees for President, Secretary and Treasurer - the outcome of ballot was as detailed in item 12.

Finally, the Editor of Pigment Cell Research (Dr. Vince Hearing) sent a list of people who have published in the field of pigment cells. 110 were identified who are not currently

members of the ESPCR. Professor Mac Neil sent letters to each of them enclosing details of the Society and the benefits of joining them and a copy of the application form which is held on the ESPCR website.

5. Treasurer's Report

Professor Peter reported that the Treasurer's Report would be ready for presentation to the ESPCR members at the ESPCR General Assembly to be held on Sunday, 1 October at 9.00 am.

6. ESPCR Bulletin Report

Professor Ghanem reported that there had been no problems in preparing or printing the Bulletin and no increase in costs. The Council members wished to record a vote of thanks to Professor Ghanem for his management of the Bulletin. He did point out, however, that there was little recognition for the International Editorial Board which currently comprises 10 members covering a range of topics. Professor Pavel pointed out that all members of the International Editorial Board now receive a free subscription to Pigment Cell Research. Professor Ghanem also suggested that it might be appropriate for contributors to also receive a free registration for ESPCR meetings. The Council supported this suggestion but it was noted that the financial responsibility for this should rest with the ESPCR Council rather than the local organisers of ESPCR meetings.

There was also discussion of the status of Professor Ghanem as Manager of the ESPCR Website. Professor Ghanem wished to note that he was happy to remain as an ex-officio member of the ESPCR Council as a Manager of the Website and, as noted in our revised Constitution, would therefore always be present at Council meetings irrespective of whether he is a member of the Council or not.

7. Report on ESPCR Website

There was considerable discussion on two issues related to the management of the website: the issue of disclosure of members' contact details and the issue of what privileges should be behind the ESPCR members' "gate". With respect to the membership details, the issues which were discussed were that of confidentiality of contact information versus ease of contact versus advertising of the membership of the ESPCR.

The key issue was whether membership contact information on the ESPCR website should be:

open to all
open to all but with the option of individuals choosing to restrict access to their particular contact information to members only
restricted to members only

There was no clear consensus at the Council Meeting other than that this was something that needed bringing to the attention of the membership as a whole and possibly getting feedback on via a discussion/ballot of the membership.

Another issue that was discussed at some length and viewed as important was access to the Pigment Cell Bulletin. Here, the issues seemed to be whether access should be:

open to all
advertised in terms of contents pages on an open site but with the contents restricted to members only (as it is as present)
restricted to members only

A number of issues relevant to the thinking were a general inability of Council members to remember their access code issued by Professor Ghanem every few months. Professor Ghanem confirmed that there were indeed very few hits on the members only page of the website. Another issue raised by Professor Dorothy Bennett was that it might be interesting to look into a cooperation with the Pan American Society of Pigment Cell Research with respect to their Bulletin. There was considerable interest in this latter suggestion with the view that it merited exploration but there was no need to make any immediate decision.

Professor Ghanem pointed out that there was reciprocal swapping of reports on meetings which was useful. Other items that have been added to the website of late have been the abstracts of Ph.D. theses on pigmented cell biology.

There was discussion of whether the abstracts for the European meetings should appear on the web prior to the meeting but the consensus view was that the current system of publishing these in Pigment Cell Research and having this available approximately 2 weeks before the meeting seemed the most sensible. To do this, the deadline for abstracts must be at least 9 weeks before the meeting in camera ready form.

8. Matters Relating to Ulm Meeting

Professor Peter reviewed some of the arrangements: both social and scientific of the Ulm Meeting. The Council wished to record their thanks to Professor Peter and his team for taking on the organisation of the Ulm Meeting at short notice.

9. Travel Awards

The Travel Awards Committee of Dr. Friedo Beermann, Professor Bennett and Professor José García-Borrón reported that they received 10 applications (3 too late to consider). Of the 7 that were considered, 4 were funded, 1 was funded completely and 3 funded partially. There was some discussion of the issue of getting some publicity for these Travel Awards and it was agreed that Professor Pavel would announce the successful Travel Awards at the start of the Ulm Meeting and that the ESPCR members receiving Travel Awards would also have this recorded on the ESPCR web page.

Dr. Beermann reported on some small and sensible changes which the Travel Awards Committee have made to the running of these awards. It was agreed that there should be a general policy for how much funding could be made available for Travel Awards for each European meeting and it was agreed that 20% of the ESPCR budget at any time maximum should be made available for Travel Awards.

10. Venues for Next ESPCR Meetings

The venues for the next meetings of the ESPCR are:

Rome - organised by Professor Mauro Picardo
2002 Scheveningen - organised by Professor Stan Pavel
2003 At present there is no venue and Council members were urged to consider whether they could host an ESPCR meeting for 2003. Professor Garcia-Borron agreed to discuss it with his colleagues in Murcia.

11. Statutes for Continuing ESPCR Beyond 2000

Professor Pavel reported that the outcome of a small Committee consisting of himself, the Secretary, Professor Patrick Riley, Professor Ghanem and Professor Peter meeting in January 2000 was to revise the statutes of the Society to allow its continuation beyond December 2000 and to take the opportunity to make some small changes to the Constitution. Following this, there was the need to ballot the members to seek support for the continuation of the ESPCR

beyond 2000. The Secretary sent out 206 letters and received 105 replies all supporting the continuation of the ESPCR (at present, our estimated membership is around 180/190).

Professor Peter asked whether it was necessary to register the new Constitution with any authority in the UK. Sheila Mac Neil replied that, from recollection, Professor Riley had thought that this was not necessary but the consensus view of the Council was that Professor Riley should be contacted to confirm this information or find out who it is necessary to register the new Constitution with. The question of where a bank account is to be held was also raised but not resolved at this point.

12. Ballot for New Society Officers
Sheila Mac Neil reported that there were, in total, 92 replies to the ballot for new Officers. The successful candidates for President, Secretary and Treasurer are Professor Dorothy Bennett, Professor Jose Carlos Garcia-Borron Martinez and Dr. Lionel Larue respectively.

13. Any Other Business

14. Close of Meeting
The meeting was closed by Professor Pavel.

MINUTES OF THE ESPCR COUNCIL MEETING

ULM, GERMANY
Sunday, 1 October 2000

1. The meeting was opened by the new President (Professor Dorothy Bennett) who passed on apologies for absence from Dr. Friedrich Beermann, Professor José García-Borrón and Dr Lionel Larue.

2. Professor Bennett then thanked the outgoing Council Officers and discussed how transfer of functions should occur. Professor Mac Neil reported that she had already had a fairly extensive briefing with Professor Garcia-Borron and that she would be sending him the Minutes of the meetings as soon as possible following her return to the UK.

   With respect to the transfer of functions for the Treasurer, it was agreed that Professor Bennett would look both into the registration of the Society in London and to the opening of a bank account in London with a large bank with branches in Europe - candidate banks (City Bank and HSBC?). It was agreed that we should have three Officers as signatories on the account (the President, Treasurer and Secretary). Professor Ghanem pointed out that we should have an upper limit for cheque signatures for any one individual. After some discussion, it was agreed that this should be 5000 Euros. It was agreed that Professor Patrick Riley's advice would be sought both on the issue of registering the Society in London and on the issue of opening a bank account that could be used by different nationalities particularly as he has had recent relevant experience for the IFPCS.

3. Professor Bennett then raised the issue of membership of the Travel Grants Committee. She pointed out that, as President, she felt it wasn't appropriate to also stay on the Travel Grants Committee. The Council agreed with this view. Friedrich Beermann has agreed to continue to Chair this Committee and Jose Garcia-Borron was happy to stay on it if the Members thought that this was appropriate which they did. Professor Mac Neil volunteered that she would be

willing to act as the third member at least for the coming year subject to confirmation of her status on the Council.

Professor Pavel pointed out that the next point of election for Council Officers will be 2002 at which point Professor Mac Neil would be eligible to be re-elected. Until then, the Council could co-opt anyone to assist them and, in this respect, they would wish to co-opt Professor Mac Neil for 2001. This was supported by the Council Members and Professor Mac Neil agreed to be the third representative on the Travel Committee.

4. Professor Bennett then discussed potential initiatives for the ESPCR to expand the membership and make sure that we do not have under-represented research areas. Related to this was her suggestion that a Members only membership list could contain e-mail addresses and a few lines of description of our research interests.

She pointed out that there were many members of, for example, melanoma research consortiums who did not attend ESPCR meetings. Professor Ghanem said that one way to attract such scientists from outside the ESPCR would be to use the ESPCR as a focus for EC funding applications in particular areas. He said that the EC has a website which has information on applications for funding by scientific meetings.

Professor Bennett then went on to the issue of whether it would be desirable to elect the Officers of the Society a year before they start their period of office. In the Pan American Society, Officers are elected three years in advance - we agreed that electing Officers one year in advance would be sensible. Thus, in 2002, elections would be held for new Council Members and also for Officers Elect for the Society who would commence their term of office in 2003.

5. Any Other Business - Professor Tony Thody made the suggestion that it would be good to consider a Workshop Meeting in Sorrento to celebrate the 15 years that the Society has been running following its inception by Professor Giuseppe Prota and Professor Patrick Riley.

6. The meeting was then closed by Professor Bennett.

SMN/SLMA
5 October 2000

CURRENT LITERATURE

1. Melanins and other pigments chemistry

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NOT AVAILABLE

2. Biology of pigment cells and pigmentary disorders

(Dr. M. Picardo)

Abdel-Malek and co-workers underline the role of MC1R in the regulation of human cutaneous pigmentation. The authors previously studied and underline several characteristics of the MC1R; the receptor can bind alpha-MSH and ACTH with equal affinity and these agents are equivalent in regulating the proliferation and melanonogenic process in human melanocytes. The activation of the receptor is important for the modulation of the response of human melanocytes to ultraviolet irradiation. MC1R binds agouti signalling protein (ASP) inhibiting in this way the melanogenic process. The expression of the receptor is regulated by its owns ligands alpha-MSH and ACTH as well as by UVR and endothelin-1.
More recently the authors individuated some genetic variants in the receptors and analysed their different influence on the degree of functionality. The author underline the importance of a normally functioning of MC1R in the response of melanocyte to melanocortins, ASP and ultraviolet radiation.

- There is considerable debate regarding melanogenesis in the Retinal pigment epithelial (RPE) cells during adulthood. Many authors report a complete lack of tyrosinase activity both *in vivo* and *in vitro*. By contrast, other autohors have demonstrated that tyrosinase activity can be found in the RPE cells of adult animal models ad in adult humans. Abul-Hassan and co-workers studied the regulation of tyrosinase gene expression and activity in cultured human pigment epithelial cells and they demonstrated that the tyrosinase promoter is not only active but that it can also be regulated in response to various melanogenic agents. However it appears that RPE cells in culture lack a post-transcriptional and/or translational modification point(s), which are necessary for tyrosinase enzymatic activity.
- Germline mutations in p16 or CDKN2A are found in a significative percentage of relatively rare melanoma families, but p16 mutations are uncommon in sporadic tumours. P16 may still be involved by other mechanisms of inactivation; however it is clear that other melanoma genes remain to be discovered. Recent public health campaigns have not been very successful in changing behaviour regarding tanning and the relationship between sun exposure and melanoma is very complex . With the understanding of genetic alterations leading to this tumour, follow-up strategies and behavioural interventions may be more specifically designed to target high risk groups.
- Stem cell factor (SCF) and its receptor c-kit are important for melanocyte survival during development and mutations in these genes result in unpigmented hairs. Botchkareva and co-workers show that during the cycling of hair follicular re-generation, in C57BL/6 mice, proliferating, differentiating and melanin producing melanocytes express c-kit, whereas presumptive melanocyte precursor do not. During the induced hair cycle in C57BL/6 mice, dose dependent administration of anti-c-kit antibody decreases hair pigmentation and leads to partially depigmented or fully depigmented hairs. This phenomenon is associated with significant decreases in melanocyte proliferation and differentaition. However, in the next hair cycle, the previously treated animals grow fully pigmented hairs with the normal number and distribution of melanocytes. The results suggest that melanocytes stem cells are not dependent on SCF/C kit and when appropriately stimulated can generate melanogenicaly active melanocytes.
- Dorr and co-workers administrated subcutaneous injections of a superpotent synthetic analogue of alpha MSH for a period of two weeks in normal volunteers with tanning skin types III or IV. This compound [Nle4-D-Phe7] also called Melanotan-I (MT-I), determine the tanning and this phenomenon was strictly correlated with a significant increase in eumelanin content of the skin.
- Flanagan and co-workers analysed the contribution, as regard the phenotipic aspect, of the different allelic variant of the melanocortin 1 receptor (MC1R) in 174 individuals from 11 large kindreds with a preponderance of red hair and in an additional 99 unrelated redheads. The study confirmed that red hair is usually inherited as a recessive characteristic with peculiar allelic variant at this locus. However, the presence in heterozygosis, as regard some allelic variant, determine a significatively elevated risk of red hair. The shade of red hair frequently differs in heterozygotes from that in homozygotes/compound heterozygotes and there is also evidence for a heterozygote effect on beard hair colour, skin type and freckling. The data provide evidence for a dosage effect of MC1r variants on hair as well as skin colour.
- Gibbs et al., describes the establishment of pigmented reconstructed epidermis with autologous keratinocytes and melanocytes that can be kept in culture for a period of at least 6 weeks. They reported, for the first time, the *in vitro* formation of supranuclear melanin caps above the keratinocyte nuclei. In this experimental model the complete program of melanogenesis occurs: melanosome synthesis, melanosome transport to keratinocytes, supranuclear capping of keratinocyte

nuclei and tanning of the epidermis. This enables sustained application of pigment stimulators over a prolonged period of time and also repeated application of pigment stimulators to be studied.
- Although the melanogenic properties of the pigment cells of Amphibia and Reptilia liver, derived from Kupffer cells, have been amply demonstrated by cytological biochemical methods, there has not yet been any evaluation of the functions of the tyrosinase gene in this cell system. Guida G. and co-workers demonstrate that frog Kupffer cells posses an actie tyrosinase gene and that the increase of the tyrosinase mRNA accumulation closely correlates with phenotypic differentiation, in terms of increased DOPA oxidase activity and melanosome content. These results strong support the hypothesis that amphibian Kupffer cells posses an endogenous ability to synthesise melanin and suggests the involvement of the transcriptional level of control in the modulation of their melanogenic activity.
- Wild type tyrosinase in melanoma cells is targeted to proteolitic degradation by the 26S proteasome due to retention of the misfolded protein in the endoplasmic reticulum and its subsequent re-translocation to the cytosol. Halaban R and its collaborators demonstrate that DOPA and Tyrosine, two substrates of tyrosinase induce in melanoma cells a transition of misfolded wild type tyrosinase to the native conformer, that is resistant to proteolitic degradation, competent to exit endoplasmic reticulum and able to synthesise melanin. Since tyrosinase enzymatic activity is induced by DOPA, the authors propose that proper folding of the wild type proteins tightly linked to its catalytic state. Loss of pigmentation, therefore, in tyrosinase positive melanoma cells is a consequence of a tumour induced metabolic changes that suppress tyrosinase activity and DOPA production within these cells.
- Hearing presents a special lecture in which propose the melanosome as a perfect model for cellular responses to the environment. Depending on different inherent genetic characteristics and environmental stimulation structural organisation of melanosome can vary widely, from relatively disorganised, poorly pigmented pheo-melanosome to highly structured, melanized eumelanosome. Many are the stimuli that can modulate melanocytes and melanogenic process such as alpha-MSH, Agouti signal protein (ASP), Endothelins and ultraviolet irradiation. All known intracellular signalling pathways affects one or more parameters of pigmentation and both melanocyte-specific and basic housekeeping processes are affected by such modulation.
- Lamoreux ML propose an interesting review on the use of the inbred mouse in pigmentation research underling, in particular, the significance of a congenic developmental system. Mice of the same inbred strain, that differ at only one locus, can be used to evaluate the phenotypic effect of that one locus without complication of variation at other loci. Similarly, genetic interactions among the functions of two or more loci are evaluated by comparing them in all combinations against a uniform genetic background. The author underline that the next logical step in describing the pigment system will occur when all pigment cell researchers, who use mice, make certain that their mice are congenic with C57BL/6J. The work of all investigators will be genetically comparable. Interactions among the different gene loci, that are implicated in the pigment system will become more readily evident and the community of investigators using this experimental model will able to analyse the functional interplay of loci that regulate the entire pigment system in the same way that earlier researchers analysed one mutant allele, or the interactions of two mutant loci.
- Manga and co-workers report a genetic study on brown oculocutaneous albinism (BOCA), a pigmentation alteration, diffused in Africa, that determine a distinct pigmentation phenotype. BOCA locus mapped to the same region as the OCA 2 locus in particular to the OCA 2 locus on chromosome15q. Mutation analysis performed in 10 unrelated individuals with BOCA, revealed that 9 individuals presented one copy of the 2.7 kb deletion. No other mutation were identified.
- In order to understanding the mechanism that determine the development of solar lentigines after long period of exposition of skin to ultraviolet irradiation, Naganumaa and co-workers irradiated mice with a dose of 38 or 94 mJ/sq cm under an ultraviolet light source (Toshiba FL-SE; UVB) three times /week for various periods of time(1-8 weeks). Skin colour was monitored with a colorimeter for 78 weeks. Uniform pigmentation persisted only during exposure, disappearing completely within 2 weeks after cessation of exposure. At about 28 weeks after the first exposure, pigmented spots suddenly began to appear. Hystological examination revealed increased number of active melanocytes and melanin granules in the affected epidermis. These pigmented spots closely resembles solar lentigines in humans, and the mice should be useful as an animal model of solar lentigines
- Oetting WS proposes an interesting review on a experimental model for understanding the molecular biology of melanin formation focusing the attention on the association between mutations in the tyrosinase gene and cutaneous albinism Type 1 (OCA1). Different mutations of the tyrosinase gene (*TYR*), and their association with oculocutaneous albinism type I (OCA) has provided insight into the biology of tyrosinase, including trafficking and structure/function analysis. However there are some individuals with albinism who do not have mutations in any of the known genes and may represent other types of albinism associated with mutations in genes that have yet to be identified. Several questions still remain, including cryptic mutations that affect tyrosinase activity and the minimum amount of pigment required for normal optic development. The author underline that the next 10years should prove just as exciting as the last.
- Sox 18 gene is expressed in developing vascular endothelium and hair follicles during mouse embriogenesis. Point mutations in Sox 18 cause serious cardiovascular and hair follicle defects in ragged (Ra) mice. Pennisi and co-workers described analysis of SOX 18 (-/-) mice produced by gene targeting. Despite the profound defects seen in Ra Mice, SOX 18 (-/-) mice are viable, show not obvious cardiovascular defects and only a mild coat defect. Because of the mild effect of the mutation on the phenotype of Sox 18(-/-) mice the authors conclude that the semi-dominant nature of Ra mutations is due to a trans-dominant negative effect mediated by the mutant SOX18 proteins, rather than haploinsufficiency, as has been observed for other SOX genes.
- In order to study the mechanism underling depigmentation that occurs during melanocyte transformation, Prince and co-workers infected mouse melanocytes with a temperature-sensitive mutant of Simian Virus 40 (SV40) large tumour antigen. One of six cell line transfected gradually depigmented and this phenomenon was accompanied by enhanced growth and

down-regulation of melanocyte-specific gene expression. When the oncogene was inactivated by culture at the non-permissive temperature, the pigmented phenotype in the cells could be rescued and there was a corresponding time-dependent increase in melanocyte-specific gene expression. The results provide direct evidence for the role of the SV40 large T antigen in melanocyte de-differentiation. Expression of Pax-3, a transcriptor factor implicated in melanocyte differentiation, was unaltered during SV40-initiated de-differentiation.
- Richards KA and co-workers identified a novel KIT mutation in a 8-year-old girl and in her mother who had unusual piebaldism of a progressive nature. Genomic DNA was extracted from the blood of affected and unaffected family members and the KIT gene was sequenced. Genetic analysis of genomic DNA from the mother and daughter revealed a novel VAL620Ala (1859T>C) mutation not observed in the others individuals analysed. This mutation influence the intracellular tyrosine kinase domain. Although other KIT mutations in the vicinity of the codon 620 lead to the standard phenotype of static piebaldism, the Val620Ala now described, is novel and may result in a previously undescribed phenotype with melanocyte instability, leading to progressive loss of pigmentation as well as the progressive appearance of the hyperpigmented macules.
- The tyrosinase enzyme complex and related proteins have been studied in detail, while the process of polymerisation of colourless monomers to melanin has hardly been investigated. An alkaline environment seems to be essential for polymerisation to take place, melanin polymerisation however occurs only in coated vesicles in melanocytes, which are known to be acidic. The process of dimerisation of monomers end further elongation of polymers in fact requires a deprotonation step which is not favoured in an acidic environment. Wagh and co-workers tried to investigate the polymerisation of melanin in the acidic environment of melanosomes. The authors hypothesised that the amminoacid side chains of melanosomal proteins acts as proton acceptors to initiate polymerisation and that the protonated basic groups serve to attract the negatively charged oligomers thus aiding polymerisation and binding to proteins. They show that basic model proteins and basic premelanosomal proteins promote polymerisation at an acidic pH and that positively charged surfaces allow binding of growing melanin polymers. Whit progressive polymerization and exhaustion of the proton abstracting ability of melanosomal proteins, melanosomal pH drops further, which probably could be an additional controlling step that limits tyrosinase activity and melanin polymerisation.

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Correlation between diffuse pigmentation and keratinocyte-derived endothelin-1 in systemic sclerosis. Int J Dermatol 39 (12): 899-902, 2000.

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Melanosomal Proteins Promote Melanin Polymerization. Pig Cell Res 13: 442-448, 2000.

3. MSH, MCH, other hormones, differentiation

(Dr. B. Loir)

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Basic fibroblast growth factor and ultraviolet b transform melanocytes in human skin. Am J Pathol. 158(3):943-53, 2001.

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Multi-facet expressions of adenylate cyclase isoforms in B16-F10 melanoma cells differentiated by forskolin treatment. Exp Mol Med. 32(4):235-42, 2000.
Comments : "The terminal differentiation of malignant melanoma cells is known to be induced by activating cAMP signaling pathway with alpha-MSH or cAMP analogues." However, sustained activation of this signaling system also induces the desensitization of the pathway at the receptor level. Therefore, the authors investigated (in B16/F10 murine melanoma cells) changes in the expression of adenylate cyclase (AC) isoforms as an adaptation mechanism. Their results suggest that sustained activation of cAMP system induces differential expression of AC isoforms, which results in increase of cAMP accumulation.

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Mechanisms regulating c-met overexpression in liver-metastatic B16-LS9 melanoma cells. J Cell Biochem. 81(3):477-87, 2001.
Summary: The authors investigated the molecular mechanisms regulating expression of the proto-oncogene c-met, the cellular receptor for hepatocyte growth factor/scatter factor in melanoma cells with low (parental line B16-F1) and high expression levels (liver-specific B16-LS9). This c-met overexpression was observed at the protein and mRNA levels in B16-LS9. They also "found evidence that autonomous activation of the melanocortin receptor-1 (MCR-1) is at least partially responsible for c-met upregulation in B16-LS9 cells."

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The CpG island promoter of the human proopiomelanocortin gene is methylated in nonexpressing normal tissue and tumors and represses expression. Mol Endocrinol. 15(2):338-48, 2001.

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Pleiotropic effects of corticotropin releasing hormone on normal human skin keratinocytes. In Vitro Cell Dev Biol Anim. 37(1):50-4, 2001.

4. Photobiology

(Dr. E. Wenczl)

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Basic fibroblast growth factor and ultraviolet B transform melanocytes in human skin. Am J Pathol 158:943-953, 2001.

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Activating transcription factor 2-derived peptides alter resistance of human tumor cell lines to ultraviolet irradiation and chemical treatment. 7:331-342, 2001.
Comments: This study identified a critical domain of activating transcription factor 2 (ATF2) that may be used to sensitize melanoma cells to irradiation and chemical treatment-induced apoptosis and that can induce apoptosis when combined with inhibition of ATF2 kinase, p38.

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Intermediate-effect biomarkers in I prevention of skin cancer. IACR Sci Publ 154:81-91, 2001.

- Gibbs S, Murli S, De Boer G, Mulder A, Mommaas AM, Ponec M.
Melanosome capping of keratinocytes in pigmented roconstructed epidermis—effect of ultraviolet rediation and 3-isobutil-1-methylxanthine on melanogenesis. 13:459-466, 2000.
Comments: Establishment of pigmented reconstructed epidermis with autologous keratinocytes and melanoctes is described that can be kept in culture for a period of at least 6 weeks. It was shown that in this model system the complete program of melanogenesis occurs: melanosome synthesis, melanosome transport to keratinocytes, supranuclear capping of keratinocytes nuclei and tanning of the epidermis.

- Jimbow K, Chen H, Park J, Thomas P.

Increased sensitivity of melanocytes to oxidative stress and abnormal expression of tyrosinase-related protein in vitiligo. Br J Dermatol 144:55-65, 2001.
Comments: The objective of the study was to clarify the biological role of human tyrosinase-related protein 1 (TRP-1) in melanocyte survival. The results suggested that the early cell death of vitiligo melanocytes is related to their increased sensitivity to oxidative stress, which may arise from complex processes of abnormal synthesis and processing of TRP-1 and its interaction with calnexin.

- Ley RD.
Dose response for ultraviolet radiation A-induced focal melanocytic hyperplasia and nonmelanoma skin tumors in Monodelphis domestica. Photochem Photobiol 73:20-23, 2001.
Comments: The results of this study indicate that the efficacy of UVA to induce focal melanocytic hyperplasia in the opossum is not as great as would be predicted from the action spectrum for melanoma induction in a fish model.

- Mitchell DL, Byrom M, Chiarello S, Lowery MG.
Attenuation of DNA damage in the dermis and epidermis of the albino hairless mouse by chronic exposure to ultraviolet A and –B radiation. Photochem Photobiol 73:83-89, 2001.
Comments: Skh-1 albino hairless mice were treated for 60 d with UVA or UVB radiation. They measured the frequency of cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts induced by a single acute sunburn dose of UVB at different stages of the chronic treatment. It was shown that both UVA and UVB exposure produced a photoprotective response in the dermis and epidermis and that the degree of photoproduct attenuation was dependent on dose, wavelength and the type of damage induced. Although epidermal thickening was important, the data suggested that UV protective compounds other than melanin may be involved in mitigating the damaging effects of sunlight in the skin.

- Naganumaa M, Yagi E, Fukuda M.
Delayed induction of pigmented spots on UVB-irradiated hairless mice. 25:29-35, 2001.

- Pfalberg A, Kolmel KF, Gefeller O.
The Febim Study Group, Timing of excessive ultraviolet radiation and melanoma: epidemiology does not support the existance of a critical period of high susceptibility to solar ultraviolet radiation-induced melanoma. Br J Dermatology 144:471-475, 2001.
Comments: The results of this paper do not provide supporting evidence for the existance of a so called ´critical period´ in melanoma etiology. The hazardous impacts of sunburns seems to persist lifelong and thus activities concerned with melanoma prevention should be directed to the entire population rather than being focused only on younger groups.

- Scott G, Zhao Q.
Rab3a and SNARE proteins: potential regulators of melanosome movement. J Invest Dermatol 116:296-304, 2001.

- Whiteman DC, Whiteman CA, Green AC.
Childhood sun exposure as risk factor for melanoma: a systematic review of epidemiologic studies. Cancer Causes Control 12:69-82, 2001.
Comments: The goal of the study was to review the evidence that childhood is a period of particular susceptability to the carcinogenic effects of solar rediation. They concluded that ecological studies provided better-quality evidence than case-control studies for examining the effects of exposure to sunlight during specific age periods. Exposure to high levels sunlight in childhood is a strong determinant of melanoma risk, but sun exposure in adulthood also plays a role.

5. Neuromelanins

(Prof. M. d'Ischia)

The critical issue of iron storage and homeostasis in the substantia nigra and other brain regions continues to attract the interests of researchers involved in studies of the role of neuromelanin in Parkinson's disease. Zecca et al. (J Neurochem 2001 Mar 15;76(6):1766-1773) monitored both the levels of neuromelanin and the molecular distribution and aging trend of brain iron in normal subjects from 1 to 90 years old. The results indicated similar trends for neuromelanin, iron, H-ferritin and L-ferritin levels, with a marked raise from the first years to the second-to-fourth decade followed by a much lower increase (for neuromelanin) or a stabilization (for iron and ferritin) up to the eighth-ninth decade. On the basis of these and other data the authors concluded that neuromelanin is the main iron sink in substantia nigra neurones in healthy normal subjects, an observation that may bear important implications in relation to the biochemical pathology of Parkinson's disease. In this regard, in a reviewing paper Double et al. (J Neural Transm Suppl 2000;(60):37-58) surveyed iron homeostasis in Parkinson's disease. Based on the established observation that increased iron is only apparent in the

advanced stages of the disease, they concluded that iron-neuromelanin interaction is unlikely to be of importance for the primary aetiology of PD, but may be important as a secondary mechanism by increasing the oxidative load on the cell, thereby driving neurodegeneration.
Redox aspects of signalling by catecholamines and their metabolites were critically examined by Smythies (Antioxid Redox Signal 2000 Fall;2(3):575-83) who presented evidence suggesting that abnormalities of catecholamine oxidative metabolism may be implicated in the pathogenesis of Parkinson's disease and schizophrenia by toxic mechanisms causing synaptic deletion.
The molecular mechanism of dopamine-induced apoptosis were investigated by Barzilai et al. (J. Neural Transm Suppl 2000;(60):59-76) who, using the differential display approach, sought to isolate and characterize genes whose expression is altered in response to DA toxicity. The results indicated an upregulation of the collapsin response mediator protein (CRM) and TCP-1delta in sympathetic neurons which undergo dopamine-induced apoptosis. A possible functional role for collapsin-1 and TCP-1delta as positive mediators of DA-induced neuronal apoptosis was suggested.
Finally, based on the role of oxidative stress in the etiology of Parkinson's disease, Kidd (Altern Med Rev 2000 Dec;5(6):502-29) proposed guidelines for a rational, integrative management of PD, including (1) dietary revision to lower calories; (2) rebalancing of essential fatty acid intake toward anti-inflammatory prostaglandins; (3) aggressive repletion of glutathione and other nutrient antioxidants and cofactors; (4) energy nutrients acetyl L-carnitine, coenzyme Q10, NADH, and the membrane phospholipid phosphatidylserine (PS), (5) chelation as necessary for heavy metals; and (6) liver P450 detoxification support.

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  Impaired iron homeostasis in Parkinson's disease. J Neural Transm Suppl. 2000;(60):37-58, 2000.

- Kidd PM.
  Parkinson's disease as multifactorial oxidative neurodegeneration: implications for integrative management. Altern Med Rev. 5(6):502-29, 2000.

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  Redox aspects of signaling by catecholamines and their metabolites. Antioxid Redox Signal. 2(3):575-83, 2000.

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  Iron, neuromelanin and ferritin content in the substantia nigra of normal subjects at different ages: consequences for iron storage and neurodegenerative processes. J Neurochem. 76(6):1766-73, 2001.

6. Genetics, molecular and developmental biology

(Dr. F. Beermann)

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  Regulation of tyrosinase expression and activity in cultured human retinal pigment epithelial cells. Pigment Cell Research 13(6):436-441, 2000.

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  Diverse prevalence of large deletions within the OA1 gene in ocular albinism type 1 patients from Europe and North America. Human Genetics 108:51-54, 2001.

- Bertolotto C, Busca R, Ballotti R, Ortonne JP.
  Cyclic AMP is a key messenger in the regulation of skin pigmentation [French]. M S Medecine Sciences 17(2):177-185, 2001.

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  Benzo(a)pyrene and X-rays induce reversions of the pink-eyed unstable mutation in the retinal pigment epithelium of mice. Mutation Research Fundamental & Molecular Mechanisms of Mutagenesis 457(1-2):31-40, 2000.

- Britsch S, Goerich DE, Riethmacher D, Peirano RI, Rossner M, Nave KA, Birchmeier C, Wegner M.
  The transcription factor Sox10 is a key regulator of peripheral glial development. Genes & Development 15(1):66-78, 2001.

Summary: The authors have generated a knock-out of the transcription factor Sox10, and have identified effects on different cell types, for example glial cells and Schwann cells. However, they also describe an effect of Sox10 on melanoblasts and melanocytes, and their results suggest, that (1) Sox10 is controlling melanoblast development and (2) Mitf and Dct are target genes of Sox10. (see also paper by Lee et al. - below)

- Coupry I, Taine L, Goizet C, Soriano C, Mortemousque B, Arveiler B, Lacombe D.
Leucodystrophy and oculocutaneous albinism in a child with an 11q14 deletion. Journal of Medical Genetics 38(1):35-38, 2001.

- Faraco CD, Vaz SAS, Pastor MVD, Erickson CA.
Hyperpigmentation in the Silkie fowl correlates with abnormal migration of fate-restricted melanoblasts and loss of environmental barrier molecules. Developmental Dynamics 220(3):212-225, 2001.

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Clear cell sarcoma shows immunoreactivity for microphthalmia transcription factor: Further evidence for melanocytic differentiation. Modern Pathology 14(1):6-9, 2001.

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A biochemical function for attractin in agouti-induced pigmentation and obesity. Nature Genetics 27(1):40-47, 2001.

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Expression of the melanin-concentrating hormone receptor in porcine and human ciliary epithelial cells. Investigative Ophthalmology & Visual Science 42(1):206-209, 2001.

- Hou L, Panthier JJ, Arnheiter H.
Signaling and transcriptional regulation in the neural crest-derived melanocyte lineage: interactions between KIT and MITF. Development 127(24):5379-5389, 2000.
Conclusion: The results thus demonstrate that the presence of MITF is not sufficient for tyrosinase expression in melanoblasts and that KIT signaling influences gene expression during melanocyte development in a gene-selective manner.

- Hume AN, Collinson LM, Rapak A, Gomes AQ, Hopkins CR, Seabra MC.
Rab27a regulates the peripheral distribution of melanosomes in melanocytes. Journal of Cell Biology 152(4):795-808, 2001.

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Oa1 knock-out: new insights on the pathogenesis of ocular albinism type 1. Human Molecular Genetics 9(19):2781-2788, 2000.
Abstract: Ocular albinism type I (OA1) is an X-linked disorder characterized by severe reduction of visual acuity, strabismus, photophobia and nystagmus, Ophthalmologic examination reveals hypopigmentation of the retina, foveal hypoplasia and iris translucency. Microscopic examination of both retinal pigment epithelium (RPE) and skin melanocytes shows the presence of large pigment granules called giant melanosomes or macromelanosomes, In this study, we have generated and characterized Oa1-deficient mice by gene targeting (KO), The KO males are viable, fertile and phenotypically indistinguishable from the wild-type littermates. Ophthalmologic examination shows hypopigmentation of the ocular fundus in mutant animals compared with wild-type. Analysis of the retinofugal pathway reveals a reduction in the size of the uncrossed pathway, demonstrating a misrouting of the optic fibres at the chiasm, as observed in OA1 patients. Microscopic examination of the RPE shows the presence of giant melanosomes comparable with those described in OAl patients. Ultrastructural analysis of the RPE cells, suggests that the giant melanosomes may form by abnormal growth of single melanosomes, rather than the fusion of several, shedding light on the pathogenesis of ocular albinism

- Ivanovich J, Mallory S, Storer T, Ciske D, Hing A.
12-year-old male with Elejalde syndrome (neuroectodermal melanolysosomal disease). American Journal of Medical Genetics 98(4):313-316, 2001.

- Kawaguchi N, Ono T, Mochii M, Noda M.
Spontaneous mutation in Mitf gene causes osteopetrosis in silver homozygote quail. Developmental Dynamics 220(2):133-140, 2001.

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Microphthalmia transcription factor expression in cutaneous benign, malignant melanocytic, and nonmelanocytic tumors. American Journal of Surgical Pathology 25(1):51-57, 2001.

- Kuramoto T, Kitada K, Inui T, Sasaki Y, Ito K, Hase T, Kawagachi S, Ogawa Y, Nakao K, Barsh GS, Nagao M, Ushijima T, Serikawa T.
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The inbred mouse in pigmentation research: Significance of a congenic developmental system. Pigment Cell Research 13(6):421-430, 2000.

- Lee M, Goodall J, Verastegui C, Ballotti R, Goding CR.
Direct regulation of the Microphthalmia promoter by Sox10 links Waardenburg-Shah syndrome (WS4)-associated hypopigmentation and deafness to WS2. Journal of Biological Chemistry 275(48):37978-37983, 2000.
Abstract: The transcription factor Sox10 is genetically linked with Waardenburg syndrome 4 (WS4) in humans and the Dominant megacolon (Dom) mouse model for this disease. The pigmentary defects observed in the Dom mouse and WS4 are reminiscent of those associated with mutations in the microphthalmia (Mitf) gene, which encodes a transcription factor essential for the development of the melanocyte lineage. We demonstrate here that wild type Sox10 directly binds and activates transcription of the MITF promoter, whereas a mutant form of the Sox10 protein genetically linked with WS4 acts as a dominant-negative repressor of MITF expression and can reduce endogenous MITF protein levels. The ability of Sox10 to activate transcription of the MITF promoter implicates Sox10 in the regulation of melanocyte development and provides a molecular basis for the hypopigmentation and deafness associated with WS4
(see also paper by Britsch et al. - above)

- Li JH, Holmes LM, Franek KJ, Wagner TE, Wei YZ.
Murine tyrosinase expressed by a T7 vector in bone marrow-derived dendritic progenitors effectively prevents and eradicates melanoma tumors in mice. Cancer Gene Therapy 7(11):1448-1455, 2000.

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In southern Africa, brown oculocutaneous albinism (BOCA) maps to the OCA2 locus on chromosome 15q: P-gene mutations identified. American Journal of Human Genetics 68(3):782-787, 2001.

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The Tyrosinase gene in gorillas and the albinism of 'snowflake'. Pigment Cell Research 13(6):467-470, 2000.

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Mutational analysis of endothelin receptor b1 (rose) during neural crest and pigment pattern development in the zebrafish Danio rerio. Developmental Biology 227(2):294-306, 2000.

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Distinct protein sorting and localization to premelanosomes, melanosomes, and lysosomes in pigmented melanocytic cells. Journal of Cell Biology 152(4):809-823, 2001.

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The apical ectodermal ridge, fibroblast growth factors (FGF-2 and FGF-4) and insulin-like growth factor I (IGF-I) control the migration of epidermal melanoblasts in chicken wing buds. Anatomy & Embryology 203(2):137-146, 2001.

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Intracellular distribution and late endosomal effects of the ocular albinism type 1 gene product: consequences of disease-causing mutations and implications for melanosome biogenesis. Traffic 2:202-211, 2001.

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7. Tyrosinase, TRPs, other enzymes

(Prof. J.C. Garcia-Borron)

The possibility that Agouti signaling protein (ASP) might be a ligand for a still uncharacterised receptor has been often discussed. The work by Abdel-Malek et al. (J Cell Sci 2001 Mar;114(Pt 5):1019-24) provides very strong evidence pointing to the lack of such as specific receptor, and showing that the changes in the melanogenic pathway elicited by ASP are mediated by its interaction with the melanocortin 1 receptor. The main strength of this study is the conceptual simplicity and elegance of the experimental approach, consisting in the comparison of the response to ASP of mouse melanocytes with different genetic backgrounds and mutations in the melanocortin 1 receptor.
Olivares et al. (Biochem J 2001 Feb 15;354(Pt 1):131-9) report on the DHICA oxidase activity of human tyrosinase. From this and previous reports from Y. Mishima's laboratory, it is clear that human tyrosinase is able to oxidize DHICA. This finding raises several questions, and maybe the most intriguing one is that of the funtion of human Tyrp1. Indeed, whilst most of us will agree in that mouse tyrp1 functions as a DHICA oxidase, no such activity has been shown for the human enzyme. And since human tyrosinase is able to oxidize DHICA, a DHICA oxidase activity for human Tyrp1 seems redundant and might just not occur. Therefore, what is (are) the real role(s) of human Tyrp1? One possibility is that, as convincingly shown for the mouse enzyme by V. Hearing's laboratory, human Tyrp1 effectively stabilizes tyrosinase. But can tyrosinase stabilization be the only function of human Tyrp1? From a biological point of view, this does not seem an "economically" interesting situation. And based on the sequence homology with tyrosinase and Tyrp2, it is likely that human Tyrp1 might display still uncharacterised enzymatic and/or regulatory functions. In keeping with this view, an interesting report from Jimbow et al. (Br J Dermatol 2001 Jan;144(1):55-65) describes changes in Tyrp1 mRNA expression and protein folding in vitiligo melanocytes under conditions of oxidative stress, as probably related to the higher sensitivity of vitiligo melanocytes to oxidative lysis.
Not too long ago, work from Friedo Bermann's group demonstrated tyrosinase gene expression without a concomitant tyrosinase enzymatic activity in the brain. Now, a similar observation is reported by Abul-Hassan et al (Pigment Cell Res 2000 Dec;13(6):436-41) using human retinal pigment epithelial cells. Therefore, the role of tyrosinase gene expression in extracutaneous locations remains elusive. In relation to this, a very interesting report by Guida et al. (Pigment Cell Res 2000 Dec;13(6):431-5) provides the first evidence for tyrosinase gene expression in Kupffer cells from amphibians. These cells do not belong to the melanocyte lineage, but nevertheless they are able to express the tyrosinase gene, and moreover, they display tyrosinase-like enzymatic activities. The immediate question is the role of melanin in liver. So, we have a protein without a well defined function (human Tyrp1), tyrosinase gene expression without apparent enzymatic activity (in brain and RPE), and tyrosinase gene expression plus enzymatic activity and melanin synthesis with no assigned role in the liver of amphibians ….. enough matters to think about for a while !
Three papers referenced in this issue deal with interesting regulatory aspects of melanogenesis. Brian Fuller et al. emphasize the role of pH in the regulation of melanogenesis (Exp Cell Res 2001 Jan 15;262(2):197-208). The possible role of pH was also recently revisited by Anthony Thody's laboratory with similar results. It therefore should be considered established that increasing melanosomal pH leads to increases in melanosynthesis by stimulating tyrosinase activity. The novel, and highly interesting aspect of B. Fuller's paper is that it shows that changes in melanosomal pH could actually be in the "in vivo" regulation of pigmentation in normal skin, and not only in response to external stimuli or to certain drugs, or under pathological conditions. Moreover, the authors go on showing differences in the melanosomal pH of Caucasian and Black skin-derived melanocytes. This opens very interesting perspectives, and calls for a deep study of the molecular machinery of pH regulation in the melanosomes. On the other hand, Kosano et al. (Biochim Biophys Acta 2000 Dec 11;1499(1-2):11-18) present an interesting study on the stimulation of melanogenesis by MBP, a benzimidazole derivative, in B16 melanoma cells. A puzzling feature of the process is that the effect seems cAMP-independent, but apparently dependent on PKA. Last, but not least, Ujvari et al. (J Biol Chem 2001 Feb 23;276(8):5924-31) provide new insights on the role of glycosylation in tyrosinase activity, and introduce the concept that the rate of translation is important for the correct processing of the enzyme.

- Abdel-Malek Z, Scott M, Furumura M, Lamoreux M, Ollmann M, Barsh G, Hearing V.

The melanocortin 1 receptor is the principal mediator of the effects of agouti signaling protein on mammalian melanocytes. J Cell Sci. 114(Pt 5):1019-24, 2001.

- Abul-Hassan K, Walmsley R, Tombran-Tink J, Boulton M.
Regulation of tyrosinase expression and activity in cultured human retinal pigment epithelial cells. Pigment Cell Res. 13(6):436-41, 2000.

- Bardeesy N, Bastian BC, Hezel A, Pinkel D, DePinho RA, Chin L.
Dual inactivation of RB and p53 pathways in RAS-induced melanomas. Mol Cell Biol. 21(6):2144-53, 2001.

- Buyukafsar K, Nelli S, Martin W.
Formation of nitric oxide from nitroxyl anion: role of quinones and ferricytochrome c. Br J Pharmacol 2001 Jan;132(1):165-72, 2001.

- Fuller BB, Spaulding DT, Smith DR.
Regulation of the catalytic activity of preexisting tyrosinase in black and Caucasian human melanocyte cell cultures. Exp Cell Res. 262(2):197-208, 2001.

- Guida G, Gallone A, Maida I, Boffoli D, Cicero R.
Tyrosinase gene expression in the Kupffer cells of Rana esculenta L. Pigment Cell Res. 13(6):431-5, 2000.

- Hofele K, Sedelis M, Auburger GW, Morgan S, Huston JP, Schwarting RK.
Evidence for a dissociation between MPTP toxicity and tyrosinase activity based on congenic mouse strain susceptibility. Exp Neurol. 168(1):116-22, 2001.

- Hou L, Panthier JJ, Arnheiter H.
Signaling and transcriptional regulation in the neural crest-derived melanocyte lineage: interactions between KIT and MITF. Development. 127(24):5379-89, 2000.

- Jimbow K, Chen H, Park J, Thomas P.
Increased sensitivity of melanocytes to oxidative stress and abnormal expression of tyrosinase-related protein in vitiligo. Br J Dermatol. 144(1):55-65, 2001.

- Kosano H, Kayanuma T, Nishigori H.
Stimulation of melanogenesis in murine melanoma cells by 2-mercapto-1-(beta-4-pyridethyl) benzimidazole (MPB). Biochim Biophys Acta. 1499(1-2):11-18, 2000.

- Manga P, Kromberg J, Turner A, Jenkins T, Ramsay M.
In southern africa, brown oculocutaneous albinism (boca) maps to the oca2 locus on chromosome 15q: p gene mutations identified. Am J Hum Genet 68(3):782-7, 2001.

- Martinez-Arias R, Comas D, Andres A, Abello MT, Domingo-Roura X, Bertranpetit J.
The tyrosinase gene in gorillas and the albinism of 'Snowflake'. Pigment Cell Res. 13(6):467-70, 2000.

- Olivares C, Jimenez-Cervantes C, Lozano JA, Solano F, Garcia-Borron JC.
The 5,6-dihydroxyindole-2-carboxylic acid (DHICA) oxidase activity of human tyrosinase. Biochem J. 354(Pt 1):131-9, 2001.

- Prince S, Illing N, Kidson SH.
Sv-40 large t antigen reversibly inhibits expression of tyrosinase, trp-1, trp-2 and mitf, but not pax-3, in conditionally immortalized mouse melanocytes. Cell Biol Int. 25(1):91-102, 2001.

- Rikke BA, Simpson VJ, Montoliu L, Johnson TE.
No effect of albinism on sedative-hypnotic sensitivity to ethanol and anesthetics. Alcohol Clin Exp Res 25(2):171-6, 2001.

- Samaraweera P, Shen B, Newton JM, Barsh GS, Orlow SJ.
The Mouse Ocular Albinism 1 Gene Product is an Endolysosomal Protein. Exp Eye Res. 72(3):319-29, 2001.

- Simonova M, Wall A, Weissleder R, Bogdanov A Jr.
Tyrosinase mutants are capable of prodrug activation in transfected nonmelanotic cells. Cancer Res. 60(23):6656-62, 2000.

- Udono T, Takahashi K, Yasumoto Ki K, Yoshizawa M, Takeda K, Abe T, Tamai M, Shibahara S.

Expression of tyrosinase-related protein 2/dopachrome tautomerase in the retinoblastoma. Exp Eye Res.72(3):225-34, 2001.

- Ujvari A, Aron R, Eisenhaure T, Cheng E, Parag HA, Smicun Y, Halaban R, Hebert DN.
  Translation rate of human tyrosinase determines its N-linked glycosylation level. J Biol Chem. 276(8):5924-31, 2001.

- Wagh S, Ramaiah A, Subramanian R, Govindarajan R.
  Melanosomal proteins promote melanin polymerization. Pigment Cell Res. 13(6):442-8, 2000.

- Yamaki K, Gocho K, Hayakawa K, Kondo I, Sakuragi S.
  Tyrosinase family proteins are antigens specific to Vogt-Koyanagi-Harada disease. J Immunol 2000 Dec 15;165(12):7323-9, 2000.

8. Melanosomes

(Dr. J. Borovansky)

As it has recently become almost a tradition, the most intensive research activities were devoted to proteins involved in melanosome transport and distribution (Araki et al., Bahadoran et al., Hume et al, Vancoillie et al.). New data concerning protein sorting and kinetics of melanosomal proteins were obtained by Raposo et al. Two interesting papers investigating the intramelanosomal pH indicated a role of pink protein in the generation of melanosomal pH (Puri et al.) and a possible key role of melanosomal pH in racial differences (Fuller et al.). It was shown that the amino acid side chains of melanosomal proteins act as proton acceptors to initiate melanin polymerization (Wagh et al.). Another observation supporting oxidative mechanism in melanosome degradation was put forward by Nanko et al. The phenomenon of supranuclear "melanin cap" formation was demonstrated in vitro (Gibbs et al.). Melanosomes were characterized in RPE horse cells (Altunay) and in vitiligo skin where the observation of ectopic melanosomes pointed to defective melanosome maturation and transport (Tobin et al.). As usual, papers describing melanosomes in other tumours have appeared (Cummings et al., Lao et al., Monteaudo et al.). Several reviews not primarily focused to melanosomes made at least cursory remarks on the subject.

- Altunay H.
  Fine structure of the retinal pigment epithelium, Bruch's membrane and choriocapillaries in the horse. Anat Histol Embryol 29(3): 135-139, 2000.
  Comments: Melanosomes of the RPE cells of the horse are round to spindle-shaped and highly electron dense. They are distributed throuhout the cells over the non-tapetal area, but are absent at the tapetal area (As noted earlier in other species, too).

- Araki K, Horikawa T, Chakraborty AK, Nakagawa K, Itoh H, Oka M, Funasaka Y, Pawelek J, Ichihashi M.
  Small GTPase Rab3A is associated with melanosomes in melanoma cells. Pigment Cell Res 13(5): 332-336, 2000.
  Comments: G-protein Rab3A and its putative target protein Rabphilin 3A were detected to be associated with melanosomes in pigment cells in contrast to Rab GDP dissociation inhibitor which was localized in the cytosol. The authors predict the possibility of involvement of the Rab3A-Rabphilin complex, regulated by Rab-GDP dissociation inhibitor in the intracellular transport of melanosomes.

- Bahadoran P, Aberdam E, Mantoux F, Busca R, Bille K, Yalman N, de Saint-Basile G, Casaroli-Marano R, Ortonne JP, Ballotti R.
  Rab27a: A key to melanosome transport in human melanocytes. Journal of Cell Biology 152(4): 843-849, 2001.
  Comments: Using immunofluorescence and immunoelectron microscopy the authors demonstrated colocalization of Rab27a with melanosomes in normal melanocytes in contrast to a lack of Rab27 expression and abnormal melanosome distribution in melanocytes of a patient with Griscelli syndrome (GS). Reexpression of Rab27a in GS melanocytes restored melanosome transport to dendrite tips. Rab27a was suggested to be a key component of vesicle transport machinery in melanocytes.

- Camacho-Hűbner A, Beermann F.
  Caractéristiques cellulaires et moléculaire de la pigmentation chez les mammifčres – tyrosinase et TRP. Pathol Biol 48(6): 577-583, 2000.
  Comments: A review with an emphasis to tyrosinase, TRP1 and TRP2 and their genetic regulation and expression, marginally concerning melanosomes.

- Cummings TJ, Liu K, Jordan III KJ, Dodd LG.

Fine-needle aspiration diagnosis of psammomatous melanotic Schwannoma. Diagnostic Cytopathol 23(1): 55-58, 2000.
Comments: Psammomatous melanotic schwannoma and melanoma cells share the presence of melanosomes and HMB45 and S100 positivity. Presence of psammomatous bodies makes the diagnosis of melanoma less likely.

- Fuller BB, Spaulding DT, Smith DR.
Regulation of the catalytic activity of preexisting tyrosinase in black and Caucasian human melanocyte cell cultures. Exp Cell Res 262 (2): 197-208, 2001.
Comments: A model in racial pigmentation that is based on differences in melanosome pH between Black and Caucasian melanocytes has been proposed. Staining with fluorescent acridine orange showed that melanosomes of Caucasian melanocytes unlike those of Black melanocytes are acidic organelles. Treatment with lysosomotropic compounds and ionophores as well as inhibition of the vacuolar proton pump V-ATPase with bafilomycin resulted in a rapid increase in tyrosinase activity (of the preexisting enzyme) in Caucasian but not in Black melanocytes.

- Gibbs S, Murli S, de Boer G, Mulder A, Mommaas AM, Ponec M.
Melanosome capping of keratinocytes in pigmented reconstructed epidermis – effect of ultraviolet radiation and 3-isobutyl-1-methylxanthine on melanogenesis. Pigment Cell Res 13(6): 458-466, 2000.
Comments: In established pigmented reconstructed epidermis with autologous keratinocytes and melanocytes the pigment cells were regularly interspersed in the basal layer producing and transfering melanosomes into keratinocytes. The phenomenon of supranuclear melanin cap formation in the keratinocytes, until now known from *in vivo* observations, was demonstrated *in vitro* and was enhanced by UV irradiation or IBMX treatment.

- Horikawa T, Araki K, Fukai K, Ueda M, Ueda T, Ito S, Ichihashi M.
Heterozygous HPS1 mutations in a case of Hermansky-Pudlak syndrome with giant melanosomes. British J Dermatol 143(3): 635-640, 2000.
Comments: A study of mutations in the HPS1 gene in relation to abnormalities in melanosome morphology and melanin production.

- Hume AN, Collinson LM, Rapak A, Gomes AQ, Hopkins CR, Seabra MC.
Rab27a regulates the peripheral distribution of melanosomes in melanocytes. Journal of Cell Biology 152(4): 795-808, 2001.
Comments: In pigmented cells Rab27a decorated melanosomes, whereas in nonpigmented cells Rab27a colocalized with melanosomal resident proteins. When dominant interfering Rab27a mutants were expressed in pigmented cells, a redistribution of melanosomes with perinuclear clustering ensued. Rab27a and myosin Va colocalized on the cytoplasmic face of peripheral melanosomes in wild type melanocytes. The amount of myosin Va in melanosomes from Rab27a-deficient ashen melanocytes was greatly reduced. Rab27a has been suggested to be necessary for the recruitment of myosin Va, so allowing the peripheral retention of melanosomes.

- Lao LM, Kumakiri M, Kizohara H, Ueda K.
Sub-populations of melanocytes in pigmented basal cell carcinoma: a quantitative, ultrastructural investigation. J Cut Pathol 28(1): 34-43, 2001.
Comments: Melanocytes are present in basal cell carcinomas. In pigmented areas melanocytes are located not only along the basal membrane but also interspersed in the central part of tumour nests and their melanosomes are often swollen. In nonpigmented areas melanocytes are only basally located frequently showing aberrant melanosomes. Melanosome complexes in tumour cells were found after the phagocytosis of the melanosome-containing apoptotic cells.

- McVey Ward D, Griffith GM, Stinchcombe JC, Kaplan J.
Analysis of the lysosomal storage disease Chediak-Higashi syndrome. Traffic 1: 816-822, 2000.
Comments: A review devoted to Chediak-Higashi syndrome (CHS), namely to the identification of the CHS/Beige gene, to characterization of LYST protein, biochemical alterations and clinical symptoms. Section "Cellular Defects" deals with melanosome abnormalities.

- Monteagudo C, Carda A, Fernandez A, Llombart-Bosch A.
HMB-45 immunostaning and ultrastructure of melanocytic hyperplasia in pigmented basal cell carcinomas. Int J Surg Pathol 7(4): 235-241, 1999.
Comments: Immunohistochemical and ultrastructural description of 21 cases of pigmented variant of basal cell carcinoma. Large melanocytes with both immature and mature melanosomes (often with defects) were found among epithelial tumour cells some of which also contained melanosomes.

- Nanko H, Mutoh Y, Atsumi R, Kobayashi Y, Ikeda M, Yoshikawa N, Fukuda S, Kawa Y, Mizoguchi M.
Hair discoloration of Japanese elite swimmers. J Dermatol 27(10): 625-634, 2000.
Comments: 61% of swimmers of the Japanese National Swimming team suffered from hair discoloration. EM revealed decreased quantity of melanosomes in the cortex. Melanosomes were swollen, irregularly shaped with

variable electron density. X-ray microanalysis detected chlorine in them. The authors conclude that hair discoloration resulted from cuticle damage with a subsequent oxidation and denaturation of melanosomes by hypochlorous acid penetrating from water.

- Ortonne JP, Ballotti R.
  Melanocyte biology and melanogenesis: what's new? Journal of Dermatological Treatment 11(suppl.1): S15-S26, 2000.
  Comments: A review covering genes regulating pigmentation, melanogenesis and the cell signalling pathways and transcription factors, roles of proopiomelanocortin peptides and melanocortin receptor, molecular mechanisms of photoinduced melanogenesis, gene therapy, photoaging. A section "Regulation of melanosome formation dendritogenesis and melanosomes and transport" deals with GTP binding protein Rho, the AP3 complex and LYST protein in relation to Chediak-Higashi syndrome.

- Puri N, Gardner JM, Brilliant MH.
  Aberrant pH of melanosomes in pink-eyed dilution (p) mutant melanocytes. Journal of Invest Dermatol 115(4):607-613, 2000.
  Comments: Immunohistochemistry and confocal microscopy were used to show that the p protein plays an important role in the generation or maintenance of melanosomal pH. Acidic vesicles were identified with 3-(2,4-dinitroanilino)-3'-amino-N-methyldipropylamine (DAMP) incorporation. In C57BL/6 wild type melanocytes almost all vesicles showed colocalization of TRP1 and DAMP, unlike p-mutant cell lines with colocalization of the both markers in 7-8% of the vesicles.

- Raposo G, Tenza D, Murphy DM, Berson JF, Marks MS.
  Distinct protein sorting and localization to premelanosomes, melanosomes, and lysosomes in pigmented melanocytic cells. Journal of Cell Biology 152(4): 809-823, 2001.
  Comments: Melanosomal resident proteins Pmel 17 and TRP1 localized to separate vesicular structures that were distinct from those enriched in lysosomal proteins. Pmel17 was most enriched along the intralumenal striations of premelanosomes; increased pigmentation was accompanied by a decrease in Pmel 17 and by an increase in TRP1 in the limiting membrane. Both proteins were largely excluded from lysosomal compartments rich in LAMP1 and cathepsin D. Premelanosomal proteins segregated from endocytic markers within an unusual endosomal compartment which displayed a cytoplasmic planar clathrin-containing coat.

- Tobin DJ, Swanson NN, Pittelkow MR, Peters EM, Schallreuter KU.
  Melanocytes are not absent in lesional skin of long duration vitiligo. J Pathol 191(4): 407-416, 2000.
  Comments: Demonstration of aberrant melanosomes in rare melanocytes in depigmented epidermis in vitiligo and of stage IV melanosomes in basal and suprabasal keratinocytes in these areas. Single and clustered premelanosomes and ripe melanosomes were present in keratinocytes both in non-affected and affected regions in vitiligo epidermis. The observation of ectopic premelanosomes suggests defective melanosome maturation and transfer in vitiligo skin. In addition, melanin granules were found also extracellularly.

- Vancoillie G, Lambert Jo, Haeghen YV, Westbroek W, Mulder A, Koerten HK,, Mommaas AM, Van Oostveldt P, Naeyaert JM.
  Colocalization of dynactin subunits P150^{glued} and P50 with melanosomes in normal human melanocytes. Pigment Cell Res 13(6): 449-457.
  Comments: Immunofluorescence double labelling (including antibody against melanosomal marker silver protein) showed colocalization of two dynactin isoforms with melanosomes. Immunoelectron microscopy detected P50 on the surface of the majority of melanosomes in melanocytes. Since the interaction of cytoplasmic dynein with its cargos is thought to be mediated by dynactin complex, a possible linking mechanism for dynein with melanosomes was found.

- Wagh S, Ramaiah A, Subramanian R, Govindarajan R.
  Melanosomal proteins promote melanin polymerization. Pigment Cell Res 13(6): 442-448, 2000.
  Comments: The authors experimentally supported a hypothesis suggesting that the amino acid side chains of melanosomal proteins act as proton acceptors to initiate melanin polymerization and that the protonated basic groups serve to attract the negatively charged oligomers thus aiding binding between pigment and protein moieties.

- Wierzbicki H.
  Effect of melanin biosynthesis on the coat colour of animals. *(In Polish).* Medycyna Wet. 56(11): 695-699, 2000.
  Comments: A review on melanogenesis and genetic determination of coat colour of animals, marginally mentioning melanosomes.

9. Melanoma experimental, Cell culture

(Dr. N. Smit)

Brar and colleagues give an interesting point of view about the endogenous formation of ROS in melanoma cells by quinone reductase (or DT-diaphorase, NQO) . In this paper the authors describe that the reduction of ubiquinone by NQO and its redox cycling with molecular oxygen may be responsible for the generation of superoxide anion resulting in constitutive activation of NF-κB. Interestingly no role for melanin metabolism in the process of redox cycling is considered. Nevertheless the proposed mechanism may be important for tumor cells in general since NQO has been described to be overexpressed in many tumors. An approach of using antioxidant strategies has been suggested for interruption of oxidant signaling to inhibit melanoma cell growth.
Eisenhut et al. describe new N-(2-diethylaminoethyl)benzamide derivatives which could be used for melanoma imaging in patients and possibly for radionuclide therapy. The compounds were tested in C57BI/6 mice bearing B16 melanoma and it was shown for one of the radiolabeled benzamides (IMBA) that the labelling was associated with melanin containing granules.
Lant et al. have synthesized a range of new compounds which are analogues of N-acetyl-4-S-cysteaminylphenol, a compound which has been thoroughly studied as a melanoma prodrug. Significant improvement in antimelanoma activity (tested in six melanoma cell lines) was observed with a new type of analogue containing three carbon atoms between the sulphur and nitrogen. One of those compounds showed activity comparable to cisplatin for several of the cell lines.
Two separate papers describe the involvement of changes in mitochondria in the process of apoptosis. Serafino et al used transmission electron microscopy to visualize that adriamycin treatment of tumor cell lines (including melanoma TVM-A12 clone 2) leads to evident morphological changes in mitochondria . Also the mitochondrial transmembrane potential rapidly decreased as a result of the treatment which was shown by a potential-sensitive dye using confocal microscopy. Next to this Thomas and coworkers also describe changes in the mitochondrial membrane potential (MMP) which is correlated strongly with the apoptosis induced in cultured melanoma cells by TNF-related apoptosis inducing ligand (TRAIL). In this case the fluorescent probe Rhodamine 123 was used and it was observed that the induction of apoptosis was accompanied by clustering of mitochondria around the nucleus.

- Bolling B, Fandrey J, Frosch PJ, Acker H.
  VEGF production, cell proliferation and apoptosis of human IGR 1 melanoma cells under nIFN-alpha/beta and rIFN-gamma treatment. Exp.Dermatol. 9:327-335, 2000.

- Brar SS, Kennedy TP, Whorton AR, Sturrock AB, Huecksteadt TP, Ghio AJ, Hoidal JR
  Reactive oxygen species from NAD(P)H:quinone oxidoreductase constitutively activate NF-kappaB in malignant melanoma cells. Am. J. Physiol Cell Physiol 280:C659-C676, 2001.

- Demary K, Wong L, Spanjaard RA.
  Effects of retinoic acid and sodium butyrate on gene expression, histone acetylation and inhibition of proliferation of melanoma cells. Cancer Lett. 163:103-107.

- Eisenhut M, Hull WE, Mohammed A, Mier W, Lay D, Just W, Gorgas K, Lehmann WD, Haberkorn U.
  Radioiodinated N-(2-diethylaminoethyl)benzamide derivatives with high melanoma uptake: structure-affinity relationships, metabolic fate, and intracellular localization. J.Med.Chem. 43:3913-3922, 2000.

- Folini M, De Marco C, Orlandi L, Daidone MG, Zaffaroni N.
  Attenuation of telomerase activity does not increase sensitivity of human melanoma cells to anticancer agents. Eur.J.Cancer. 36:2137-2145, 2000.

- Grimm EA, Smid CM, Lee JJ, Tseng CH, Eton O, Buzaid AC.
  Unexpected cytokines in serum of malignant melanoma patients during sequential biochemotherapy. Clin.Cancer Res. 6:3895-3903, 2000.

- Hosaka Y, Higuchi T, Tsumagari M, Ishii H.
  Inhibition of invasion and experimental metastasis of murine melanoma cells by human soluble thrombomodulin. Cancer Lett. 161:231-240, 2000.

- Kouzi SA, Chatterjee P, Pezzuto JM, Hamann MT.
  Microbial transformations of the antimelanoma agent betulinic acid. J.Nat.Prod. 63: 1653-1657, 2000.

- Lant NJ, McKeown P, Kelland LR, Rogers PM, Robins DJ.
  Synthesis and antimelanoma activity of analogues of N-acetyl-4-S-cysteaminylphenol. Anticancer Drug Des 15:295-302, 2000.

- Liu S, Netzel-Arnett S, Birkedal-Hansen H, Leppla SH.
Tumor cell-selective cytotoxicity of matrix metalloproteinase-activated anthrax toxin. Cancer Res. 60:6061-6067, 2000.

- Mohammed MQ, Retsas S.
Oxaliplatin is active in vitro against human melanoma cell lines: comparison with cisplatin and carboplatin. Anticancer Drugs 11:859-863, 2000.

- Pelayo BA, Fu YM, Meadows GG.
Inhibition of B16BL6 melanoma invasion by tyrosine and phenylalanine deprivation is associated with decreased secretion of plasminogen activators and increased plasminogen activator inhibitors. Clin.Exp.Metastasis 17:841-848, 1999.

- Serafino A, Sinibaldi-Vallebona P, Lazzarino G, Tavazzi B, Di Pierro D, Rasi G, Ravagnan G.
Modifications of mitochondria in human tumor cells during anthracycline-induced apoptosis. Anticancer Res. 20:3383-3394, 2000.

- Thomas WD, Zhang XD, Franco AV, Nguyen T, Hersey P.
TNF-related apoptosis-inducing ligand-induced apoptosis of melanoma is associated with changes in mitochondrial membrane potential and perinuclear clustering of mitochondria. J.Immunol. 165:5612-5620, 2000.

ANNOUNCEMENTS & RELATED ACTIVITIES

Calendar of events

2001 International Workshop on Molecular Mechanisms of Tanning

Nice, France, Apr 27 - 29

Contact: Prof. JP ORTONNE, Dr R. BALLOTTI
IWMMT Congress Office - Maryse Clappier
Hôpital l'Archet 2 - Service de dermatologie
BP 3079
F - 06202 Nice cedex 3
Phone: 33 (0)4 92 03 61 19
Fax: 33 (0)4 92 03 65 32
E-Mail : mailto:maryse.clappier@unice.fr

2001 Xth PASPCR Meeting

Minneapolis, MN, June 14-17

Contact: Dr. Richard KING
University of Minnesota
Depts of Medecine and Pediatrics
Box 485 UMHC
420 Delaware Street
USA - Minneapolis, MN 55455
E-Mail: king@mail.ahc.umn.edu

2001 8th World Congress on Cancers of the Skin

Zürich, July 18-21

Contact: Reinhard DUMMER, M.D.
Dept. of Dermatology
University Hospital of Zürich
Gloriastrasse 31
CH- 8091 Zurich
Phone: +41 1 255 25 07
Fax: + 41 1 255 89 88
E-mail: luethim@derm.unizh.ch
Web: http://www.usz.unizh.ch/skincancer

2001 Stratum Corneum III

Basel, September 12-14

Contact: Annick GALMICHE and Silvia SCHWEIZER
Pentapharm Ltd.
P.O. Box, Engelgasse 109
CH- 4002 Basel, Switzerland
Phone: +41 61 706 48 48
Fax: +41 61 706 48 00
E-mail: annick.galmiche@pentapharm.com

2001 Xth Annual Meeting of the ESPCR

Rome, Italy, Sept 26-29

Contact: Dr. M. PICARDO
Lab. Cutaneous Physiopathology
San Gallicano Dermatological Institute
00153 Rome - Italy
Tel: 39-06-58543662
Fax: 39-06-58543740
E-Mail: picardo@crs.ifo.it
Web : http://www.ulb.ac.be/medecine/loce/espcr/rome.htm

2001 15th Japanese Society for Pigment Cell Research Meeting (JSPCR)

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Contact: Prof. S. SHIBAHARA
E-Mail : shibahar@mail.cc.tohoku.ac.jp

2002 XVIIIth International Pigment Cell Conference

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University Hospital Leiden
Dept of Dermatology, PO Box 9600
NL - 2300 RC LEIDEN
Tel: 31-(71) 526 1952
Fax: 31-(71) 524 8106
E-mail: SPavel@algemeen.azl.nl

2003 XIth Annual Meeting of the PanAmerican Society for Pigment Cell Research

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Contact: Dr. Jean BOLOGNIA
E-mail: jean_bolognia@qm.yale.edu

2003 XIth Meeting of the ESPCR

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2004 XIIth Meeting of the ESPCR

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2005 XIVth International Pigment Cell Conference (IPCC)

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As most members will know, Pigment Cell Research is the journal of the International Federation of Pigment Cell Societies. Each year, in recent years, the IFPCS has been able to offer 35 free subscriptions to PCR to each of its 3 component societies, to be awarded to members. This is possible through the generosity of several sponsors (currently L'Oreal, Unilever, Shiseido and Johnson & Johnson), and in turn through the success of the IFPCS President, Shosuke Ito, in maintaining this sponsorship. ESPCR Council wish to express their gratitude and congratulations to Professor Ito, and to announce that ESPCR's free subscriptions for 2001 have been awarded to members in the following categories:

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Members living in economically less favoured countries,
New members who joined during the previous year (2000).

Some members in these categories were able to share a subscription with a colleague. The resulting final list of 35 recipients is given here.

Dr J Ancans, Dr R Baba, Dr J Borovansky, Dr R Busca, Prof R Cicero, Dr S Commo, Dr G Drewa, Dr J Duchon, Prof JC García-Borrón, Prof GE Ghanem, Dr E Healy, Dr M Hoogduijn, Dr V Horak, Dr M d'Ischia, Dr J Lambert, Dr L Montoliu, Dr L Nieuweboer-Krobotova, Dr R Pandhi, Dr D Parsad, Dr J Peter, Dr M Picardo, Dr S Prince, Dr A Ramaiah, Dr M Rozanowska, Dr T Sarna, Dr F Shamsi, Dr J Simon, Dr N Smit, Dr M Stöckli, Dr A Tjarta, Dr D. Tobin, Dr J Vachtenheim, Mr F Van Nieuwpoort, Dr L Wainwright, Dr E Wenczl

Many congratulations once more to all those receiving these awards.

THESIS

THE DUAL ROLE OF MELANINS IN UV-INDUCED GENOTOXICITY

Induction of DNA Strand-Breaks and Chromosomal Aberrations in Cultured Human Melanocytes

Dr. Eniko Wenczl

15th November, 2000

University of Leiden, The Netherlands
Promotor: Prof. Dr. R. Willemze
Co-Promotor: Dr. A. A. Schothorst

CONCLUSIONS

The goal of the studies presented in this thesis was to evaluate the role of melanin pigments in UV-induced genotoxicity in human melanocyte cultures. For this purpose, we used a melanocyte monoculture model system where melanin synthesis can be stimulated under controlled conditions and melanin content/ composition can be monitored. We concentrated on the induction of DNA damage since this is a primary event in carcinogenesis and, in addition, we also investigated chromosomal aberrations as a consequence of DNA damage.

Our results demonstrated that UVA-irradiated melanocytes from a skin type I subject were photosensitized by induced (pheo)melanin and/or melanin synthesis-related molecules, which resulted in increased ssb induction. Further, we have shown in the same experimental model that stimulation of the melanogenesis provided protection against UVB- but not against UVA-induced chromosomal aberrations and cell cycle delay.

The data obtained in this thesis in melanocytes support the view that UVB as well as UVA irradiation may play a causative role in melanoma induction. Therefore, limiting the exposure to the sun, sunbeds and an adequate sunprotection against both UVB and UVA appears to be the most effective way to reduce the risk. The results also indicate that melanins and/or melanin synthesis-related molecules act as a chromophore for UV light. Their effect, however, depends apart from the melanin content and composition also on the wavelength of the irradiation and can be photoprotective upon UVB as well as photosensitizing, perhaps even photocarcinogenic upon UVA irradiation. Fair skin contains relatively more pheomelanin than dark skin and our data suggest that stimulation of melanogenesis in fair skin is likely to result in even more increased pheomelanin levels leading to photosensitization and probably photocarcinogenesis upon UVA exposure. Therefore, it is proposed that especially people with fair skin avoid exposure to UVA.

NEWS FROM THE IFPCS

Advertisements and related…

Dear Sir:
We appreciate that the 17th International Pigment Cell Conference (IPCC), held in Nagoya in 1999, was considered a great success. The Proceedings of the IPCC, published as Supplement 8, comprises 25 selected papers based on invited presentations and summaries of the 14 Symposia, 2 Evening Sessions, and 4 Satellite Meetings. Those 25 papers cover a broad range of scientific disciplines: the chemistry and
biochemistry of melanins, the cellular and molecular biology of melanogenesis, the comparative and developmental biology of melanocytes, and basic & clinical aspects of melanoma and pigmentary disorders. {Ed Note - the Table of Contents and
Abstracts for these articles are available on the Web Site}
Although Supplement 8 has been sent to all subscribers to Pigment Cell Research, and to all participants of the IPCC Nagoya, we purchased a limited number of extra copies to sell to those interested. Those issues cost 5,000 yen (about $45) each. If you would like to reserve and order a copy, please contact me, Dr. Kazumasa Wakamatsu, by email at 'kwaka@fujita-hu.ac.jp', and send the following information at the same time.

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Sincerely yours,

Kazumasa Wakamatsu, Ph.D.
Fujita Health University
School of Health Sciences
Toyoake, Aichi 470-1192 JAPAN

IPCC-Nagoya Organizers are purchasing a limited number of extra copies to sell to those interested. Those issues will cost 5,000 yen (about $50), and if you would like to reserve and order a copy, please contact Dr. kazumasa Wakamatsu at kwaka@fujita-hu.ac.jp, and he will send you the information you need.

IFPCS Visiting Scientist Awards, 2001-2002
Call for applications

The International Federation of Pigment Cell Societies (IFPCS) offers grants to support members of the regional Pigment Cell Societies who wish to visit other laboratories (preferably in countries covered by the other two Pigment Cell Societies – the Americas or the region around Japan), to learn specialized techniques and/or to establish collaborations. Each Visiting Scientist Award will be for a maximum of **US $3,000,** intended to support such visits for periods of approximately 2-3 months. Each regional Society normally awards one IFPCS Visiting Scientist Award per year. This year, a previous award has been returned to ESPCR following illness, and so we will be able to offer this to another scientist. Thus, depending on confirmation of the continuing funding of the scheme, either one or two Visiting Scientist Awards will be available to ESPCR members in 2001 and 2002. The number will be confirmed shortly. These grants will be awarded competitively by the ESPCR Travel Awards Committee, who are Dr Friedo Beermann (Chair of Committee), Prof José-Carlos García-Borrón (ESPCR Secretary) and Prof Sheila Mac Neil.

Applications will include details of the applicant (an ESPCR member), the laboratory to be visited, a title and short description of the proposed project or reason for the visit, and the expected costs. The complete proposed visit should fall between approximately September 2001 and August 2002. The expected deadline for applications is **July 1st, 2001.**

For more detailed instructions on how to apply, **please contact either Dr Beermann or Prof García-Borrón,** preferably by e-mail. Details are also expected to be available on the ESPCR web site shortly.

Dr Friedrich Beermann
Swiss Institute for Experimental Cancer Research (ISREC)
Chemin des Boveresses 155
CH-1066 Epalinges
Switzerland

Friedrich.Beermann@isrec.unil.ch

Prof. J.-C. García-Borrón
Biochemistry and Molecular Biology,
Faculty of Medicine
Campus de Espinardo
University of Murcia
Apartado Correos 4021
E-30100 Murcia, Spain

gborron@um.es