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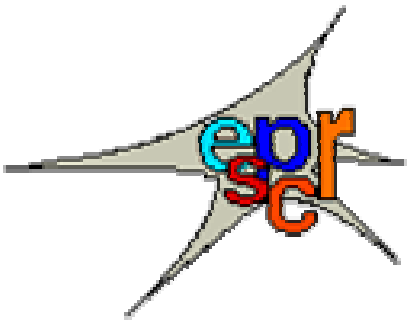

EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH *BULLETIN*

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MARIE CURIE FELLOWSHIP: A CHANCE FOR THE FUTURE

by Despina KOKKINOU
Department of Vitreoretinal Surgery , University Eye Hospital Tübingen, Germany

Unfortunately, making your dreams come true in our difficult job market often lies in the sphere of fantasy. A permanent position is sometimes a solution to the fear of unemployment, but is often far away from the dreams of our youth. I am a physician sharing all the problems related to speciality and future certitude of my generation. Nowadays medical specialisation itself is almost not enough.

The Marie Curie Fellowship came into my life right on time. The idea of this training site, founded by the European Commission, is to give young scientists the opportunity to pursue their doctoral thesis and post-doctoral research at universities and commercial laboratories all over Europe. I was accepted in the program “Fight Blindness” with a scholarship in experimental ophthalmology at the University of Cologne, founded by grants from the University of Tübingen.

During this time I worked on my M.D. thesis investigating “the role of melanin under physiological and pathological conditions in the eye”. I had the possibility of learning the latest experimental methods in cell biology, electron microscopy and immuncytochemistry. I was able to connect the knowledge of the clinical symptoms of severe eye diseases with fundamental pathophysiological mechanisms and become familiar with in vivo experimental animal models.

The daily interconnection of different academic fields widened my medical way of thinking. The interdisciplinary contact with colleagues from anatomy, biology, pharmacology, as well as technical personal opened up my mind and helped me to see complex eye diseases as an overall result. I worked on my dissertation using the most up-to-date methods and found new aspects and directions. The possibility of working in a non-clinical field will surely help me, even if I continue with a clinical career.

Excellent technical equipment and outstanding human resources made every “crazy” idea that I had during this year reality. Finally, I realised that the word “failure” has no meaning in the scientific community. No results or negative results are also a fact that must be taken under consideration. There is no right or wrong, but different ways to find answers. I was fascinated by the idea that I could be a small member of a future therapeutical approach to a severe eye disease.

On the other hand, the laboratory was only one aspect of the Marie Curie training site. The opportunity to meet new people, a new culture and way of life must be emphasised. At the laboratory I worked with people from Germany, Poland, Bulgaria and West Guinea, people working with the same aim, realising every day the meaning of a united world.

Furthermore, my fellowship gave me the opportunity to meet personally most of the leading scientists in experimental and clinical ophthalmology. Author names from my heavy medical books were suddenly flesh and blood, always ready to explain, teach and share their own experience during their long professional careers with young researchers. I was also encouraged to participate in

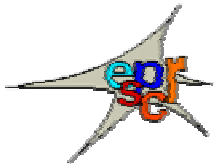
international congresses presenting my work in posters and oral presentations, discovering unknown skills I never new I had.

The guidance and support of my supervisor (the German word for supervisor is “Doktorvater” i.e. doctor father) was always a great help. His scientific background and advice gave me solutions to problems occurring in my doctor thesis.

I do not yet know what my further steps in the future will be. Just one year before, I had never thought I would live and work in Germany. Now I have a contract as a scientist in the same research area and the possibility to use my knowledge in the clinical field.

I would like to encourage all young scientists to join this or similar training programs. I am confident that such fellowships become a lifetime experience. I do not underestimate the existing difficulties that exist. Language barriers, bureaucracy, being far away from family and friends are criteria that can decrease the enthusiasm for a new beginning. But the result is worth every effort. Last but not least, a high qualification is a benefit for ever.

For more information on the Marie Curie program, see: http://www.cordis.lu/fp6/mobility.htm



CURRENT LITERATURE

1. Chemistry of Melanins and other Pigments

Some papers have appeared that address the binding properties of melanin to many different drugs. The affinities of melanins for alkaloids were shown to markedly depend on the pigment type (eumelanins versus pheomelanins and mixed type melanins) and the charge exhibited by the drug (Borges *et al.*). Possible binding sites of the pigment were proposed and a model non-covalent adduct of amphetamine with a catechol dimer was studied by tandem mass spectrometry. Significant differences in the binding of hair to codeine as a function of color were reported in another study (Rollins *et al*) aimed at assessing possible bias in the currently used test of drug intake.

Applications of imaging technologies and ultrafast spectroscopy to the investigation of the structural properties of natural melanins have been reviewed by Liu and Simon.

An interesting paper by Hoogduijn *et al* reports the protecting properties of melanins against H_2O_2-induced DNA strand breaks in both melanocytes and keratinocytes; the effect is attributed to the ability of melanin to bind Ca^{2+} thus suggesting an important role of melanin in regulating intracellular Ca^{2+} homeostasis.

A series of papers address the inhibitory /promoting effects of different compounds on the production of melanin mediated by tyrosinase. Among inhibitors of the enzymatic activity esculetin and other coumarins (Masamoto *et al*), glycolic and lactic acid (Usuki *et al*), *N*,*N*-dilinoleylcysteamine (Hwang *et al*), lysophosphatidic acid (Kim *et al*) and luteolin (Lee *et al*). The potential of the latter as well as of alkoxybenzoate and alkoxycynnamate (Kang *et al*) as whitening/depigmenting agents was also investigated.

Production of melanin like pigments by various pathogenic fungi and the role of the pigment in the infection process was studied by different research groups. Of particular interest a structural investigation of the pigment produced by Cryptococcus Neoformans a human pathogenic fungus that melanizes only when provided with exogenous substrate. A novel approach based on treatment of the microorganism with ^{13}C labelled dopa followed by solid state NMR analysis of the biosynthesized melanin after proper swelling in different solvents allowed identification of key structural features of the pigment. Such experimental strategy may expectedly provide new insights into the structure of other melanin pigments.

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MELANIN REACTIVITY AND PROPERTIES:

- Borges CR, Roberts JC, Wilkins DG, Rollins DE.
  Cocaine, benzoylecgonine, amphetamine, and N-acetylamphetamine binding to melanin subtypes. J Anal Toxicol. 27(3):125-34, 2003.

- Buszman E, Rozanska R.
  Interaction of thioridazine with ocular melanin in vitro. Acta Pol Pharm. 60(4):257-61, 2003.

- Hoogduijn MJ, Cemeli E, Ross K, Anderson D, Thody AJ, Wood JM.
  Melanin protects melanocytes and keratinocytes against H(2)O(2)-induced DNA strand breaks through its ability to bind Ca(2+). Exp Cell Res. 294(1):60-7, 2004.

- Kiuchi Y, Terakawa N, Nakata T, Yamasaki K, Saito Y, Ito N, Okada K.
  Binding affinity of bunazosin, dorzolamide, and timolol to synthetic melanin. Jpn J Ophthalmol. 48(1):34-6, 2004.

- Liu Y, Simon JD.
  Isolation and biophysical studies of natural eumelanins: applications of imaging technologies and ultrafast spectroscopy.Pigment Cell Res. 16(6):606-18, 2003.

- Marco FD, Foppoli C, Coccia R, Blarzino C, Perluigi M, Cini C, Marcante ML.
  Ectopic deposition of melanin pigments as detoxifying mechanism: a paradigm for basal nuclei pigmentation. Biochem Biophys Res Commun. 314(2):631-7, 2004.

- Ono C, Yamada M, Tanaka M.
Absorption, distribution and excretion of 14C-chloroquine after single oral administration in albino and pigmented rats: binding characteristics of chloroquine-related radioactivity to melanin in-vivo. J Pharm Pharmacol. 55(12):1647-54, 2003.

- Rollins DE, Wilkins DG, Krueger GG, Augsburger MP, Mizuno A, O'Neal C, Borges CR, Slawson MH.
The effect of hair color on the incorporation of codeine into human hair. J Anal Toxicol. 27(8):545-51, 2003.

BIOSYNTHESIS

- Carlie G, Ntusi NB, Hulley PA, Kidson SH.
KUVA (khellin plus ultraviolet A) stimulates proliferation and melanogenesis in normal human melanocytes and melanoma cells in vitro. Br J Dermatol. 149(4):707-17, 2003.

- Hwang JS, Choi H, Rho HS, Shin HJ, Kim DH, Lee J, Lee BG, Chang I.
Pigment-lightening effect of N,N'-dilinoleylcystamine on human melanoma cells. Br J Dermatol. 150(1):39-46, 2004.

- Kang HH, Rho HS, Hwang JS, Oh SG.
Depigmenting activity and low cytotoxicity of alkoxy benzoates or alkoxy cinnamate in cultured melanocytes. Chem Pharm Bull (Tokyo). 51(9):1085-8, 2003.

- Kim DS, Park SH, Kwon SB, Joo YH, Youn SW, Sohn UD, Park KC.
Temperature regulates melanin synthesis in melanocytes. Arch Pharm Res. 26(10):840-5, 2003.

- Kim DS, Park SH, Kwon SB, Youn SW, Park KC.
Effects of lysophosphatidic acid on melanogenesis. Chem Phys Lipids. 127(2):199-206, 2004.

- Lee KE, Park SM, Kim JH, Lee BC, Pyo HB.
PP-34 Luteolin as a whitening agent with IL-1alpha, IL-6 and melanogenesis inhibitory effect from zostera marina L. Pigment Cell Res. 16(5):604, 2003.

- Masamoto Y, Murata Y, Baba K, Shimoishi Y, Tada M, Takahata K.
Inhibitory effects of esculetin on melanin biosynthesis. Biol Pharm Bull. 27(3):422-5, 2004.

- Usuki A, Ohashi A, Sato H, Ochiai Y, Ichihashi M, Funasaka Y.
The inhibitory effect of glycolic acid and lactic acid on melanin synthesis in melanoma cells. Exp Dermatol. 12 Suppl 2:43-50, 2003.

OTHER PIGMENTS

- Alviano DS, Franzen AJ, Travassos LR, Holandino C, Rozental S, Ejzemberg R, Alviano CS, Rodrigues ML.
Melanin from Fonsecaea pedrosoi induces production of human antifungal antibodies and enhances the antimicrobial efficacy of phagocytes. Infect Immun. 72(1):229-37, 2004.

- Hung YC, Sava V, Hong MY, Huang GS.
Inhibitory effects on phospholipase A2 and antivenin activity of melanin extracted from Thea sinensis Linn. Life Sci. 74(16):2037-47, 2004.

- Icenhour CR, Kottom TJ, Limper AH.
Evidence for a melanin cell wall component in Pneumocystis carinii. Infect Immun. 71(9):5360-3, 2003.

- Icenhour CR, Kottom TJ, Limper AH.
Melanin-like pigments in Pneumocystis carinii. J Eukaryot Microbiol. 50 Suppl:621, 2003.

- Maruyama H, Okamoto S, Kubo Y, Tsuji G, Fujii I, Ebizuka Y, Furihata K, Hayakawa Y, Nagasawa H, Sakuda S.
Isolation of abikoviromycin and dihydroabikoviromycin as inhibitors of polyketide synthase involved in melanin biosynthesis by Colletotrichum lagenarium. J Antibiot (Tokyo). 56(9):801-4, 2003.

- Morris-Jones R, Youngchim S, Gomez BL, Aisen P, Hay RJ, Nosanchuk JD, Casadevall A, Hamilton AJ.

Synthesis of melanin-like pigments by Sporothrix schenckii in vitro and during mammalian infection. Infect Immun. 71(7):4026-33, 2003.

- Nagai M, Kawata M, Watanabe H, Ogawa M, Saito K, Takesawa T, Kanda K, Sato T.
Important role of fungal intracellular laccase for melanin synthesis: purification and characterization of an intracellular laccase from Lentinula edodes fruit bodies. Microbiology. 149(Pt 9):2455-62, 2003.

- Nosanchuk JD, Casadevall A.
Budding of melanized Cryptococcus neoformans in the presence or absence of L-dopa. Microbiology. 149(Pt 7):1945-51, 2003.

- Tian S, Garcia-Rivera J, Yan B, Casadevall A, Stark RE.
Unlocking the molecular structure of fungal melanin using 13C biosynthetic labeling and solid-state NMR. Biochemistry. 42(27):8105-9, 2003.

- Tsuji G, Sugahara T, Fujii I, Mori Y, Ebizuka Y, Shiraishi T, Kubo Y.
Evidence for involvement of two naphthol reductases in the first reduction step of melanin biosynthesis pathway of Colletotrichum lagenarium. Mycol Res. 107(Pt 7):854-60, 2003.

- Youngchim S, Morris-Jones R, Hay RJ, Hamilton AJ.
Production of melanin by Aspergillus fumigatus. J Med Microbiol. 53(3):175-181, 2004.

2. Biology of pigment cells and pigmentary disorders

(Dr. M. Picardo)

Riebeling et al investigated in melanoma cell lines and primary melanocytes both expression and activity of phospholipase D, a key enzyme of lipid-mediated signal transduction pathways. Considering that protein kinase C and Rho family proteins have been reported to act as regulator of the phospholipase D activity and to have an implication in the metastatic potential of melanoma, an up-regulation of phospholipase activity in melanoma cells can be expected . The authors found that all the examined melanoma cell lines exhibited a high phospolipase D activity compared with the primary human melanocytes. Western blot analyses provide a good explanation for the different enzyme activities, showing that the expression of the isoenzyme phospolipase D1(PLD1) was lower in melanocytes than in melanoma cells. Moreover Rho protein mRNA was elevated in all the melanoma cell lines. Thus, in human melanoma cells there is a strong up-regulation of both activity and expression of the isoenzyme PLD1, which requires protein kinase C and Rho proteins for full activity.

Employing mouse B16 melanoma cells, **Ohguchi K and co-workers** demonstrated that over-expression of PLD1 resulted in a merked inhibition of melanogenesis induced by alpha-MSH. The inhibition of melanogenesis was strongly correlated with the decrease in the tyrosinase activity as well as its expression. In this experimental model, PLD1 acts as negative regulator of melanogenic response, by modulating the expression of tyrosinase. The effect of topical application of a protein kinase C inhibitor in skin and hair pigmentation have been investigated by Park et al. It is well known that protein kinase C-β (PKC-β) is able to activate tyrosinase, by phosphorylating serine residues at amino acid positions 505 and 509 and that a loss of PKC-β prevents melanogenesis in cultured cells. To test the hypothesis that inhibition of PKC-β activity would decrease and phoshorylation of tyrosinase and subsequent decrease tyrosinase activity in vitro, the authors employed two different experimental models. The treatment of human melanocytes with a tyrosinase mimetic peptide was found to induce a competitive inhibition of the phosphorylation of tyrosinase by PKC-β. Moreover, the pre-treatment of primary human melanocytes with bisindolylmaleimide (Bis), a selective PKC-β inhibitor, was capable of blocking the TPA-induced increase in tyrosinase activity. Similar effects have been observed also in vivo. Topical application of Bis reduced basal pigmentation and prevented ultraviolet induced melanin synthesis in guinea pigs. In mice, topical application of Bis to depilated skin determined the lightening of the color of re-growing hair. Thus, the inhibition of PKC-β activity reduces both basal and UV-induced pigmentation in vivo and in vitro, suggesting further therapeutical applications of PKC-β inhibitors as depigmenting agents.

Several studies have demonstrated that linoleic acid and palmitic acid, which are abundant components of cell membranes in the epidermis, are able to regulate of tyrosinase metabolism via post-transcriptional events. **Ando H and coworkers** evaluated the effects of fatty acids on the ubiquitin-proteasomepathway, where membrane proteins are selectively degraded, and they further explored thepossibility whether this pathway could be involved in the fatty acid-induced regulation of tyrosinase degradation. This study focused on the diverse contributions of unsaturated and saturated fatty acids in the ubiquitin-proteasome pathway-mediated degradation of tyrosinase in melanocytes and in melanoma cells. Linoleic acid and palmitic acid regulate the proteasomal degradation of tyrosinase in contrasting manners by way of relative increases or decreases in the ubiquitination of tyrosinase. Linoleic acid (unsaturated fatty acid, C18:2) accelerated the spontaneous degradation of tyrosinase while palmitic acid (saturated fatty acid, C16:0) retarded the proteolysis. The linoleic acid-induced acceleration of tyrosinase degradation could be abrogated by inhibitors of proteasomes, the multicatalytic proteinase complexes that selectively degrade intracellular ubiquitinated proteins. These findings suggest a novel mechanism for the involvement of fatty acids in regulating the selective degradation of membrane glycoproteins, such as tyrosinase via the ubiquitin-proteasome pathway, and possibly in the modulation of the functions of other proteins.

Masamoto et al investigated the structure-activity relationship of coumarins in terms of their inhibitory activity on mushroom tyrosinase. Among the examined compounds, esculetin exhibited potent inhibitory activity on tyrosinase and demonstrated the relevance of the 6,7-dihydroxy moiety. Furthermore, esculetin suppressed melanin production in B16 melanoma cells and epidermal sheet. However, the exact antyrosinase mechanism of esculetin has not been elucidated. Several factors, such as the high penetration of esculetin inside melanocytes, or the capacity to inhibit in a competitive manner the oxidation of DOPA by tyrosinase, or its antioxidant action, which can also inhibit oxidative polymerization of melanin intermediates can explain the antimelanogenic activity of esculetin. Yamakoshi J and co-workers studied the lightening effect on UV-induced

pigmentation of guinea pig skin by oral administration of proanthocyanidin –rich extract from grape seeds. Its inhibitory activity on mushroom tyrosinase as well as on melanogenesis of cultured B16 mouse melanoma cells was also investigated. The mechanism of the anitmelanogenic activity of the grape seed extract (GSE) seems to be related to its antioxidant effect. In the experimental model employed in that study, in fact, the authors induced pigmentation in guinea pigs by repeated UV irradiation and in such conditions a strong generation of DNA oxidation products, such as 8-OHdG, which are related to the proliferation of melanocytes as well as melanin-containing keratinocytes in UV-exposed skin, is observed. Oral administration of GSE is able to induce a lightening of UV-mediated pigmented skin of guinea pigs, accompanied with a reduction of DOPA-positive cells. Moreover GSE was also capable of inhibiting mushroom purified tyrosinase activity as well as melanogenesis in cultured B16 mouse melanoma cells. These results suggest that the depigmenting action of GSE is mainly related to the inhibition of melanin synthesis by tyrosinase in melanocytes and ROS-related proliferation of melanocytes in UV-irradiated guinea pig skin. However, due to the fact that GSE can also inhibit NO production in macrophages further studies are needed to clarify the contribution to this effect to its lightening action.

Kang and co-workers investigate the expression of PPARs in human melanocytes and the effect of PPAR activators on melanocyte growth and melanogenesis. They demonstrated, with western blotting methods an mRNA analysis, that all three PPAR subtypes (PPAR alpha, beta/delta and gamma) were expressed in melanocytes. Moreover they analysed a possible relationship between the expression of these receptors and the proliferation rate of the cell. Activators for PPAR-alpha (WY-14643) and PPAR-gamma (Ciglitazone) stimulated the melanin synthesis and inhibited proliferation of melanocytes in a dose-dependent manner. On the contrary, bezafibrate, a preferential activator for PPAR beta/delta had not effect. Morphological changes were associated with the growth inhibition produced by WY-14643 and Ciglitazone. These morphological modification were characterised by an increased number of dendrites and an enlarged cell area respect to the control.

Boehm N and co-workers examined the expression of RAR-beta and RXR-alpha, two Retinoic acid and Retinoic X receptor family members, in normal skin, melanocytic tumours and nevus cells. In healthy skin RXR alpha was localised in epidermis, sebaceous glands and hair follicles. RAR-beta on the contrary RAR-beta was detectable only in melanocytes and stratum granulosum. In melanocytic tumours in naevi and in melanomas RXR-alpha was not detected. RAR-beta in turn was present in nevus cells and was absent from melanoma cells. These results suggest that in melanoma cells, RAR-beta decrease and RXR-alpha absence may be responsible for the RA-resistance of most melanoma cell lines.

Berking and Co-workers demonstrate in vivo, for the first time, that an unbalance physiological factor associated with an environmental carcinogen, can lead to transformation of normal skin tissue. The agents implicated in this melanocyte transformation process were UVB in association with an increased expression of three growth factors, basic fibroblast growth factor, stem cell factor and endothelin-3, respectively. Melanoma lesion invasion, in particular, was found in skin from newborn donors, whereas in adults, melanomas were of an non-invasive type only, suggesting a possible correlation between skin tumour susceptibility and age.
UV irradiation is implicated in the induction and melanoma progression, however, the molecular mechanism behind melanoma carcinogenesis are still poorly understood. Alteration of cellular proliferation proteins, such as p73, Nup88 and p27 have been considered to play a critical role in melanoma progression**.**

Zhang and Rosdahl investigated the effect of UV irradiation on the expression of these proteins and on the cellular growth and proliferative response. The authors conclude that UVA and UVB differently induce intracellular protein expression in human skin melanocytes, suggesting the existence of two possible patways in melanoma promotion

It was previously demonstrated by **Eisenmann and Co-workers**, that the inhibition of MAPK signalling cascade induces apoptosis in melanoma cells but not in normal melanocytes, suggesting that the MAPK pathway propagates essential survival signal in melanoma cells. In the present work the authors report that the proapoptotic protein Bad is constitutively phosphorylated and then inactivated by RSK, an effector of MAPK patway, thereby mediating the tumour survival in melanoma. In contrast, in normal melanocytes, Bad is also highly phoshporylated at multiple residues but in a MAPK pathway independent manner. In the present work these authors demonstrate that the MAPK pathway mediates melanoma specific survival signalling by differentially regulating RSK-mediated phosphorylation of the pro-poptotic protein Bad.

– Ando H, Watabe H, Valencia JC, Yasumoto KI, Furumura M, Funasaka Y, Oka M Ichihashi M and Hearing VJ.

Fatty acids regulate pigmentation via proteasomal degradation of tyrosinase- A new aspect of ubiquitin-proteasome function. J Biol Med Jan 22 [Epub ahead of print], 2004.

– Berkng C, Takemoto R, Satyamoorthy K, Shirakawa T, Eskandarpour M, Hansson J, VanBelle PA, Elder DE, Herlyn M.
Induction of melanoma phenotypes in human skin by growth factors and ultraviolet. B Cancer Res 64: 807-811, 2004.

- Boehm N, Samama B, Cribier B, Rochette-Egly C.
Retinoic-acid receptor beta expression in melanocytes. Eur J Dermatol 14 19-23, 2004.

– Eisenmann KM, VanBrocklin MW, Staffend NA, Kitchen SM and Koo HM.
Mitogen –activated protein kinase pathway-dependent tumor-specific survival signalling in melanoma cells through inactivation of the pro-apoptotic protein Bad. Cancer Res 63: 8330-8337, 2003.

– Higuchi K, Kawashima M, Ichikawa Y, Imokawa G.
Sphingosylphosphorylcholine is a melanogenic stimulator for human melanocytes. Pigment Cell Res 16 (6): 670-678, 2003

– Hirobe T, Wakamatsu K, Ito S.
Changes in the proliferation and differentiation of neonatal mouse pink-eyed dilution melanocytes in the presence of excess tyrosine. Pigment Cell Res 16(6):619-628, 2003.

– Hoogduijn MJ, Cemeli E, Ross K, Anderson D, Thody AJ, Wood JM.
Melanin protects melanocytes and keratynocites against H2O2-induced DNA strand breaks through its ability to bind Ca2+. Exp Cell Res 294 (1): 60-67, 2004.

– Huber WE, Price ER, Widlund HR, Du J, Davis IJ, Wegner M, Fisher DE.
A tissue-restricted cAMP transcriptional response: SOX10 modulates alpha-melanocyte-stimulating hormone-triggered expression of microphthalmia-associated transcription factor in melanocytes. J Biol Chem 278 (46): 45224-45230, 2003.

– Ludwig A, Rehberg S, Wegner M.
Melanocyte-specific expression of dopachrome tautomerase is dependent on synergistic gene activation by the Sox10 and Mitf transcription factors. FEBS Lett 556 (1-3): 236-244, 2004.

– Kang HY, Chung E, Lee M, Cho Y, Kang WH.
Expression and function of peroxisome proliferators-activated receptors in human melanocytes. Br J Dermatol: 150 462-468, 2004.

– Maeda K, Hatao M.
Involvement of photooxidation of melanogenic precursors in prolonged pigmentation induced by ultraviolet A. J Invest Dermatol 122 (2): 503-509, 2004.

– Masamoto Y, Murata Y, Baba K, Shimoishi Y, Tada M and Takahata K.
Inhibitory effect of esculetin on melanin biosynthesis. Biol Pharm Bull 27: 422-425, 2004.

– Miller AJ, Du J, Rowan S, Hershey CL, Widlund HR, Fisher DE.
Transcriptional regulation of the melanoma prognostic marker melastatin (TRPM1) by MITF in melanocytes and melanoma. Cancer Res 64 (2): 509-516, 2004.

- Nagata H, Takekoshi S, Takeyama R, Homma T, Yoshiyuki Osamura R.
Quercetin enhances melanogenesis by increasing the activity and synthesis of tyrosinase in human melanoma cells and in normal human melanocytes. Pigment Cell Res 17 (1): 66-73, 2004.

– Ohguchi K, Banno Y, Akao Y, and Nozawa Y.
Involvement of phospholipase D1 in melanogenesis of mouse B16 melanoma cells. J Biol Chem. 279: 3408-3412, 2003.

– Park HY, Lee J, Gonzales S, Middelkamp-Hup MA, Kapasi S, Peterson S, Gilchrest BA.
Topical Application of a protein kinase C inhibitor reduces skin and hair pigmentation. J Invest Dermatol. 122: 159-166, 2004.

- Riebeling C, Mullet C and Geilen CC.
  Expression and regulation of phospholipase D isoenzymes in human melanoma cells and primary melanocytes. Melanoma Res. 13: 555-562, 2003.

- Rouzaud F, Annereau JP, Valencia JC, Costin GE, Hearing VJ.
  Regulation of melanocortin 1 receptor expression ta the mRNA and protein levels by its natural agonist and antagonist. FASEB J 17 (14): 2154-2156, 2003.
- Yamakoshi J, Otsuka F, Sano A, Tokutake S, Saito M, Kikuchi M and Kubota Y.
  Lightening effct on ultraviolet –induced pigmentation of guinea pig skin by oral administration of a proanthocyanidin-rich extract from grape seeds. Pigment Cell Res. 16: 629-638, 2003.

- Zhang H, Rosdahl I.
  Ultraviolet A and B differently induc intracellular protein expression in human skin melanocytes-a speculation o separate pathways in initiation of melanoma. Carcinogenesis 24: 1929-1934, 2003.

- Zhang RZ, Zhu WY, Xia MY, Feng Y.
  Morphology of cultured human epidermal melanocytes observed by atomic force microscopy. Pigment Cell Res 17 (1): 62-65, 2004.

3. MSH, MCH, other hormones, differentiation

(Dr. R. Morandini)

1. Regulation and signal transduction

- Hoggard N, Hunter L, Duncan JS, Rayner DV.
  Regulation of adipose tissue leptin secretion by alpha-melanocyte-stimulating hormone and agouti-related protein: further evidence of an interaction between leptin and the melanocortin signalling system. J Mol Endocrinol. 32(1):145-53, 2004.

- Teare KA, Pearson RG, Shakesheff KM, Raisman G, Haycock JW.
  alpha-MSH inhibits inflammatory signalling in olfactory ensheathing cells. Neuroreport. 14(17):2171-5, 2003.

2. Global effect on cell *in vitro*

- Babu RJ, Kikwai L, Jaiani LT, Kanikkannan N, Armstrong CA, Ansel JC, Singh M.
  Percutaneous absorption and anti-inflammatory effect of a substance P receptor antagonist: spantide II. Pharm Res. 21(1):108-13, 2004.

- Catania A, Gatti S, Colombo G, Lipton JM.
  Targeting melanocortin receptors as a novel strategy to control inflammation. Pharmacol Rev. 56(1):1-29, 2004.

- Gao XB, Ghosh PK, van den Pol AN.
  Neurons synthesizing melanin-concentrating hormone identified by selective reporter gene expression after transfection in vitro: transmitter responses. J Neurophysiol. 90(6):3978-85, 2003. Epub 2003 Oct 22.

- Han G, Haskell-Luevano C, Kendall L, Bonner G, Hadley ME, Cone RD, Hruby VJ.
  De novo design, synthesis, and pharmacology of alpha-melanocyte stimulating hormone analogues derived from somatostatin by a hybrid approach. J Med Chem. 47(6):1514-26, 2004.

- Katsuki H, Akaike A.
  Excitotoxic degeneration of hypothalamic orexin neurons in slice culture. Neurobiol Dis. 15(1):61-9, 2004.

- Yasuda T, Masaki T, Kakuma T, Yoshimatsu H.
  Hypothalamic melanocortin system regulates sympathetic nerve activity in brown adipose tissue. Exp Biol Med (Maywood). 229(3):235-9, 2004.

3. Clinical investigation

- Cheng Z, Chen J, Quinn TP, Jurisson SS.
  Radioiodination of rhenium cyclized alpha-melanocyte-stimulating hormone resulting in enhanced radioactivity localization and retention in melanoma. Cancer Res64(4):1411-8, 2004.

- Deng J, Hu X, Yuen PS, Star RA.
  Alpha-melanocyte-stimulating hormone inhibits lung injury after renal ischemia/reperfusion. Am J Respir Crit Care Med. 169(6):749-56, 2004. Epub 2004 Jan 07.

- Froidevaux S, Calame-Christe M, Schuhmacher J, Tanner H, Saffrich R, Henze M, Eberle AN.
  A gallium-labeled DOTA-alpha-melanocyte- stimulating hormone analog for PET imaging of melanoma metastases. J Nucl Med. 45(1):116-23, 2004.

- Jahovic N, Arbak S, Tekeli O, Alican I.
  Alpha-melanocyte stimulating hormone has beneficial effects on cerulein-induced acute pancreatitis. Peptides. 25(1):129-32, 2004.

- Roth J, Zeisberger E, Vybiral S, Jansky L.
  Endogenous antipyretics: neuropeptides and glucocorticoids. Front Biosci. 9:816-26, 2004.

- Schiller M, Brzoska T, Bohm M, Metze D, Scholzen TE, Rougier A, Luger TA.
  Solar-simulated ultraviolet radiation-induced upregulation of the

melanocortin-1 receptor, proopiomelanocortin, and alpha-melanocyte-stimulating hormone in human epidermis in vivo. J Invest Dermatol. 122(2):468-76, 2004.

- Yasuda T, Masaki T, Kakuma T, Yoshimatsu H.
Hypothalamic melanocortin system regulates sympathetic nerve activity in brown adipose tissue. Exp Biol Med (Maywood). 229(3):235-9, 2004.

4. Others

- Allaeys I, Bouyer K, Loudes C, Faivre-Bauman A, Petit F, Ortola C, Cardinaud B, Epelbaum J, Nahon JL.
Characterization of MCH-gene-overprinted-polypeptide-immunoreactive material in hypothalamus reveals an inhibitory role of pro-somatostatin1-64 on somatostatin secretion. Eur J Neurosci. 19(4):925-36, 2004.

- Cho MK, Kim SS, Lee MR, Shin J, Lee J, Lim SK, Baik JH, Yoon CJ, Shin I, Lee W.
NMR studies on turn mimetic analogs derived from melanocyte-stimulating hormones. J Biochem Mol Biol.;36(6):552-7, 2003.

- Ellacott KL, Cone RD.
The Central Melanocortin System and the Integration of Short- and Long-term Regulators of Energy Homeostasis. Recent Prog Horm Res. 59:395-408, 2004.

- Meij BP, van der Vlugt-Meijer RH, van den Ingh TS, Rijnberk A.
Somatotroph and corticotroph pituitary adenoma (double adenoma) in a cat with diabetes mellitus and hyperadrenocorticism. J Comp Pathol. 130(2-3):209-15, 2004.

- Shiratori K, Ohgami K, Ilieva IB, Koyama Y, Yoshida K, Ohno S.
Inhibition of endotoxin-induced uveitis and potentiation of cyclooxygenase-2 protein expression by alpha-melanocyte-stimulating hormone. Invest Ophthalmol Vis Sci. 45(1):159-64, 2004.

- Van der Salm AL, Pavlidis M, Flik G, Wendelaar Bonga SE.
Differential release of alpha-melanophore stimulating hormone isoforms by the pituitary gland of red porgy, Pagrus pagrus. Gen Comp Endocrinol. 135(1):126-33, 2004.

4. Photobiology

(Dr. N. Smit)

In the previous bulletin (47) the paper by Zhang and Rosdahl in Carcinogenesis 24, was included dealing with different effects of UVA and UVB on induction of proteins involved in cell growth and cell proliferation. The authors speculated that UVB and UVA could induce melanoma via separate pathways of initiation. In a study from Sydney, Australia (Agar et al) specific UVB and UVA fingerprint p53 mutations have been detected in the stratum granulosum and stratum basale of eight solar keratoses and eight squamous cell carcinomas collected from 16 patients. The authors demonstrate that in the regions of stratum basale UVB fingerprint mutations are rarely found and that UVA or other mutations that could be attributable indirectly to UVA via production of reactive oxygen species. The authors discuss the the importance of mutations in basally located stem cells for the malignant transformation in human skin. These results may have serious implications for skin protection strategies and may also be important for damage induced in melanocytes and melanocytic lesions located at the basal layer.

Berking et al describe the induction of melanoma phenotypes in human skin grafts by UVB. The grafts, on a severe combined immunodeficiency mouse, were injected intradermally with adenoviral vectors of basic fibroblast growth factor, stem cell factor and endothelin-3. The combination of the three growth factors and UVB irradiations (with some UVA) of the grafted mice resulted in 89% of pigmented lesions, occurrence of suprabasal melanocytes and melanocytic nests and for the UV treated mice 34% showed the standard histopathological criteria of melanoma. Mutation analysis was done for N-RAS and BRAF and were negative for most of the lesions studied. Interestingly the V599E BRAF mutation was found in two newborn lesions in a small proportion of cells. Since this mutation does not display a UV signature it may have pre-existed or induced by mechanisms other than UV.

Kolias and coworkers (Ou-Yang) studied some of the characteristics of soluble melanin that resembles the spectrum of melanin in native skin more closely than insoluble melanin. This soluble melanin could play an important part in UVA induced pigment in the skin. The authors conclude that UVA induces significant photochemical alterations in the skin with increased photoprotection in the visible range but reduced protection in the ultraviolet A range.

The review by Heck et al summarizes some of the mechanisms by which ultraviolet light alters signaling pathways as well as the genes important in the beneficial and toxic effects of ultraviolet light. Some interesting facts are reported, e.g. the generation of ROS by UVB and the identification of catalase in keratinocytes forming ROS in response to UV-light. Although many of the UV responses are reported for epidermal cells in general they may be relevant for the melanocytes in particular.

- Agar NS, Halliday GM, Barnetson RS, Ananthaswamy HN, Wheeler M, Jones M.
  The basal layer in human squamous tumors harbors more UVA than UVB fingerprint mutations: A role for UVA in human skin carcinogenesis. Proc.Natl.Acad.Sci.U.S.A 2004.

- Berking C, Takemoto R, Satyamoorthy K, Shirakawa T, Eskandarpour M,
  Hansson J, VanBelle PA, Elder DE, Herlyn M.
  Induction of melanoma phenotypes in human skin by growth factors and ultraviolet B. Cancer Res. 64:807-811, 2004.

- Boissy RE
  Melanosome transfer to and translocation in the keratinocyte. Exp.Dermatol. 12 Suppl 2:5-12? 2003.

- Chakraborty AK, Funasaka Y, Araki K, Horikawa T, Ichihashi M.
  Evidence that the small GTPase Rab8 is involved in melanosome traffic and dendrite extension in B16 melanoma cells. Cell Tissue Res. 314:381-388, 2003.

- Choi SY, Kim S, Hwang JS, Lee BG, Kim H, Kim SY.
  Benzylamide derivative compound attenuates the ultraviolet B-induced hyperpigmentation in the brownish guinea pig skin. Biochem.Pharmacol. 67:707-715, 2004.

- de Leeuw J, van der BN, Maierhofer G, Neugebauer WD.

A case study to evaluate the treatment of vitiligo with khellin encapsulated in L-phenylalanin stabilized phosphatidylcholine liposomes in combination with ultraviolet light therapy. Eur.J.Dermatol. 13:474-477, 2003.

- Heck DE, Gerecke DR, Vetrano AM, Laskin JD.
  Solar ultraviolet radiation as a trigger of cell signal transduction.
  Toxicol.Appl.Pharmacol. 195:288-297, 2004.

- Hosaka E, Soma Y, Kawa Y, Kaminaga H, Osumi K, Ooka S, Watabe H, Ito M, Murakami F, Mizoguchi M.
  Effects of Ultraviolet Light on Melanocyte Differentiation: Studies with Mouse Neural Crest Cells and Neural Crest-derived Cell Lines. Pigment Cell Res. 17:150-157, 2004.

- Imokawa G.
  Autocrine and paracrine regulation of melanocytes in human skin and in pigmentary disorders.
  Pigment Cell Res. 17:96-110, 2004.

- Kadekaro AL, Kavanagh RJ, Wakamatsu K, Ito S, Pipitone MA, Abdel-Malek ZA.
  Cutaneous photobiology. The melanocyte vs. the sun: who will win the final round? Pigment Cell Res. 2003, 16:434-447, 2003.
  This review summarizes the current state of knowledge about the role of melanin and the melanocyte in photoprotection, the responses of melanocytes to UV, the signaling pathways that mediate the biological effects of UV on melanocytes, and the most common genetic alterations that lead to melanoma

- Kim SM, Han S.
  Tyrosinase scavenges tyrosyl radical. Biochem.Biophys.Res.Commun. **312:**642-649, 2003.
  Melanosomes scavenged tyrosyl radical that was generated by ultraviolet irradiation of tyrosine. Purified mushroom tyrosinase also removed tyrosyl radical in a dose-dependent manner.

- Krengel S, Groteluschen F, Bartsch S, Tronnier M.
  Cadherin expression pattern in melanocytic tumors more likely depends on the melanocyte environment than on tumor cell progression. J.Cutan.Pathol. 31:1-7, 2004.

- Maeda K, Hatao M.
  Involvement of photooxidation of melanogenic precursors in prolonged pigmentation induced by ultraviolet A. J.Invest Dermatol. 122:503-509, 2004.

- Ou-Yang H, Stamatas G, Kollias N.
  Spectral responses of melanin to ultraviolet A irradiation. J.Invest Dermatol. 122:492-496, 2004.

- Parsad D, Wakamatsu K, Kanwar AJ, Kumar B, Ito S.
  Eumelanin and phaeomelanin contents of depigmented and repigmented skin in vitiligo patients.
  Br.J.Dermatol. 149:624-626, 2003.

- Quast T, Wehner S, Kirfel G, Jaeger K, De Luca M, Herzog V.:
  sAPP as a regulator of dendrite motility and melanin release in epidermal melanocytes and melanoma cells. FASEB J. 17:1739-1741, 2003.

- Rivers JK.
  Is there more than one road to melanoma? Lancet 363:728-730, 2004.

- Scott G.
  Photo protection begins at the cellular level: microparasols on the job. J.Invest Dermatol. 121:viii, 2003.

- Weller R.
Nitric oxide: a key mediator in cutaneous physiology. Clin.Exp.Dermatol. 28:511-514, 2003.

- Zhang YG, Hu QH, Wang XZ, Qi ZL, Lin XX, Fang JL, Dai CC.
[The regulating effect of antisense-S-Oligo on TYR gene expression and melanin production of melanocytes]. Zhonghua Zheng.Xing.Wai Ke.Za Zhi. 19:285-287, 2003.

5. Neuromelanins

(Prof. M. d'Ischia)

During the last months of 2003 and the beginning of 2004 a number of papers on neuromelanin have appeared dealing mainly with its origin, metal and drug binding properties and role in neuronal degeneration. Jameson et al. (2003) investigated the kinetics of the reaction of cysteine with dopamine quinone to gain further insights into the mechanism of formation of the neuromelanin precursor cysteinyldopamine. Using also a model thiol, mercaptoacetic acid, it could be demonstrated that cysteine reacts via the initial reversible formation of an intermediate adduct which then decomposes to form mainly 5-S-cysteinyldopamine and little 2-S-cysteinyldopamine.

Galazka-Friedman et al. (2004) studied the role of iron in the degeneration of nervous cells in Parkinson's disease (PD) by means of Mossbauer spectroscopy (MS) and enzyme-linked immunoabsorbent assay (ELISA), and were able to demonstrate substantial differences ascribed to the presence in parkinsonian SN of about 8% of non-ferritin-like iron due possibly to a decreased ability of ferritin to bind iron in a tight form. They suggest that iron release from ferritin or neuromelanin may trigger oxidative stress and neuronal degeneration in PD. The potential role of iron in dopaminergic neurone degeneration is also the focus of a paper by Ide-Ektessabi et al. (2004) addressing systematically the distribution and chemical states of iron in parkinsonian substantia nigra. Oestergren et al (2004) studied the binding of -carbolines in the brain of pigmented and albino mice and in frogs, as well as to dopamine-melanin and melanin granules from Sepia officinalis, by tape-section and light-microscopic autoradiography. The results revealed a high affinity binding to melanin and a long-term retention (up to 30 days) in pigmented tissues, including neuromelanin-containing neurons of frogs after a single injection, drawing attention to the potential role of food-derived carboline accumulation in the induction of idiopathic PD.
Finally, De Marco et al. (2004) demonstrated that non-melanocytic cell strains (i.e., primary human keratinocytes) may accumulate melanin following exposure to quinones, and went on to suggest that in the basal nuclei, exposed to high level of catecholaminergic neurotransmitters, NM deposition represents a mechanism of detoxification by trapping toxic quinones and semiquinones and protecting neurons from accumulating damage over many years.

- De Marco F, Foppoli C, Coccia R, Blarzino C, Perluigi M, Cini C, Marcante ML.
  Ectopic deposition of melanin pigments as detoxifying mechanism: a paradigm for basal nuclei pigmentation. Biochemical and Biophysical Research Communications 314(2), 631-637, 2004.

- Galazka-Friedman Jolanta, Bauminger Erika R, Koziorowski Dariusz, Friedman Andrzej.
  Mossbauer spectroscopy and ELISA studies reveal differences between Parkinson's disease and control substantia nigra. Biochimica et Biophysica Acta 1688(2), 130-136, 2004.

- Ide-Ektessabi Ari, Kawakami Takuo, Watt Frank.
  Distribution and chemical state analysis of iron in the Parkinsonian substantia nigra using synchrotron radiation micro beams. Nuclear Instruments & Methods in Physics Research, Section B: Beam Interactions with Materials and Atoms 213 590-594, 2004.

- Jameson Guy N. L., Zhang Jie, Jameson Reginald F.,Linert Wolfgang.
  Kinetic evidence that cysteine reacts with dopaminoquinone via reversible adduct formation to yield 5-cysteinyl-dopamine: an important precursor of neuromelanin. Organic & Biomolecular Chemistry 2(5), 777-782, 2004.

- Oestergren A, Annas A, Skog K, Lindquist N. G, Brittebo E. B.
  Long-term retention of neurotoxic -carbolines in brain Journal of Neural Transmission 111(2), 141-157, 2004.

6. Genetics, molecular and developmental biology

(Dr. F. Beermann)

- Baxter LL, Pavan WJ.
Pmel17 expression is Mitf-dependent and reveals cranial melanoblast migration during murine development. Gene Expr Patterns 3(6):703-707, 2003.

- Bear J, Hong Y, Schartl M.
Mitf expression is sufficient to direct differentiation of medaka blastula derived stem cells to melanocytes. Development 130(26):6545-6553, 2003.

- Brewer S, Feng W, Huang J, Sullivan S, Williams T.
Wnt1-Cre-mediated deletion of AP-2alpha causes multiple neural crest-related defects. Dev Biol 267(1):135-152, 2004.

- Burdon KP, Wilkinson RM, Barbour JM, Dickinson JL, Stankovich JM, Mackey DA, Sale MM.
Investigation of albinism genes in congenital esotropia. Mol Vis 9: 710-714, 2003.

- Candille SI, Raamsdonk CD, Chen C, Kuijper S, Chen-Tsai Y, Russ A, Meijlink F, Barsh GS.
Dorsoventral Patterning of the Mouse Coat by Tbx15. PLoS Biol 2(1):E3. Epub 2004.
Shortened abstract: We have studied how a classical mouse mutation, *droopy ear (de(H)*), affects dorsoventral skin characteristics, especially those under control of the Agouti gene. We identify a 216 kb deletion in *de(H)* that removes all but the first exon of the Tbx15 gene, whose embryonic expression in developing mesenchyme correlates with pigmentary and skeletal malformations observed in *de(H)/de(H*) animals. Construction of a targeted allele of Tbx15 confirmed that the de(H) phenotype was caused by Tbx15 loss of function. Early embryonic expression of Tbx15 in dorsal mesenchyme is complementary to Agouti expression in ventral mesenchyme; in the absence of Tbx15, expression of Agouti in both embryos and postnatal animals is displaced dorsally. Transplantation experiments demonstrate that positional identity of the skin with regard to dorsoventral pigmentation differences is acquired by E12.5, which is shortly after early embryonic expression of Tbx15. Fate-mapping studies show that the dorsoventral pigmentation boundary is not in register with a previously identified dermal cell lineage boundary, but rather with the limb dorsoventral boundary. Embryonic expression of Tbx15 in dorsolateral mesenchyme provides an instructional cue required to establish the future positional identity of dorsal dermis. These findings represent a novel role for T-box gene action in embryonic development, identify a previously unappreciated aspect of dorsoventral patterning that is widely represented in furred åmammals, and provide insight into the mechanisms that underlie region-specific differences in body morphology.

- Cheung M, Briscoe J.
Neural crest development is regulated by the transcription factor Sox9. Development 130(23):5681-5693. Epub 2003 Oct 5681., 2003.
Shortened abstract: Group E Sox genes (Sox8, Sox9 and Sox10) are expressed in the prospective neural crest and Sox9 expression precedes expression of premigratory neural crest markers. Here, we show that group E Sox genes act at two distinct steps in neural crest differentiation. Forced expression of Sox9 promotes neural-crest-like properties in neural tube progenitors at the expense of central nervous system neuronal differentiation. Subsequently, in migratory neural crest cells, SoxE gene expression biases cells towards glial cell and melanocyte fate, and away from neuronal lineages. Although SoxE genes are sufficient to initiate neural crest development they do not efficiently induce the delamination of ectopic neural crest cells from the neural tube consistent with the idea that this event is independently controlled. Together, these data identify a role for group E Sox genes in the initiation of neural crest development and later SoxE genes influence the differentiation pathway adopted by migrating neural crest cells.

- Commo S, Gaillard O, Bernard BA.
Human hair greying is linked to a specific depletion of hair follicle melanocytes affecting both the bulb and the outer root sheath. Br J Dermatol 150(3):435-443, 2004.

- Cook AL, Donatien PD, Smith AG, Murphy M, Jones MK, Herlyn M, Bennett DC, Leonard JH, Sturm RA.
Human melanoblasts in culture: expression of BRN2 and synergistic regulation by fibroblast growth factor-2, stem cell factor, and endothelin-3. J Invest Dermatol 121(5):1150-1159, 2003.

- Cronin CA, Ryan AB, Talley EM, Scrable H.
Tyrosinase expression during neuroblast divisions affects later pathfinding by retinal ganglion cells. J Neurosci 23(37):11692-11697, 2003.

- Deng SH, Gao J, Ren J, Chen KF, Ding NS, Ai HS, Lin WH, Wang WJ, Liu BS, Lai FJ, Huang LS.
[Studies of the relationship of melanocortin receptor 1(MC1R) gene with coat color phenotype in pigs]. Yi Chuan Xue Bao 30(10):949-954, 2003.

- Dinakar C, Lewin S, Kumar KR, Harshad SR.
Partial albinism, immunodeficiency, hypergammaglobulinemia and Dandy-Walker cyst--a Griscelli syndrome variant. Indian Pediatr 40(10):1005-1008, 2003.

- Evrard YA, Mohammad-Zadeh L, Holton B.
Alterations in Ca(2+)-dependent and cAMP-dependent signaling pathways affect neurogenesis and melanogenesis of quail neural crest cells in vitro. Dev Genes Evol 26(26, 2004.

- Fargnoli MC, Chimenti S, Keller G, Hofler H, Peris K.
Identification of four novel melanocortin 1 receptor (MC1R) gene variants in a Mediterranean population. Hum Mutat 21(6):655, 2003.

- Frudakis T, Thomas M, Gaskin Z, Venkateswarlu K, Chandra KS, Ginjupalli S, Gunturi S, Natrajan S, Ponnuswamy VK, Ponnuswamy KN.
Sequences associated with human iris pigmentation. Genetics 165(4):2071-2083, 2003.

- Goodall J, Martinozzi S, Dexter TJ, Champeval D, Carreira S, Larue L, Goding CR.
Brn-2 Expression Controls Melanoma Proliferation and Is Directly Regulated by beta-Catenin. Mol Cell Biol. 24(7):2915-2922, 2004.
Abstract: Constitutive activation of the Wnt/beta-catenin signaling pathway is a notable feature of a large minority of cases of malignant melanoma, an aggressive and increasingly common cancer. The identification of target genes downstream from this pathway is therefore crucial to our understanding of the disease. The POU domain transcription factor Brn-2 has been implicated in control of proliferation and melanoma survival, and its expression is strongly upregulated in melanoma. We show here that in vivo Brn-2 is expressed in melanocytes but not in embryonic day 11.5 melanoblasts and that its expression is directly controlled by the Wnt/beta-catenin signaling pathway in melanoma cell lines and in transgenic mice. Moreover, silent interfering RNA-mediated inhibition of Brn-2 expression in melanoma cells overexpressing beta-catenin results in significantly decreased proliferation. These results, together with the observation that BRAF signaling also induces Brn-2 expression, reveal that Brn-2 is a focus for the convergence of two key melanoma-associated signaling pathways that are linked to cell proliferation.

- Hosaka E, Soma Y, Kawa Y, Kaminaga H, Osumi K, Ooka S, Watabe H, Ito M, Murakami F, Mizoguchi M.
Effects of Ultraviolet Light on Melanocyte Differentiation: Studies with Mouse Neural Crest Cells and Neural Crest-derived Cell Lines. Pigment Cell Res 17(2):150-157, 2004.

- Hou L, Loftus SK, Incao A, Chen A, Pavan WJ.
Complementation of melanocyte development in SOX10 mutant neural crest using lineage-directed gene transfer. Dev Dyn 229(1):54-62, 2004.
Abstract: An in vitro gene complementation approach has been developed to dissect gene function and regulation in neural crest (NC) development and disease. The approach uses the avian RCAS virus to express genes in NC cells derived from transgenic mice expressing the RCAS receptor TVA, under the control of defined promoter elements. Constructs for creating TVA transgenic mice were developed using site-specific recombination GATEWAY (GW), compatible vectors that can also be used to facilitate analysis of genomic fragments for transcriptional regulatory elements. By using these GW vectors to facilitate cloning, transgenic mouse lines were generated that express TVA in SOX10-expressing NC stem cells under the control of the Pax3 promoter. The Pax3-tv-a transgene was bred onto a Sox10-deficient background, and the feasibility of complementing genetic NC defects was demonstrated by infecting the Pax3-tv-a cells with an RCAS-Sox10 expression virus, thereby rescuing melanocyte development of Sox10-deficient NC cells. This system will be useful for assessing genetic hierarchies in NC development.

- Iida A, Inagaki H, Suzuki M, Wakamatsu Y, Hori H, Koga A.
The tyrosinase gene of the I albino mutant of the medaka fish carries a transposable element insertion in the promoter region. Pigment Cell Res 17(2):158-164, 2004.

- Inagaki K, Suzuki T, Shimizu H, Ishii N, Umezawa Y, Tada J, Kikuchi N, Takata M, Takamori K, Kishibe M, Tanaka M, Miyamura Y, Ito S, Tomita Y.
Oculocutaneous albinism type 4 is one of the most common types of albinism in Japan. Am J Hum Genet 74(3):466-471. Epub 2004 Feb 2011, 2004.

- Kang HY, Chung E, Lee M, Cho Y, Kang WH.
Expression and function of peroxisome proliferator-activated receptors in human melanocytes. Br J Dermatol 150(3):462-468, 2004.

- Khaled M, Larribere L, Bille K, Ortonne JP, Ballotti R, Bertolotto C.

Microphthalmia associated transcription factor is a target of the phosphatidylinositol-3-kinase pathway. J Invest Dermatol 121(4):831-836, 2003.

- Klovins J, Haitina T, Fridmanis D, Kilianova Z, Kapa I, Fredriksson R, Gallo-Payet N, Schioth HB.
The Melanocortin System in Fugu: Determination of POMC/AGRP/MCR Gene Repertoire and Synteny, As Well As Pharmacology and Anatomical Distribution of the MCRs. Mol Biol Evol 21(3):563-579. Epub 2003 Dec 2023, 2004.

- Knight RD, Javidan Y, Nelson S, Zhang T, Schilling T.
Skeletal and pigment cell defects in the lockjaw mutant reveal multiple roles for zebrafish tfap2a in neural crest development. Dev Dyn 229(1):87-98, 2004.

- Kunisada T, Yamane T, Aoki H, Yoshimura N, Ishizaki K, Motohashi T.
Development of melanocytes from ES cells. Methods Enzymol 365: 341-349, 2003.

- Ludwig A, Rehberg S, Wegner M.
Melanocyte-specific expression of dopachrome tautomerase is dependent on synergistic gene activation by the Sox10 and Mitf transcription factors. FEBS Lett 556(1-3):236-244, 2004.

- Matichard E, Verpillat P, Meziani R, Gerard B, Descamps V, Legroux E, Burnouf M, Bertrand G, Bouscarat F, Archimbaud A, Picard C, Ollivaud L, Basset-Seguin N, Kerob D, Lanternier G, Lebbe C, Crickx B, Grandchamp B, Soufir N.
Melanocortin 1 receptor (MC1R) gene variants may increase the risk of melanoma in France independently of clinical risk factors and UV exposure. J Med Genet 41(2):e13, 2004.

- Miller AJ, Du J, Rowan S, Hershey CL, Widlund HR, Fisher DE.
Transcriptional regulation of the melanoma prognostic marker melastatin (TRPM1) by MITF in melanocytes and melanoma. Cancer Res 64(2):509-516, 2004.

- Montoliu L, Larue L, Beermann F.
On the use of regulatory regions from pigmentary genes to drive the expression of transgenes in mice. Pigment Cell Research 17: 188-190, 2004.

- Mottonen M, Lanning M, Baumann P, Saarinen-Pihkala UM.
Chediak-Higashi syndrome: four cases from Northern Finland. Acta Paediatr 92(9):1047-1051, 2003.

- Niwa T, Shibusawa M, Matsuda Y, Terashima A, Nakamura A, Shiojiri N.
The Bh (black at hatch) gene that causes abnormal feather pigmentation maps to chromosome 1 of the Japanese quail. Pigment Cell Res 16(6):656-661, 2003.

- Ohguchi K, Banno Y, Akao Y, Nozawa Y.
Involvement of phospholipase D1 in melanogenesis of mouse B16 melanoma cells. J Biol Chem 279(5):3408-3412. Epub 2003 Nov 3413, 2004.

- Pak BJ, Lee J, Thai BL, Fuchs SY, Shaked Y, Ronai Z, Kerbel RS, Ben-David Y.
Radiation resistance of human melanoma analysed by retroviral insertional mutagenesis reveals a possible role for dopachrome tautomerase. Oncogene 23(1):30-38., 2004.

- Peters EM, Maurer M, Botchkarev VA, Jensen K, Welker P, Scott GA, Paus R.
Kit is expressed by epithelial cells in vivo. J Invest Dermatol 121(5):976-984, 2003.

- Pla P, Solov'eva O, Moore R, Alberti C, Kunisada T, Larue L.
Dct::lacZ ES Cells: A Novel Cellular Model to Study Melanocyte Determination and Differentiation. Pigment Cell Res 17(2):142-149., 2004.

- Poser I, Bosserhoff AK.
Transcription factors involved in development and progression of malignant melanoma. Histol Histopathol 19(1):173-188, 2004.

- Richards GM, Oresajo CO, Halder RM.
Structure and function of ethnic skin and hair. Dermatol Clin 21(4):595-600, 2003.

- Rothhammer T, Hahne JC, Florin A, Poser I, Soncin F, Wernert N, Bosserhoff AK.

The Ets-1 transcription factor is involved in the development and invasion of malignant melanoma. Cell Mol Life Sci 61(1):118-128, 2004.

- Rundshagen U, Zuhlke C, Opitz S, Schwinger E, Kasmann-Kellner B.
Mutations in the MATP gene in five German patients affected by oculocutaneous albinism type 4. Hum Mutat 23(2):106-110, 2004.

- Saran A, Spinola M, Pazzaglia S, Peissel B, Tiveron C, Tatangelo L, Mancuso M, Covelli V, Giovannelli L, Pitozzi V, Pignatiello C, Milani S, Dolara P, Dragani TA.
Loss of tyrosinase activity confers increased skin tumor susceptibility in mice. Oncogene 1-6, 2004.

- Scheinfeld NS.
Syndromic albinism: a review of genetics and phenotypes. Dermatol Online J 9(5):5. 2003.

- Schmutz SM, Berryere TG, Ciobanu DC, Mileham AJ, Schmidtz BH, Fredholm M.
A form of albinism in cattle is caused by a tyrosinase frameshift mutation. Mamm Genome 15(1):62-67, 2004.

- Takeda K.
[Regulatory network of transcription factor MITF in pigment cells]. Seikagaku 75(11):1444-1448, 2003.

- Tosney KW.
Long-distance cue from emerging dermis stimulates neural crest melanoblast migration. Dev Dyn 229(1):99-108., 2004.

- Trentin A, Glavieux-Pardanaud C, Le Douarin NM, Dupin E.
Self-renewal capacity is a widespread property of various types of neural crest precursor cells. Proc Natl Acad Sci U S A 15(15, 2004.
Shortened abstract: We explored the stem cell properties of quail NC cells by means of in vitro serial subcloning. We identified types of multipotent and oligopotent NC progenitors that differ in their developmental repertoire, ability to self-maintain, and response to exogenous endothelin 3 according to their truncal or cephalic origin. The most striking result is that bipotent progenitors are endowed with self-renewal properties. Thus glia-melanocyte and glia-myofibroblast progenitors behave like stem cells in that they are able both to self-renew and generate a restricted progeny. In our culture conditions, glia-myofibroblast precursors display a modest capacity to self-renew, whereas glia-melanocyte precursors respond to endothelin 3 by extensive self-renewal. These findings may explain the etiology of certain multiphenotypic NC-derived tumors in humans. Moreover, the presence of multiple stem cell phenotypes along the NC-derived lineages may account for the rarity of the "totipotent NC stem cell" and may be related to the large variety and widespread dispersion of NC derivatives throughout the body.

- Tsai KL, Guyon R, Murphy KE.
Identification of isoforms and RH mapping of canine KIT. Cytogenet Genome Res 102(1-4):261-263, 2003.

- Vachtenheim J, Drdova B.
A dominant negative mutant of microphthalmia transcription factor (MITF) lacking two transactivation domains suppresses transcription mediated by wild type MITF and a hyperactive MITF derivative. Pigment Cell Res 17(1):43-50, 2004.

- Wilkie AL, Jordan SA, Sharpe JA, Price DJ, Jackson IJ.
Widespread tangential dispersion and extensive cell death during early neurogenesis in the mouse neocortex. Dev Biol 267(1):109-118.,2004.
Comment: Dct is expressed in telencephalon. Here, this property is used in Dct::laacZ transgenic mice (Wilkie et al., Development, 2002) to analyse clonality of precursors in brain.

- Yajima I, Endo K, Sato S, Toyoda R, Wada H, Shibahara S, Numakunai T, Ikeo K, Gojobori T, Goding CR, Yamamoto H.
Cloning and functional analysis of ascidian Mitf in vivo: insights into the origin of vertebrate pigment cells. Mech Dev 120(12):1489-1504, 2003.

7. Tyrosinase, TRPs, other enzymes

(Prof. J.C. Garcia-Borron)

- Casella L, Granata A, Monzani E, Pievo R, Pattarello L, Bubacco L.
  New aspects of the reactivity of tyrosinase. Micron. 35(1-2):141-2, 2004.

- Chen K, Minwalla L, Ni L, Orlow SJ.
  Correction of defective early tyrosinase processing by bafilomycin A1 and monensin in pink-eyed dilution melanocytes. Pigment Cell Res. 17(1):36-42, 2004.

- Chen Q, Chen QX, Qiu L, Song KK, Huang H.
  Inhibitory effect of 4-cyanobenzaldehyde and 4-cyanobenzoic acid on mushroom (Agaricus bisporus) tyrosinase. J Protein Chem. 22(7-8):607-12, 2003.

- Chen QX, Huang H, Kubo I.
  Inactivation kinetics of mushroom tyrosinase by cetylpyridinium chloride. J Protein Chem. 22(5):481-7, 2003.

- Cook AL, Donatien PD, Smith A, Murphy M, Jones M, Herlyn M, Bennett DC, Leonard JH, Sturm RA.
  Human melanoblasts in culture: expression of BRN2 and synergistic regulation by fibroblast growth factor-2, stem cell factor, and endothelin-3. J Invest Dermatol. 121(5):1150-9, 2003.

- Cronin CA, Ryan AB, Talley EM, Scrable H.
  Tyrosinase expression during neuroblast divisions affects later pathfinding by retinal ganglion cells. Neurosci. 17;23(37):11692-7, 2003.

- Fan Y, Flurkey WH.
  Purification and characterization of tyrosinase from gill tissue of Portabella mushrooms. Phytochemistry. 65(6):671-8, 2004.

- Fenoll LG, Garcia-Ruiz PA, Varon R, Garcia-Canovas F.
  Kinetic study of the oxidation of quercetin by mushroom tyrosinase. J Agric Food Chem. 51(26):7781-7, 2003.

- Fenoll LG, Penalver MJ, Rodriguez-Lopez JN, Garcia-Ruiz PA, Garcia-Canovas F, Tudela J.
  Deuterium isotope effect on the oxidation of monophenols and o-diphenols by tyrosinase. Biochem J. Pt. [Epub ahead of print] , 2004.

- Fenoll LG, Penalver MJ, Rodriguez-Lopez JN, Varon R, Garcia-Canovas F, Tudela J.
  Tyrosinase kinetics: discrimination between two models to explain the oxidation mechanism of monophenol and diphenol substrates. Int J Biochem Cell Biol. 36(2):235-46, 2004.

- Fiore G, Poli A, Di Cosmo A, d'Ischia M, Palumbo A.
  Dopamine in the ink defence system of Sepia officinalis: biosynthesis, vesicular compartmentation in mature ink gland cells, nitric oxide (NO)/cGMP-induced depletion and fate in secreted ink. Biochem J. 378(Pt 3):785-91, 2004.

- Gimenez E, Lavado A, Giraldo P, Montoliu L.
  Tyrosinase gene expression is not detected in mouse brain outside the retinal pigment epithelium cells. Eur J Neurosci. 18(9):2673-6, 2003.

- Gomez Sarosi LA, Rieber MS, Rieber M.
  Hydrogen peroxide increases a 55-kDa tyrosinase concomitantly with induction of p53-dependent p21 waf1 expression and a greater Bax/Bcl-2 ratio in pigmented melanoma. Biochem Biophys Res Commun. 312(2):355-9, 2003.

- Guida G, Zanna P, Gallone A, Argenzio E, Cicero R.
  Melanogenic response of the kupffer cells of rana esculenta L. To melanocyte stimulating hormone. Pigment Cell Res. 17(2):128-34, 2004.

- Hasegawa T, Matsuzaki M, Takeda A, Kikuchi A, Furukawa K, Shibahara S, Itoyama Y.
  Increased dopamine and its metabolites in SH-SY5Y neuroblastoma cells that express tyrosinase. J Neurochem. 87(2):470-5, 2003.

- Higuchi K, Kawashima M, Ichikawa Y, Imokawa G.
Sphingosylphosphorylcholine is a Melanogenic Stimulator for Human Melanocytes. Pigment Cell Res. 16(6):670-8, 2003.

- Hwang JS, Choi H, Rho HS, Shin HJ, Kim DH, Lee J, Lee BG, Chang I.
Pigment-lightening effect of N,N'-dilinoleylcystamine on human melanoma cells. Br J Dermatol. 150(1):39-46, 2004.

- Iida A, Inagaki H, Suzuki M, Wakamatsu Y, Hori H, Koga A.
The tyrosinase gene of the I albino mutant of the medaka fish carries a transposable element insertion in the promoter region. Pigment Cell Res. 17(2):158-64, 2004.

- Jung JH, Choi SW, Han S.
Indirect oxidation of 6-tetrahydrobiopterin by tyrosinase. Biochem Biophys Res Commun. 314(4):937-42, 2004.

- Kang HY, Chung E, Lee M, Cho Y, Kang WH.
Expression and function of peroxisome proliferator-activated receptors in human melanocytes. Br J Dermatol. 150(3):462-8, 2004.

- Kim DS, Park SH, Kwon SB, Youn SW, Park KC.
Effects of lysophosphatidic acid on melanogenesis. Chem Phys Lipids.127(2):199-206, 2004.

- Kim SM, Han S.
Tyrosinase scavenges tyrosyl radical. Biochem Biophys Res Commun. 312(3):642-9, 2003.

- Lee MH, Osaki T, Lee JY, Baek MJ, Zhang R, Park JW, Kawabata S, Soderhall K, Lee BL.
Peptidoglycan recognition proteins involved in 1,3-beta-D-glucan-dependent prophenoloxidase activation system of insect. J Biol Chem. 279(5):3218-27, 2004. Epub 2003.

- Nagata H, Takekoshi S, Takeyama R, Homma T, Yoshiyuki Osamura R.
Quercetin enhances melanogenesis by increasing the activity and synthesis of tyrosinase in human melanoma cells and in normal human melanocytes. Pigment Cell Res. 17(1):66-73, 2004.

- Ohguchi K, Banno Y, Akao Y, Nozawa Y.
Involvement of phospholipase D1 in melanogenesis of mouse B16 melanoma cells. J Biol Chem. 279(5):3408-12, 2004. Epub 2003.

- Pak BJ, Lee J, Thai BL, Fuchs SY, Shaked Y, Ronai Z, Kerbel RS, Ben-David Y.
Radiation resistance of human melanoma analysed by retroviral insertional mutagenesis reveals a possible role for dopachrome tautomerase. Oncogene. 23(1):30-8, 2004.

- Park HY, Lee J, Gonzalez S, Middelkamp-Hup MA, Kapasi S, Peterson S, Gilchrest BA.
Topical application of a protein kinase C inhibitor reduces skin and hair pigmentation. J Invest Dermatol. 122(1):159-66, 2004.

- Park YD, Jung JY, Kim DW, Kim WS, Hahn MJ, Yang JM.
Kinetic inactivation study of mushroom tyrosinase: intermediate detection by denaturants. J Protein Chem. 22(5):463-71, 2003.

- Park YD, Lee JR, Park KH, Hahn HS, Hahn MJ, Yang JM.
A new continuous spectrophotometric assay method for DOPA oxidase activity of tyrosinase. J Protein Chem. 22(5):473-80, 2003.

- Park YD, Lee SJ, Park KH, Kim SY, Hahn MJ, Yang JM.
Effect of thiohydroxyl compounds on tyrosinase: inactivation and reactivation study. J Protein Chem. 22(7-8):613-23, 2003.

- Saran A, Spinola M, Pazzaglia S, Peissel B, Tiveron C, Tatangelo L, Mancuso M, Covelli V, Giovannelli L, Pitozzi V, Pignatiello C, Milani S, Dolara P, Dragani TA.
Loss of tyrosinase activity confers increased skin tumor susceptibility in mice. Oncogene. 2004 Mar 8 [Epub ahead of print]

- Scalia M, Pietro CD, Poma M, Ragusa M, Sichel G, Corsaro C.

The spleen pigment cells in some amphibia. Pigment Cell Res.17(2):119-27, 2004.

- Shareefi Borojerdi S, Haghbeen K, Asghar Karkhane A, Fazli M, Saboury AA.
Successful resonance Raman study of cresolase activity of mushroom tyrosinase. Biochem Biophys Res Commun. 314(4):925-30, 2004.

- Soddu G, Sanjust E, Murgia S, Rescigno A.
Interference of some tryptophan metabolites in the formation of melanin in vitro. Pigment Cell Res. 17(2):135-41, 2004.

- Tepper AW, Bubacco L, Canters GW.
Stopped-flow fluorescence studies of inhibitor binding to tyrosinase from streptomyces antibioticus. J Biol Chem. 2003 Dec 29 [Epub ahead of print]

- Usuki A, Ohashi A, Sato H, Ochiai Y, Ichihashi M, Funasaka Y.
The inhibitory effect of glycolic acid and lactic acid on melanin synthesis in melanoma cells. Exp Dermatol. 12 Suppl 2:43-50, 2003.

- Van Neste D, Tobin DJ.
Hair cycle and hair pigmentation: dynamic interactions and changes associated with aging. Micron. 5(3):193-200, 2004.

- Watabe H, Valencia JC, Yasumoto K, Kushimoto T, Ando H, Muller J, Vieira WD, Mizoguchi M, Appella E, Hearing VJ.
Regulation of tyrosinase processing and trafficking by organellar pH and by proteasome activity. J Biol Chem. 279(9):7971-81, 2004. Epub 2003.

- Wu H, Park HY.
Protein kinase C-beta-mediated complex formation between tyrosinase and TRP-1. Biochem Biophys Res Commun. 311(4):948-53, 2003.

- Yamakoshi J, Otsuka F, Sano A, Tokutake S, Saito M, Kikuchi M, Kubota Y.
Lightening effect on ultraviolet-induced pigmentation of guinea pig skin by oral administration of a proanthocyanidin-rich extract from grape seeds. Pigment Cell Res. 16(6):629-38, 2003.

- Yukitake J, Otake H, Inoue S, Wakamatsu K, Olivares C, Solano F, Hasegawa K, Ito S.
Synthesis and selective in vitro anti-melanoma effect of enantiomeric alpha-methyl- and alpha-ethyl-4-S-cysteaminylphenol. Melanoma Res. 13(6):603-9, 2003.

8. Melanosomes

(Dr. J. Borovansky)

Articles from recent period can be divided into several categories: a) review articles of various level (*Barsh versus Nakatsu & Ohno and Setaluri*); b) EM observations of melanosomes under normal (*Altunay, Cracknell et al*) and pathological conditions (*Busam et al, Cracknell et al, Nuber et al, Zanardo et al*); c) melanosome transport and distribution (*Byers et al, , Futter et al, Maniak, Tolmachova et al*), d) protein sorting in melanosome biogenesis (*Chen et al, Nakatsu&Ohno, Setaluri*); e) participation of melanosomes in radical scavenging (*Kim&Han*) and f) atomic force microscopy was exploited to get more information on melanosome transfer into keratinocytes (*Zhang et al*).

- Altunay H.
  Fine structure of the retinal pigment epithelium, Bruch's membrane and choriocapillaries in the ostrich (Struthio camelus). Anat Histol Embryol-J Vet Med ser.C 33(1): 38-41, 2003.
  Comments: Another article from a series describing RPE in various species (previously horse -see *Anat Histol Embryol 29(3):135-140, 2000*). As for the ostrich, in the light adapted state melanosomes were located in the apical region and in apical processes of epithelial cells.

- Barsh GS.
  What controls variation in human skin color? PLOS Biology 1(1):19-22, 2003.
  Comments: Popular-science article mentioning differences between eu- and phaeomelanosomes, some melanosomal proteins and differences in melanosome distribution in keratinocytes in individuals of Caucasian, African and Asian origin.

- Busam KJ, Wolchok J, Jungbluth AA, Chapman P.
  Diffuse melanosis after chemotherapy-induced tumor lysis syndrome in a patient with metastatic melanoma. J Cutaneous Pathol 31(3): 274-280, 2004.
  Comments: Melanosis has been repeatedly explained as a deposition of pigment arising from polymerization of leaked melanin precursors/metabolites (e.g. *J Invest Dermatol 22:163-172, 1954, Acta Derm Venereol 66:468-473,1986*). This EM study revealed the presence of melanosomes in the serum of a patient with stage IV melanoma; histiocytes and dendritic cells were the main cell types containing pigment in the skin, but it was present also extracellularly. Conclusion has been made that diffuse melanosis may result from tumour lysis with the release of melanosomes into the bloodstream, thus confirming the suggestion of Silberberg et al *(Arch Dermatol 97:671-677,1968).*

- Byers HR, Maheshwary S, Amodeo DM, Dykstra SG.
  Role of cytoplasmic dynein in perinuclear aggregation of phagocytosed melanosomes and supranuclear melanin cap formation in human keratinocytes. J Invest Dermatol 121(4): 813-820, 2003.
  Comments: Conclusion, announced in the title, is based on the following findings: cytoplasmic dynein intermediate chains were expressed in human keratinocytes and colocalized with the supranuclear melanin cap. Antisense oligonucleotides directed against dynein heavy chain 1 were able to induce dispersal of keratinocyte perinuclear melanophagolysosomal aggregates.

- Chen K, Minwalla L, Ni L, Orlow SJ.
  Correction of defective early tyrosinase processing by bafilomycin A1 and monensin in pink-eyed dilution melanocytes. Pigment Cell Res 17(1):36-42, 2004.
  Comments: Mouse melan-p1 melanocytes cultured from mice null at the pink-eyed dilution locus, exhibit defective melanin production due to the retention of misfolded tyrosinase in the ER. EM analysis revealed that after treatment with bafilomycin A1 or monensin melan-p1 cells contained mature melanosomes which suggested that each compound could restore tyrosinase trafficking to melanosomes (schematically summarized in Fig.5). Role of pH in regulating the size and shape of melanosomes was underlined.

- Cracknell KPB, Grierson I, Hogg P, Appleton P, Pffeifer N.
  Latanoprost-induced iris darkening: a morphometric study of human peripheral iridectomies. Exp Eye Res 77(6): 721-730, 2003.
  Comments: An EM study comparing the melanocytes of peripheral iridectomy specimens from two eyes that had latanoprost-induced iris darkening (LIID) with those of the fellow untreated eyes in an attempt to ascertain what is the morphological basis of LIID. There were no significant differences in the numbers of immature melanosomes or melanin granules in the melanocytes. However, there was a significant increase in the diameter of melanin granules in treated eyes that was more pronounced in the anterior border layer than in the deeper stroma. In the anterior border melanocytes the increase in melanin granule size was associated with a significant increase in the percentage of area

occupied by melanosomes. Term “melanin granule” was used incorrectly in the article instead of proper terms – mature or stage IV-melanosomes.

- Futter CE, Ramalho JS, Jaissle GB, Seeliger MW, Seabra MC.
The role of Rab27a in the regulation of melanosome distribution within retinal pigment epithelial cells. Mol Biol Cell 2004 – in press.
Comments: First evidence has been brought on the ability of melanosomes in mammalian (mouse) RPE cells to exhibit movement in response to light. Rab 27a and myosin VIIa (unlike myosin Va typical of skin melanocytes) are likely to be required for the association with and movement through the apical actin cytoskeleton which is a prerequisite for entry into the apical processes.

- Kim MS, Han S.
Tyrosinase scavenges tyrosyl radicals. Biochem Biophys Res Commun 312(3): 642 –649, 2003.
Comments: Sonicated melanosomes (of B16 melanoma origin) scavenged tyrosyl radical that was generated by UV irradiation of tyrosine. Purified mushroom tyrosinase could substitute melanosomes in the tyrosyl radical removal.

- Maniak M
Organelle transport: A park-and-ride system for melanosomes. Current Biology 13(23): R917-R919, 2003.
Comments: Short editorial article on the molecular motors that mediate transport of pigment-containing vesicles on microtubules and actin.

- Nakatsu F, Ohno H.
Adaptor protein complexes as the key regulators of protein sorting in the post-Golgi network. Cell Structure Function 28(5): 419-429, 2003.
Comments: Review devoted to the quaternary structure and function of AP-1A, AP-1B, AP-2, AP-3A, AP-3B and AP-4 complexes accompanied with nice figures summarizing sorting pathways mediated by AP complexes and explaining molecular machinery of endocytosis.

- Nuber UA, Tinschert S, Mundlos S, Hausser I.
Dyschromia universalis hereditaria: Familial case and ultrastructural skin investigation. Am J Med Genetics 125A(3): 261-266, 2004.
Comments: A familial case of dyschromia universalis hereditaria (DUH) is reported. Light and electron microscopy showed normal number of active melanocytes in the basal layer of epidermis , but different amounts of fully melanized melanosomes in hyper- and hypopigmented macules. DUH is not disorder of melanocyte number, but it appears to be a disorder of melanosome synthesis or in addition melanocyte activity. The causative gene has remained unknown.

- Setaluri V.
The melanosome: Dark pigment granule shines bright light on vesicle biogenesis and more. J Invest Dermatol 121(4): 650-660, 2003.
Comments: Well-written review covering the following topics: The nature and origin of melanosome. Melanosome biogenesis. Pathways to melanosome biogenesis. Melanosomal protein sorting. The lysosome connection. How to assemble a melanosome. Hermansky-Pudlak syndrome – a treasure trove for vesicle biogenesis.

- Tolmachova T, Anders R, Stinchcombe J, Bossi G, Griffith GM, Huxley C, Seabra MC.
A general role for Rab27a in secretory cells. Mol Biol Cell 15(): 332-344, 2004.
Comments: Rab27a is associated with melanosomes in pigmented cells and regulates melanosome transport via its interaction with actin-based cellular motors. A mouse model that expresses tissue- and cell-specific Rab27a fused to enhanced green fluorescent protein was constructed. The subsequent analyses showed that Rab27a was expressed in a broad range of specialized secretory cells – including exocrine, endocrine, ovarian and haemopoietic cells, most of which undergo regulated exocytosis.

- Torabian ZS, Grahn JC, Liu FT, Isroff RR.
Galectin-3 localizes to melanosome membrane in normal human melanocytes. J Invest Med 52(1): S164-S164, 2004.

- Zanardo L, Stolz W, Schmitz G, Kaminski W, Vikkula M, Landthaler M, Vogt T.
Progressive hyperpigmentation and generalized lentiginosis without associated systemic symptoms: a rare hereditary pigmentation disorder in south-east Germany. Acta Dermato-Venereol 84(1): 57-60, 2004.
Comments: Clinical and histological description of rare and perhaps novel variant of a familial progressive disorder of hyperpigmentation. Ultrastructural analysis showed a normal mode of Caucasian melanogenesis with varying content of melanosome complexes within keratinocytes.

- Zhang RZ, Zhu WY, Xia MY, Feng Y.

Morphology of cultured human epidermal melanocytes observed by atomic force microscopy. Pigment Cell Res 17(1): 62-65, 2004.
Comments: Atomic force microscopy was used to image the morphology of human epidermal melanocytes grown in vitro and to observe the mode of melanosome transfer.In addition to dendrites melanosome containing filopodia arising both from dendrite tips and the melanocyte cell body were demonstrated. Not only the dendrite tips but also secondary, tertiary and subordinate branches might take part in transfering melanosomes into keratinocytes.

9. Melanoma experimental, Cell culture

(NOT AVAILABLE)

ANNOUNCEMENTS & RELATED ACTIVITIES

Calendar of events

2004 Dubai World Dermatology & Laser Conference & Exhibition

April 27-29, Dubai, United Arab Emirates
Contact : Ibrahim Galadari
The International Academy of Cosmetic Dermatology
Index Conferences & Exhibitions Organisation Est.,
PO Box 13636,
Dubai, United Arab Emirates
Phone : +971 4 265 1585 Fax : +971 4 265 1581
E-mail : index@emirates.net.ae
Web site : www.indexexhibitions.com

2004 65th Annual Meeting of the Society for Investigative Dermatology (SID)

April 29 - May 1, Providence, Rhode Island, USA.
Contact: Kate Rader
Society for Investigative Dermatology
Suite 340
Superior Avenue
Cleveland, Ohio
Phone : +1 216 57 993 00
Fax : +1 216 57 993 33
E-mail : krader@sidnet.org
Web site : www.sidnet.org

2004 2nd Spring Symposium of the European Academy of Dermatology & Venereology (EADV)

April 29 - May 1, Budapest, Hungary.
Contact: Alice Sipos
The Hungarian Academy of Dermatology
MOTESZ Congress and Travel agency
Federation of Hungarian Medical Societies
H-1051 Budapest, Nador, U 36
Phone : +36 13 11 6687 Fax : +36 13 83 7918
E-mail : congress@motesz.hu
Web site : www.eadvbudapest2004.com

2004 8th Congress of the European Society of Pediatric Dermatology (ESPD)

May 13-15, Budapest, Hungary.
Contact : Eva Torak

Budapest Congress Centre
Convention Budapest KFT,
H-11461 Budapest
Phone : +36 1 216 1121 Fax : +36 1 456 0888
E-mail : convention.budapest@mail.datanet.hu
Web site : www.convention.hu

2004 37th Annual Scientific of the Australian College of Dermatologists

May 16-19, Sydney, Australia.
Contact: Rodney Sheaves
Australasian College of Dermatologists (ACD)
The Australasian College of Dermatologists,
136 Pittwater Road,
Gladesville NSW 2111
E-mail : admin@dermcoll.asn.au
Web site : www.dermcoll.asn.au

2004 ACW (Advanced Course and Workshops) on Aesthetic Dermatology

May 28-29, Paris, France.
Contact: Catherine Decuyper
Euromedicom
30 rue Baudin
92400 Courbevoire, France
Phone : +33 143 34 50 99 Fax : +33 143 34 50 39

2004 X World Congress of Pediatric Dermatology

June 7-10, Rome, Italy.
Contact: Giuseppe Fabrizi
Catholic University of Sacred Heart
The Catholic University of Sacred Heart
Department of Pediatric Dermatology
8-00168 Rome, Italy
Phone : +39 06 301 32 50 Fax : +39 06 301 32 50
E-mail : fabrizidermo@virgilio.it
Web site : www.ispdrome2004.supereva.it

2004 14th International Congress on Photobiology

June 10-15, Jungmoon, Jeju (Cheju), Korea.

2004 Stratum Corneum IV Congress

June 17-19, Paris, France.
Contact: Philippe Fournier
11 rue Solférino, 75007 Paris
MCI France
Phone : +33 1 43 17 31 25 Fax : +33 1 43 17 30 37
E-mail : sc2004@mci-group.com
Web site : www.stratumcorneum2004.com

2004 XIIth Annual Meeting of the PanAmerican Society for Pigment Cell Research

June 24-27, Orange County, California, USA.
Organizers:Dr. Frank MEYSKENS (UC-Irvine) and Dr. Rogers BOWERS (Cal State-LA)

Contact: Joyce Merchant
Chao Family Comprehensive Cancer Centre
University of California
Irvine Orange - California 92868
Phone : +1 714 4566 310 Fax : +1 714 4562 240
E-mail : jamercha@uci.edu
Web : www.paspcr.org

2004 84th Annual Meeting of the British Association of Dermatologists (BAD)

July 6-9, Belfast, Ireland
Contact: Emma Clayton
The British Association of Dermatologists (BAD)
9 Fitzroy Square, London W1T 6EH
Phone : +44 2 73 83 02 66 Fax : +44 2 73 885 263
E-mail : emmac@bad.org.uk
Web site : www.bad.org.uk/doctors/meetings

2004 International Skin Cancer Conference

July 22-24, Zurich, Switzerland.
Contact: Reinhard Dummer, M.D.
Department of Dermatology University Hospital of Zürich
Gloriastrasse 31
CH - 8091 Zürich
Phone: +41 1 255 88 37 Fax: +41 1 255 44 03
E-mail: nicole.fauchere@usz.ch
Web : www.skincancer.ch

2004 Annual Meeting of the New Zealand Dermatological Society

August 18-21, Queenstown, Australia.
Contact: Ken Macdonald
New Zealand Dermatological Society
202 Bealey Avenue,
AUS - Christchurch
Phone : +03 379 9467 Fax : +03 366 8607
E-mail : macdonald@derm.co.nz
Web : www.dermnetnz.org

2004 34th European Society for Dermatological Research

September 9-11, Vienna, Austria
Contact: AIMS International Congress Services
"34th Annual ESDR Meeting – Vienna"
Mariannengasse 32
1090 Vienna, Austria
Tel: +41 402 77 55 – 97/ -38 Fax: +43 1 402 77 31
E-mail: esdr2004@ahr-aims.com
Web: www.esdr.org

2004 25th Symposium of the International Society of Dermatopathology (ISDP)

September 16-18, Lisbon, Portugal
Contact: Saudade Leitao
International Society of Dermatopathology (ISDP)

Mundiconvenius,
Rua do Embaiwador, 13-2°
1300-215 Lisbon, Portugal
Phone : +351 21 364 94 98 Fax : +351 21 364 95 23
E-mail : saudade_leitao@mundiconvenius.pt
Web : www.intsocdermpath.org

2004 XIIth Meeting of the ESPCR

September 22-25, Paris, France

Contact: Dr. Lionel LARUE
E-mail: Lionel.Larue@curie.fr

Congress Secretariat :
Teranga
89 rue Damrémont
F - 75018 Paris
tel : +33-1-44-92-36-36 fax :+ 33-1-44-92-36-30
E-mail : info-espcr2004@curie.fr
Web : http://espcr2004.curie.fr/

2004 The International Society of Dermatology's 7th International Congress of Dermatology

September 29-2 october, Tehran, Iran

Contact: Yahya Dowlati
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PO Box 14155-6383, Tehran, Iran
Phone : +98 218 97 8190 Fax : +98 218 96 3804
E-mail : info@iranderm.org
Web : www.iranderm.org

2004 International Congress on Epidemiology Causes and prevention of Skin diseases

October 10-12, Venice, Italy

Contact: Luigi Naldi
International Dermatoepidemiology Association (IDEA) & European Dermatoepidemiology Network (EDEN)
U.O. Dermatologia
Ospedali Ruiniti
Largo Barozzi
I - 24128 Bergamo
Phone : +39 035 400 625 Fax : +39 035 253 070
E-mail : luiginal@tin.it
Web : www.esdr.ch/announcements.htm

2004 Perspectives in Melanoma VI

November 13-14, Miami, Florida, USA

Contact: IMEDEX
70 Technology Drive
Alpharetta, GA 30005-3969 USA
Tel +1 (770) 751 7332 Fax: +1 (770) 751 7334
E-mail: meetings@imedex.com
Web: www.imedex.com

2004 13th Congress of the European Academy of Dermatology & Venereology (EADV)

November 17-21, Florence, Italy
Contact: President Office
Viale Matteotti, 7
50121 Florence, Italy
Phone : +39 055 50 35 342 Fax : +39 055 50 35 341
E-mail : president@eadv2004.org
Web : www.EADV2004.org

2004 18th Annual Meeting of the Japanese Society for Pigment Cell Research

November 27-28, Kumamoto City, Japan
Chair: Prof. Tomomichi Ono of Kumamoto University
Contact: Dr Toshiro Kageshita

2005 8th International Conference on Solar Energy and Applied Photochemistry

February 20-26, Photoenergy Center, Upper Egypt [Luxor/Aswan]
Contact: Prof. Sabry Abdel-Mottaleb
Fac. of Science, Ain Shams University,
Abbassia, 11566 Cairo, Egypt
Cellular: + 2012 216 9584
Fax: + 202 484 5941 OR + 202 634 7683
E-mail: solar05@photoenergy.org
Web: www.photoenergy.org

2005 The 10th World Congress on Cancers of the Skin

May 13-17, Vienna, Austria
Contact: Elfriede Pomp
Dept of Dermatology, Vienna General Hospital
University of Vienna
Währinger Gürtel 18-20
A - 1090 Vienna
Tel: +00431 40400 7707 Fax: +00431 40400 7699
E-mail: info@wccs.at
Web: www.wccs.at

2005 XIVth International Pigment Cell Conference (IPCC)

September 18-23, Reston, Virginia, USA
Contact: Dr. V. HEARING
E-mail: hearingv@nih.gov
Web: www.ipcc.info

2006 XIIIth Meeting of the ESPCR

Barcelona, Spain
Contact: Dr. L. Montoliu
E-mail: montoliu@cnb.uam.es

NEW MEMBERS

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

ABRAHAMS A.
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Letter from *Vincent J. Hearing*
PCR Editor

Dear Colleagues :

Time has a way of flying by and that has been quite true of my tenure as **Editor** of ***Pigment Cell Research***. The term of the Editor is 5 years, which seems like a long time at the beginning but in reality it goes by very quickly. I've been immensely pleased by the progress of the journal over that time span and I suppose all of you are aware of its expansion in terms of pages per volume, number of color figures, impact factor, and yes, even subscription fee. While we all would like to keep the price of the journal where it was for many years, the reality of inflation eventually takes a toll and after 6 years at a stagnant price, the publisher recently had to increase the price of the journal, even the discounted member cost, to keep pace with rising costs. The alternative (decreases in pages, color, etc) is simply not worth thinking about. It has taken too much to build the journal to its current state to slip backwards.

The sum of our efforts to improve the journal have paid off in many ways. I think that the Reviews featured in each issue have been extremely valuable to our members and the wide citation of those in the literature has benefited us as well. Perhaps the most common feedback I have heard over the years has been about the quality and usefulness of those Reviews. It may be transparent to you, but the number of articles submitted has risen dramatically in recent years and is at an all time-high at the moment. This means less than 50% of manuscripts submitted can be accepted for publication, which makes some authors unhappy I know, but we simply have no choice about that and the increase in quality of manuscripts keeps the pressure on to improve the status of the journal. As a measure of growth, from 44 Articles submitted in 2000, those have increased each year and in 2003, 68 Articles were submitted (this year we have 68 submissions already and the publication year is only 50% completed). The rejection rate has also slowly increased from 35% in 2000 to a current rate of >50%. We have accommodated the increase in part because of the 25% increase in allotted pages in each issue, and in part because we now pay for about 20 extra pages in each issue, either from page charges assessed to authors for exceeding the standard limit of 7 journal pages per article, or from the Editor's budget. If you want to see more details about journal activities and statistics, please visit the Web Site at www.pigment.org and look at the PCR Statistics page. I have also recently updated the Top 50 Cited Articles in PCR and you can see there the rapidly rising articles that are being highly cited.

So what does the future hold for ***Pigment Cell Research***? I think the picture is quite bright at this point. From many perspectives, the key measure of any journal is its Impact Factor and ours has been climbing steadily (for 6 straight years actually). The final number for 2003 won't be known for another month or two but if it was calculated today (early February) it would be a little above 2.50. That is quite an improvement from the days when we hovered around 1.00 and that number puts us solidly in the top half of the highly competitive Cell Biology category of Current Contents. Can we do better? Absolutely, and I think that is destined to happen as only the strongest of papers submitted will be published in ***Pigment Cell Research*** in the future.

Even better, the next Editor of the journal has been chosen by the IFPCS Council, and Prof. Colin Goding has taken on that challenge with enthusiasm. You will no doubt be hearing soon of his plans to take ***Pigment Cell Research*** to the next level, and I know that everyone will be united behind him to continue the growth and dynamics of our journal during his term. At this point, I have another 6 months or so before beginning to turn my duties over to his office and I still welcome feedback from all scientists in the field on how to improve the journal and make it more useful to all of us.

Congratulations to the two PCR Award winners for 2003. The Glynis Scott laboratory won the Outstanding Article Award for 2003 for their article entitled "The cAMP Signaling Pathway Has Opposing Effects on Rac and Rho in B16F10 Cells: Implications for Dendrite Formation in Melanocytic Cells" published in ***Pigment Cell Research*** 2003; 16: 139-148. **Dr. Mayuko Kumasaka** from the Yamamoto laboratory was selected as recipient of the Young Investigator Award for 2003; she was the first author of an article entitled "Isolation and Developmental Expression of Tyrosinase Family Genes in *Xenopus laevis*", published in ***Pigment Cell Research*** 2003; 16: 455-462. Details of those 2 awards will be published in Issue #2 and will be available soon on the web site.

Now what will I do will all my free time once my duties as Editor are completed? Well I imagine some of it will be taken up in organizing the 19th International Pigment Cell Conference to be held near NIH from September 18-22, 2005. We have an active functional web site (www.ipcc.info) that will gradually develop as the meeting matures; the outline of the scientific program and the meeting venue is already posted there. Please feel free to check it anytime to see what has been added and I'll look forward to welcoming you that meeting late next year. Let me wish continued success to all of you.

ESPCR TRAVEL AWARDS FOR ATTENDANCE AT ESPCR MEETINGS

The European Society for Pigment Cell Research will provide a limited number of travel awards for attendance at ESPCR meetings. Depending on the number of applicants selected and the funds available, awards may cover travel (economy return air, rail fare or car fuel costs), conference registration, and in some cases accommodation (economy class). Awards will be made by the ESPCR Travel Awards Committee on a competitive basis.

Applicants must:

- Be a PhD student or junior scientist (i.e. postdoctoral or medical resident).
- Be an ESPCR member in good standing (subscription paid).
- Make a contribution (oral or poster) to the conference.
- Have no other source of funds for this purpose. If funds from elsewhere are subsequently obtained, ESPCR should be informed immediately and the application for ESPCR funding withdrawn, or the ESPCR award declined/returned if already made, so that another applicant can be funded.

Deadline for applications: 17 May, 2004
12th ESPCR Annual Meeting, Paris, France

Please send an informal letter of application (e-mail or ordinary mail) to :

Dr Friedrich Beermann, Chair, ESPCR Travel Awards Committee
E-mail: Friedrich.Beermann@isrec.unil.ch ISREC (Swiss Institute for Experimental Cancer Research)
Chemin des Boveresses 155
CH - 1066 Epalinges
Switzerland

Enclosing:

- Proof of status (usually a short statement from the supervisor or Head of Department), including the date or expected date of completion of PhD or medical qualification.
- Evidence of non-availability of other funds (usually part of the statement from the supervisor or Head of Department). Please state if other applications for funding are being made (this has a positive effect on your application).
- Submitted abstract of the oral or poster contribution.
- Estimates of the costs of travel, accommodation and conference registration.
- Applicant's full address, phone and fax numbers, and e-mail address where available.

Awards:
Awards will be made by the Travel Awards Committee on a competitive basis. Any unspent funds will be added to the funds available for Travel Awards for the following year.
Applicants will be notified of the outcome by the Chair of the Committee, by letter, fax, or e-mail. The award will be paid in general after submission of all relevant receipts including the original air or train tickets and the receipt for the registration fee. In exceptional cases, the award may alternatively be paid directly to a travel agent (or railway company, airline etc), and to the conference organizers, on submission of the original invoices.

Awards Committee 2004:
F. Beermann (Chairman), L. Larue and M. Picardo