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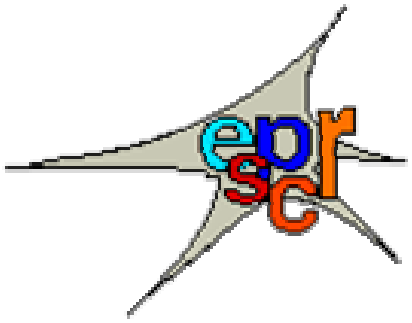

EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH *BULLETIN*

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CONTENTS

DISCUSSION

Sentinel Node Biopsy: New Boundaries (18/12/06)

Report from the 5th Biennial International Sentinel Node Society meeting Rome, 1-4 November 2006

Jenny Bryan, medical writer

Sentinel node biopsy (SNB) is transforming the management of malignant melanoma, and 84% of European Organisation for Research and Treatment of Cancer (EORTC) members who took part in a recent survey are using it for this type of cancer. But important questions remain about the survival advantages conferred by the technique, the risk of false negative results, and the implications for treatment.

These were some of the take-home messages for the nearly 400 cancer surgeons, oncologists and basic scientists who attended three packed days of state-of-the-art presentations at the meeting.

Key data from MSLT 1

SNB pioneer, **Professor Donald Morton** from the John Wayne Cancer Institute at St John's Health Centre, Santa Monica, USA, presented newly published five year data from the Multicentre Selective Lymphadenectomy Trial 1 (MSLT 1) which confirmed that using SNB to stage intermediate thickness (1.2-3.5mm) primary melanomas provides important prognostic information and identifies patients with nodal metastases who will live longer if they have immediate lymphadenectomy.

Five year disease-free survival was 78.3% in patients who had wide excision and SNB with immediate lymphadenectomy if nodal micrometastases were detected on biopsy. This compared with 73.1% in patients who had wide excision and postoperative observation of regional lymph nodes, with lymphadenectomy only if nodal relapse occurred (p=0.009). The 5 year melanoma-specific survival was similar in the two groups, though Professor Morton predicted that this may change at the next follow up, at 7 years.

Amongst node-positive patients, 5 year survival was 72.3% in the SNB group compared to 52.4% in the observation group (p=0.007). Patients in the SNB group had a mean 1.6 positive nodes, compared to 3.4 in the observation group.

In the biopsy group, the five year survival was 72.3% in those whose sentinel nodes were positive, compared with 90.2% in those with negative sentinel nodes (p<0.001).

'Sentinel node status was the most important prognostic factor. The presence or absence of micrometastases in the sentinel node is of biological importance – these are real metastases,' commented Professor Morton. 'If micrometastatic lymph nodes are left alone, they will become clinically apparent macroscopic metastases and affect survival,' he added.

Professor Morton stressed the importance of good training in SNB techniques in order to reduce the risk of false negative results; these occurred at a rate of 3% in MSLT 1. He reported that MSLT 1 data suggested that physicians needed to perform 55 'learning' cases in order to optimise their false negative rate.

False negatives with SNB in melanoma

Addressing the issue of false negative results in SNB of melanoma patients, **Dr Omgo Nieweg**, from the Netherlands Cancer Institute, Amsterdam, Netherlands, pointed out that recent improvements in technique have reduced the false negative rates reported in clinical practice from 16-40% down to 8-13%, but these figures are still well above those seen with SNB in breast cancer, and are a source of continuing concern.

'The reason for the higher false negative rate is that lymph node drainage from the skin is more variable, with 12-15% of patients having different drainage system from normal, so we don't always remove the right nodes for sentinel node biopsy,' he pointed out.

What about thin melanomas?

Another issue which needs to be resolved is whether the results achieved in intermediate thickness melanomas included in MSLT1 are applicable to thinner and thicker melanomas. **Dr Hans Starz**, from the Klinikum Augsburg, Augsburg, Germany, reported no sentinel node metastases in a series of 77 patients with melanomas under 0.76mm in depth, though one patient did go on to develop lung and brain metastases. There were no other recurrences during 71 months of follow-up.

Ten of a second group of 87 patients (12%) with melanomas of 0.76-1mm, had positive sentinel nodes, and the thinnest melanoma to produce a positive sentinel node was 0.8mm. Four of the 10 patients had complete lymph node dissection (CLND), but none of the 20 non-sentinel nodes examined from each of these patients was positive.

Dr Starz concluded that sentinel lymphonodectomy (SLNE) isn't necessary for melanomas of less than 0.76mm, but it should be used for tumours of 0.76-1mm because 10% of patients will have micrometastases. He added that, while SLNE reduces recurrence from 8% to 0%, CLND may not be necessary even in patients with positive sentinel nodes.

Autoimmunity is a positive prognostic indicator of response to interferon therapy for melanoma

Growing evidence supports the appearance of autoimmunity as a possible predictor of response in melanoma patients undergoing adjuvant interferon α-2b treatment after surgery for deep primary or regionally metastatic melanoma. **Dr Helen Gogas**, from the University of Athens, Athens, Greece, presented research which has shown that melanoma patients who develop an autoimmune response following interferon α-2b treatment do significantly better than those who do not. She reported results of a prospective multicentre phase III study of 200 patients with stage IIb, IIc or III melanoma, treated with interferon α-2b 15 MIU/m^2 iv, 5 days per week for 4 weeks and then randomised to interferon α-2b 10 MIU per day sc, three times a week, for 48 weeks (group A) or to interferon alfa 2b 15miu/m2 5 days per week for 4 weeks followed by observation (group B). Autoantibodies or autoimmunity (e.g. vitiligo or clinical symptoms) were seen in 52 (26%) patients (24% in Group A vs. 28% in Group B). Disease recurrence occurred in 115 patients, 108 of those with no autoimmunity, and 7 with autoimmunity. A total of 82 patients died – 80 with no autoimmunity and 2 with autoimmunity.

Optimising interferon treatment in melanoma

In a review of ongoing interferon research in melanoma, **Professor Axel Hauschild**, from the University of Kiel, Kiel, Germany, discussed a series of studies that are investigating the benefits of pegylated interferon α. He explained that it is hoped that prolonging the activity of interferon α by attaching a polyethylene glycol (PEG) molecule to the drug will further improve its effectiveness – as has already been shown in the treatment of hepatitis C infection.

He highlighted EORTC 18991 – a randomised, comparative trial of pegylated interferon α-2b 6μg/kg/week sc for eight weeks followed by 3μg/kg/week sc for five years, or observation, in 1388 stage IIIa/IIIb (only N1/N2 lymph node metastasis) melanoma patients. Results are expected to be presented at the American Society of Clinical Oncology (ASCO) meeting in June 2007.

Turning to the potential of neoadjuvant interferon treatment in melanoma, Professor Hauschild reviewed the recently published results of a study of 20 patients with stage IIIB-C melanoma treated with high dose interferon α (20 MIU/m^2, 5 days per week for 4 weeks) followed by complete lymphadenectomy and standard maintenance subcutaneous high dose interferon α (10 MIU/m^2 3 times per week) for 48 weeks.

Eleven out of 17 patients (55%) who had analysable pre-treatment biopsy material demonstrated an objective clinical response, and 3 patients (15%) had a complete pathologic response. At a median follow-up of 18.5 months, 10 patients had no evidence of recurrent disease. Clinical responders had significantly greater increases in endotumoral CD11c+ and CD3+ cells and significantly greater decreases in endotumoral CD83+ cells compared with nonresponders.

'Neoadjuvant interferon α was highly effective and offers an interesting approach to the study of biomarkers of melanoma. Its effects are most likely driven by indirect immunomodulatory rather than anti-proliferative activity,' concluded Professor Hauschild.

Other highlights

Widely agreed to be one of the hot topics of the meeting was the question of whether it is possible to predict the 20% of patients with positive sentinel nodes whose non sentinel nodes will also be positive, so that they can have CLND while low risk patients can be spared further surgery.

Professor Alistair Cochran, from David Geffen School of Medicine at the University of California at Los Angeles, USA, presented an analysis of pathological samples from 50 patients from MSLT 1 who had positive sentinel nodes. Factors found to be linked to poor outcome were: area of metastatic melanoma relative to area of sentinel node (p=0.03), number of metastatic foci in the sentinel node (p=0.03), maximum diameter of the largest tumour in the sentinel node (p=0.03), and metastatic tumour extending out of the capsule of the sentinel node (p=0.07) or into the lymphatics (p=0.01).

‘The amount and location of the sentinel node tumour correlates with outcome, but current indicators are insufficiently precise to direct decisions on complete lymph node dissection,’ concluded Professor Cochran. ‘We need better approaches, particularly looking at tumour characteristics, including proliferation, apoptosis, angiogenesis and lymphangiogenesis,’ he added.

Professor Richard Scolyer, from the Royal Prince Alfred Hospital, Sydney, Australia, predicted that pathologists’ workload would rise significantly if additional sentinel node measurements become a routine method of identifying patients who need CLND.

He pointed out that, while low numbers of tumour cells in the subcapsular part of the sentinel node and smaller amounts of tumour in the sentinel node overall have been consistently linked to lower risk of spread to non sentinel nodes, studies have reached variable conclusions about other predictive factors. Professor Scolyer suggested that some of the variation is likely to be due to the different ways in which pathologists prepare sections for examination. Anatomical variations from textbook descriptions of node structure can further complicate analyses.

He agreed with Professor Cochran that the evidence is not, as yet, strong enough to differentiate between patients who need CLND and those who do not.

New insights should be provided by two key phase III trials – MSLT 2 and SUNBELT. MSLT 2 is comparing sentinel lymphadenectomy and CLND versus sentinel lymphadenectomy alone in cutaneous melanoma patients with molecular or histopathological evidence of metastases in the sentinel node. Professor Morton reported that 40 sites have so far signed up to take part, and 265 of the planned 2000 melanoma patients with positive sentinel nodes have been randomised to treatment. But more sites are needed.

SUNBELT is an ongoing prospective randomised trial with over 3600 patients being treated at 79 centres in the USA and Canada, which is evaluating the role of lymph node dissection and adjuvant interferon alfa-2b for patients with early lymph node metastases. **Professor Kelly McMasters**, from the University of Louisville, Louisville, USA, reported that molecular staging with reverse transcriptase polymerase chain reaction (RT-PCR) for four melanoma markers failed to predict prognosis in patients who were sentinel node positive. However, the presence of one of the RT-PCR markers, tyrosinase – an enzyme which is essential for melanin biosynthesis – was associated with poorer prognosis. Data on the primary endpoints of the trial are expected within the next 12 months.

CURRENT LITERATURE

1. Chemistry of Melanins and other Pigments

(Dr. A. Napolitano)

A variety of properties of natural and synthetic melanins have been reported ranging from binding of calcium (Bush and Simon, *Pigm. Cell Res.*), and heavy metal ions (Boyd and Belisky *ACS meeting abs*) to the accumulation of neurotoxicants (Ostergren et al, *J. Neural Transm*). Also, a significant decrease of the antioxidant ability of melanin of RPE melanosomes have been observed following photodegradation. (Zareba et al *Photochem. Photobiol*.)
An interesting new model for eumelanin protomolecules based on cyclic oligomers of 5,6-dihydroxyindole/indolequinone units linked through the 2 and 7 position to form an inner porphyrin like ring has been considered (Kaxiras et al. *Phys Rev Lett*) and the spectrophotometric properties have been predicted by DFT calculations. Although individual oligomers and particularly tetramers give spectra with sharp features, considering an average of the spectra of 16 dominant tetramers, a largely featureless spectrum is obtained similar to that observed for DHI melanin. Such cyclic arrangements may also account for the metal binding properties of melanins. Verification that such cyclic oligomers may actually be formed during melanin polymerization represents a issue for future research work.
A number of strategies and new tyrosinase inhibitors for control of pigmentation have also been reported, including extracts from plants and notably a water-soluble polymer-wrapped derivative of fullerene (Xiao et al *Arch Dermatol Res*).
Improved easy to perform and sensitive methods for analysis of melanin in pigmented tissues have been presented. Fluorescence detection of amminohydroxyphenylalanine isomers (AHPs) formed by hydroiodic acid reductive hydrolysis of pheomelanins is reported to warrant a higher sensitivity with respect to the traditional electrochemical detection (Yang et al, *J. Chromat. A*) The rationale of the methodology is pre-column derivatization with *o*-naphthalene dialdehyde closely similar to the *o*-phtalaldehyde method used for aminoacid analysis. However the high selectivity of the electrochemical detection is apparently lost as the derivatization reaction is expected to occur on all the aminoacidic functionalities of the HI hydrolysates of the tissues. Also the specificity of the assay for true pheomelanic tissues is not assessed

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2. Biology of pigment cells and pigmentary disorders

(Dr. M. Picardo)

In the past it has been described that melanin is implicated in regulating calcium homeostasis within melanocytes and, conversely, calcium has been shown to regulate melanin production in epidermal melanocytes, by acting as a co-factor for phenylalanine hydroxylase. **Bush and Simon** show that Ca^{++} binds to carboxyl groups of *Sepia* melanin granules, which is a common binding motif observed for calcium binding to proteins. These results support the theory that melanosomes have a functional role in regulating calcium homeostasis inside the melanocyte.

A comprehensive determination of the protein composition of the melanosome has been obstructed by the melanin present. **Chi *et al*** report a novel method of removing melanin that includes in-solution digestion and immobilised metal affinity chromatography. Together with in-gel digestion, this method allowed the authors to characterize melanosome proteomes at various developmental stages by tandem mass spectrometry. This work represents a model for the study of the biogenesis of lysosome-related organelles.

Del Bino *et al* analysed the relationship between ultraviolet sensitivity and skin color type on 42 *ex vivo* skin samples, objectively classified from light to dark skin, based on their individual typology angle (ITA) values, determined by colorimetric parameters. This paper is worth reading because very few experimental data are available, showing the relationship between ultraviolet induced damage and skin type, apart from the erythemal reaction. The authors described in detail the determination the biological efficient dose (BED) for each sample, by quantifying sunburn cells after exposure to increasing doses of UV solar-stimulated radiation Furthermore they considered typical UV-induced biological markers, other than erythema, such as DNA damage, apoptosis, and p53 accumulation. They found a significant correlation between ITA and BED and, ITA and DNA damage. DNA lesions were distributed throughout all the epidermal layers and the uppermost dermal cells in light, intermediate and tanned skin, while they were restricted to suprabasal epidermal layers in brown or dark skin. The results support, at cellular level, the relationship between UV sensitivity and skin color type and emphasise the impact of DNA damage accumulation in basal layers in relation to the prevalence of skin cancer.

Vitiligo is a depigmenting disease whose aetiopathogenesis is still unclear. A central issue in vitiligo pathology concerns the fate of lesional melanocytes, if they are destroyed and consequently absent from lesions, if they depigment and become undifferentiated or if there is an imbalance in the shedding/renewal process. If the the status of lesions within the melanocytes were defined with greater accuracy this would contribute greatly towards the understanding of etiology, progression and treatment of this disorder. **Gottschalk and Kidson** carried out a molecular screen for melanocytes in lesional skin employing the sensitive and specific technique of RT-PCR, combined with Southern Blotting. The results show that, in three of the twelve patients, there was evidence of ongoing melanocyte survival, even when the lesions had been present for some years. This work opens the way for the possibility of using a range of melanocyte-specific markers for molecular staging of lesional status by RT-PCR.

The incidence of melanoma is steadily rising in the western population. The number of cases worldwide has doubled in the past 20 years. If melanoma is diagnosed early, it can be cured by surgical resection and about 80% of cases are dealt with in this way. However, metastatic malignant melanoma is largely refractory to existing therapies and has very poor prognosis, with a median survival rate of 6 months and 5-year survival rate of less than 5%, so new treatment strategies are urgently needed. Recent studies have provided a much improved understanding of melanoma biology and **Gray-Schopfer *et al*** review these findings and the exciting opportunities they are providing for new therapeutic approaches to this disease.

Considering that it has been reported that three subtypes of PPAR receptors are expressed in human melanocytes, and that their agonists in melanoma cells reduce the proliferative rates and induces some typical differentiation markers, **Lee *et al*** investigated the effect of PPAR agonists on some aspects related to melanocyte differentiation. Of the PPAR activators tested, the authors showed that PPAR-γ activator, such as ciglitazone, was the strongest subtype reducing cell proliferation and increasing pigmentation. The increase in pigmentation was due to the stimulatory action of PPAR-γ activators on DOPA oxidase activity, which eventually led to the melanin biosynthesis. Furthermore, they showed that ciglitazone induced MITF protein levels as well as tyrosinase. The present study suggests the regulatory role of PPAR-γ in differentiation of human melanocytes and offers future perspectives of PPAR-γ agonists for the treatment of pigmentary disorders, such as vitiligo.

Melanocytic cells express a set of genes specific to that lineage. Notably, in relation to immunotherapy, several melanocytic gene products have been directly shown to function as target antigens for CTLs. Heterogeneous expression of these antigens frequently occurs in melanomas and represents a potent barrier to immunotherapy. **Kono *et al*** investigated the correlation between antigen expression and the function of *BRAF*, a gene that has been found to be frequently mutated in melanomas, causing the constitutive activation of MAPK pathway. To examine this relationship directly, melanoma cells were transfected with mutant or wild-type BRAF to modulate MAPK signalling and the results indicate that blocking MAPK signalling with MEK inhibitor treatment results in up-regulation of melanoma antigen gene expression. Consequently, MAPK inhibition may assist in the targeting of melanoma in immunotherapy.

Kowalczuk *et al* compared the response of primary cultures of human melanocytes, with that of G361 melanoma cells, to ultraviolet-C, B and A radiation. They observed that G361 melanoma cells resulted more sensitive than melanocytes to killing by UVB and UVC radiation, whereas this difference in sensitivity between cell types was much less marked following UVA irradiation. The melanoma cells showed a sustained, dose-dependent G2/M block following exposure with all wavelengths and there was no apparent block to G1 cells entering S phase at any wavelength. Melanocytes, on the other hand, showed a marked G1 arrest, particularly following UVA. In conclusion the results show that G361 malignant

melanoma cells have lost the ability to regulate the cell cycle at the G1/S checkpoint and are more sensitive than melanocytes to cell killing by UVC and UVB but not UVA radiation.
Ultraviolet radiation is considered as the main agent responsible for the induction of cutaneous melanoma, moreover free radicals which are generated as by product during melanogenesis seems to have an important role in the induction of the neoplastic transformations. **Meyskens *et al*** present information from recent experimental findings that elevation of reactive oxygen species follows from melanin serving as a redox generator and that this may play an important role in the etiology and pathogenesis of cutaneous melanoma. These observations offer a new paradigm for the development of preventive and therapeutic approaches to this disease.
Panzella *et al* propose an easy-to-run method for routine analysis of eumelanin and pheomelanin in pigmented tissues. This technique is based on an improved chromatographic methodology for simultaneous determination of PTCA and BTCA as representative markers of eumelanin and pheomelanin, respectively, based on the use of an octadecylsilane column with polar end-capping with 1% formic acid (pH 2.8)/methanol as the eluant. The method requires conventional HPLC equipment and gives very good peak shapes and resolution, without a need for ion pair reagents or high salt concentrations in the mobile phase. The method can be applied to various eumelanin and pheomelanin pigmented tissues, including mammalian hair, skin and irides, and is amenable for use in population screening studies.
The review by **Passeron *et al*** has a very practical aim/focus and outlines approaches that can be used to specifically identify melanocyte subpopulation in the skin. The authors concentrate specifically on two techniques, immunohistochemistry (HIC) and tissue in situ hybridisation (TISH), that can be used to identify and study melanocytes in the skin and their response to UV or other stimuli *in situ*. They describe a method which is able to localise melanocytic antigens on formalin-fixed, paraffin-embedded tissue sections and in frozen sections, using indirect immunofluorescence with conjugated secondary antibodies. In addition the authors detail the use of TISH and its combination with IHC to study mRNA levels of genes expressed in the skin at cellular resolution.

The microphthalmia-associated transcription factor Mitf plays a critical role in regulating many aspects of melanocyte biology, such as survival, proliferation and activation of genes associated with differentiation and melanogenesis. The central role of Mitf in regulatiing so many aspects of melanocyte biology is reflected in complex regulation of Mitf expression and activity. **Saha *et al*** show that, in addition to cAMP signalling, Mitf is also regulated by lipid signalling via the p38 stress-activated kinase pathway, with a mechanism involving CREB-phosphorylation, enhanced Mitf expression and consequently increased tyrosinase expression. This work adds a new dimension in the signalling mechanism of melanogenesis and raises the possibility that lipid mediated activation of p38 signalling may represent a potential therapy for vitiligo.
The work by **Sánchez-Laorden *et al*** suggest novel and complex aspects of MC1R regulation. These include 1) differential effects of the GRKs that may provide the basis for cell type-specific regulatory patterns, 2) different desensitisation and internalisation properties for the WT and natural variants and 3) modification of key signalling properties by heterodimerisation of the WT receptor with skin cancer associated RHC alleles. The authors underline that it will be important to assess the actual impact of these regulatory mechanisms in normal human melanocytes of a defined genotype, naturally expressing different combinations of the frequent variant alleles. The authors suggest that in any case, MC1R is an excellent model to study fundamental aspects of GPCR signalling such as the role of individual units within dimeric forms.
Incidence of melanoma continues to rise, and a better understanding of its genetics will be critical to improve diagnosis and development of new treatments. **Spanjaard *et al*** employed an *in vitro* genetic screen to search for melanoma-specific genes that may serve as biomarkers and therapeutic targets. One identified cDNA encoded TROY, a member of the tumor necrosis factor receptor superfamily (TNFRSF). Results show that TROY is expressed in all primary and metastatic melanoma cells and tissue samples, but not in melanocytes found in normal skin biopsies and primary skin cell cultures, nor is TROY detectable in other (skin) tumour cells. Furthermore, TROY signalling is functional and contributes to DNA replication in melanoma cells. Together, these results identify TROY as the first TNFRSF that can serve as a biomarker for melanoma and a potentially novel cell surface signalling target for immunotherapies.
Cutaneous melanoma is the most lethal skin malignancy and most studies agree that exposure to ultraviolet radiation, phenotype susceptibility (such as light complexion, the presence of clinically atypical naevi or multiple naevomelanocytic naevi) and genetic risk, manifesting as a personal or familial history of previous melanoma, are major contributing factors. Starting from several epidemiological studies which have examined the role of the p53 codon 72 polymorpysm in different human malignances, including cutaneous cancer, with contradictory results, **Stefanaki *et al*** investigated the germline frequency of p53 codon 72 polymorphism in malignant melanoma, in a Mediterranean population and, examined possible associations with various clinicopathological factors. Starting with 107 blood specimens from Greek patients with sporadic cutaneous melanoma and 145 healthy controls, they identified that the Pro/Pro genotype was associated with an increased risk of cutaneous melanoma, compared with the Arg/Arg genotype. The authors concluded that p53 codon 72 Pro/Pro genotype could be considered as a further risk factor for the development of melanoma in the Greek population, especially in subgroups with darker skin pigmentation, as well as among non-carriers of the MC1R red hair polymorphic variants.

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3. MSH, MCH, other hormones, differentiation

( ) Not available

4. Photobiology

(Dr. N. Smit)

The first paper in the list (Int. J. Cancer) is from the working group on artificial ultraviolet light and skin cancer. They performed a systematic review about the literature on use of sunbeds. The analysis of the data of 19 informative studies revealed a positive association with cutaneous malignant melanoma, especially when first exposures to sunbeds were before the age of 35 years. In this light it seems logical that new strategies are aimed at prevention of sunbed use at younger age. In the paper by Forster et al the authors conclude that in Massachusetts laws specifying a minimum age for the use of sunbeds are ineffective. This discussion continues in the paper by Ariel Whitworth in JNCI. Some support the view that the incidence of melanoma in young adults shows epidemic proportions and sun (UV) exposure should be limited. On the other hand vitamin D deficiency is more and more the topic of studies suggesting an increased risk of other non-skin cancers, such as breast and colon cancer. The vitamin D issue has become important in photobiological research as mentioned in previous ESPCR bulletins and also remains of interest in the most recent literature. In 2 different papers Grant describes the (inverse) correlations between cancer types and UV irradiation. The results provide support for different etiologies of melanoma and NMSC and the role of vitamin D production causing reduced risk of various internal cancers. Balancing the positive effects of vitamin D with the negative effects of too much UV(B)-exposure is also discussed in the paper by Norval et al dealing with the problem of ozone depletion and climate change.
Hocker and Tsao screened the literature on "mutations and melanoma" and selected 203 studies out of 2095 results returned for a PubMed search using these keywords. The paper gives a nice overview of all the different mutations in BRAF, NRAS, CDKN2A, PTAN/MMAC1 and TP53. Especially, CDKN2A and TP53 showed typical UVB-signature changes suggesting a direct participation of UVB in the mutations.
Lin and Fisher indicate in their paper that pigmentation mutants in various species have been highly informative in our understanding of melanocyte biology including the process of photoprotection. In this respect April and Barsh describe interesting mouse models for studying gene expression profiles in the basal epidermis of two classic pigmentation mutants, viable dominant spotting (Kit^{W-v}/Kit^{W-v}) and recessive yellow ($Mc1r^{e}/Mc1r^{e}$). The effects of UVB irradiation on gene expression could thus be analysed respectively, in epidermis without viable melanocytes and in epidermis containing almost exclusively pheomelanin. Completely different sets of UVB responsive genes are described that were either Kit-dependent or MC1R-dependent. Magnoni et al compared gene profiles before and after UVB-irradiation in cultured melanocytes isolated from (unaffected) skin biopsies of healthy control subjects or sporadic melanoma patients. Significant differences in gene expression for the melanocytes from patients with vertical growth phase and radial growth phase melanoma could be observed. Some aspects of the role that melanin might play in photoprotection are described in the paper by Meredith and Sarna. The protective characteristics of melanin are mentioned briefly in the light of the specific physicochemical properties of melanin.

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  Congenital melanocytic nevi frequently harbor NRAS mutations but no BRAF mutations. J.Invest Dermatol. 127:179-182, 2007.

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A meta-analysis of second cancers after a diagnosis of nonmelanoma skin cancer: Additional evidence that solar ultraviolet-B irradiance reduces the risk of internal cancers. J.Steroid Biochem.Mol.Biol. 103:668-674, 2007.

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An ecologic study of cancer mortality rates in Spain with respect to indices of solar UVB irradiance and smoking. Int.J.Cancer. 120:1123-1128, 2007.

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5. Neuromelanins

(Prof. M. d'Ischia)

Two papers that appeared during the last months of 2006 have been selected as the focus of the present commentary.
Current work on the etiopathogenesis of Parkinson's disease (PD) emphasizes the importance of protein misfolding and aggregation as a critical correlate of neuronal degeneration. The presence of misfolded proteins can trigger a cellular stress response in the endoplasmic reticulum (ER) called the Unfolded Protein Response (UPR), which has been demonstrated in cellular models for PD. Hoozemans et al. (2007), based on immunoreactivity data for UPR activation markers, show that UPR is activated in PD but not in controls, and that UPR activation is closely associated with the accumulation and aggregation of ˜synuclein. This result may represent an important step forward in dissecting the molecular bases of PD.
In another paper, Lastres-Becker et al. (2006) provide a critical review of a newly emerging strategy for neuroprotection in PD, based on activation of the cannabinoid system. The article covers aspects concerning possible effects of cannabinoid compounds on some PD symptoms, progression of neuronal injury and inflammation. Although it is too early to predict what is the actual scope of this strategy, there is no doubt that a better understanding of the relationships between the cannabinoid system and PD may considerably increase our knowledge of the molecular basis of melanised neurone degeneration, and may hopefully expand the therapeutic armamentarium for PD.

- Hoozemans J. J. M., van Haastert E. S., Eikelenboom P., de Vos R. A. I., Rozemuller J. M., Scheper W.
  Activation of the unfolded protein response in Parkinson's disease. Biochem Biophys Res Commun 354(3):707-711, 2007.
  Abstract:
  Parkinson's disease (PD) is, at the neuropathol. level, characterized by the accumulation of misfolded proteins. The presence of misfolded proteins can trigger a cellular stress response in the endoplasmic reticulum (ER) called the Unfolded Protein Response (UPR). The UPR has been shown to be involved in cellular models for PD. In this study, we investigated UPR activation in the substantia nigra of control and PD patients. Immunoreactivity for the UPR activation markers phosphorylated pancreatic ER kinase (pPERK) and phosphorylated eukaryotic initiation factor 2 (peIF2) is detected in neuromelanin contg. dopaminergic neurons in the substantia nigra of PD cases but not in control cases. In addn., pPERK immunoreactivity is colocalized with increased -synuclein immunoreactivity in dopaminergic neurons. These data show that the UPR is activated in PD and that UPR activation is closely assocd. with the accumulation and aggregation of -synuclein.

- Hu, Zhang-Zhi; Valencia, Julio C.; Huang, Hongzhan; Chi, An; Shabanowitz, Jeffrey; Hearing, Vincent J., Appella E., Wu C.
  Comparative bioinformatics analyses and profiling of lysosome-related organelle proteomes. Intl J Mass Spectrometry 259(1-3):147-160, 2007.
  Abstract:
  Complete and accurate profiling of cellular organelle proteomes, while challenging, is important for the understanding of detailed cellular processes at the organelle level. Mass spectrometry technologies coupled with bioinformatics anal. provide an effective approach for protein identification and functional interpretation of organelle proteomes. In this study, the authors have compiled human organelle ref. datasets from large-scale proteomic studies and protein databases for seven lysosome-related organelles (LROs), as well as the endoplasmic reticulum and mitochondria, for comparative organelle proteome anal. Heterogeneous sources of human organelle proteins and rodent homologs are mapped to human UniProtKB protein entries based on ID and/or peptide mappings, followed by functional annotation and categorization using the iProXpress proteomic expression anal. system. Cataloging organelle proteomes allows close examn. of both shared and unique proteins among various LROs and reveals their functional relevance. The proteomic comparisons show that LROs are a closely related family of organelles. The shared proteins indicate the dynamic and hybrid nature of LROs, while the unique transmembrane proteins may represent addnl. candidate marker proteins for LROs. This comparative anal., therefore, provides a basis for hypothesis formulation and exptl. validation of organelle proteins and their functional roles.

- Kovacs Gabor G., Gelpi Ellen, Lehotzky Attila, Hoeftberger Romana Erdei Anna, Budka Herbert, Ovadi Judit.
  The brain-specific protein TPPP/p25 in pathological protein deposits of neurodegenerative diseases. Acta Neuropathologica 113(2), 153-161, 2007.
  Abstract:
  Immunohistochem. detection of protein components of pathol. inclusions is widely used for neuropathol. diagnosis of neurodegenerative disorders. However, different antibodies and antigen unmasking methods may account for variability between research studies and thus may affect diagnostic accuracy. Using two different antibodies raised against either a segment (184-200 aa) or the full length of human recombinant brain-specific tubulin polymn. promoting protein TPPP/p25, we immunohistochem. screened neurodegenerative disorders, both with and without pathol. -synuclein structures. We tested three different epitope unmasking methods, we applied laser confocal microscopy to evaluate double immunolabelling, and we compared the amt. of structures exhibiting TPPP/p25 and -synuclein immunoreactivity. We demonstrate that there are a variety of staining patterns depending on the epitope

retrieval method and antibody used. The antibody raised against aa 184-200 segment of TPPP/p25 is better in immunolabelling the majority of -synuclein immunopos. neuronal and glial pathol. profiles detectable in Parkinson's disease, diffuse Lewy-body disease, and multiple system atrophy, in addn. to immunostaining some extracellular huntingtin immunoreactive structures, lipofuscin, and neuromelanin particles. In contrast, the one raised against the full-length human recombinant TPPP/p25 is more suitable to immunodetect normal oligodendrocytes. Exposition of the segment aa 184-200 of TPPP/p25 in the aggregates of pathol. inclusions renders this antibody a reliable marker of all types of -synucleinopathies and suggests a role for TPPP/p25 in the aggregation process of some neurodegenerative conditions.

- Lastres-Becker I., Fernandez-Ruiz J.
An overview of Parkinson's disease and the cannabinoid system and possible benefits of cannabinoid-based treatments. Current Medicinal Chemistry 13(30):3705-3718, 2006.
Abstract:
A review Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder with a heterogeneous clin. picture and a variable rate of progression. PD is characterized by degeneration of the pigmented neuromelanin bearing cells of the pars compacta of the substantia nigra that leads to a severe dopaminergic denervation of the striatum. Current treatments for PD rely on dopamine replacement therapy, most commonly with the dopamine precursor levodopa. Despite the many recent advances in the symptomatic treatment of PD, there is still no realistic prospect for a cure. In recent years, new data support the idea of a relevant role for the cannabinoid system in PD. As cannabinoids have neuroprotective properties, they have been proposed as potentially useful neuroprotective substances in PD, as well as to alleviate some symptoms in specific circumstances (i.e. parkinsonian tremor assocd. with overactivity to the subthalamic nucleus; levodopa-induced dyskinesia). By contrast, CB1 receptor antagonists might be useful to reduce bradykinesia in patients refractory to classic levodopa treatment. The present article will review all data about the relation between PD and the cannabinoid system including: (i) the usefulness of cannabinoid-related compds. to alleviate some PD symptoms; (ii) that cannabinoid-based compds. might provide protection against the progression of neuronal injury characteristic of this disease; (iii) the influence of cannabinoids on local inflammatory events assocd. with the pathogenesis in PD. Collectively, all these evidence support that the management of the cannabinoid system might represent a new approach to the treatment of PD.

- Nagatsu T., Sawada M.
Molecular mechanism of the relation of monoamine oxidase B and its inhibitors to Parkinson's disease: possible implications of glial cells. Journal of Neural Transmission, Supplement 71(Oxidative Stress and Neuroprotection):53-65, 2006.
Abstract:
Monoamine oxidases A and B (MAO A and MAO B) are the major enzymes that catalyze the oxidative deamination of monoamine neurotransmitters such as dopamine (DA), noradrenaline, and serotonin in the central and peripheral nervous systems. MAO B is mainly localized in glial cells. MAO B also oxidizes the xenobiotic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to a parkinsonism-producing neurotoxin, 1-methyl-4-phenyl-pyridinium (MPP+). MAO B may be closely related to the pathogenesis of Parkinson's disease (PD), in which neuromelanin-contg. DA neurons in the substantia nigra projecting to the striatum in the brain selectively degenerate. MAO B degrades the neurotransmitter DA that is deficient in the nigro-striatal region in PD, and forms H2O2 and toxic aldehyde metabolites of DA. H2O2 produces highly toxic reactive oxygen species (ROS) by Fenton reaction that is catalyzed by iron and neuromelanin. MAO B inhibitors such as L-(-)-deprenyl (selegiline) and rasagiline are effective for the treatment of PD. Concerning the mechanism of the clin. efficacy of MAO B inhibitors in PD, the inhibition of DA degrdn. (a symptomatic effect) and also the prevention of the formation of neurotoxic DA metabolites, i.e., ROS and dopamine derived aldehydes have been speculated. As another mechanism of clin. efficacy, MAO B inhibitors such as selegiline are speculated to have neuroprotective effects to prevent progress of PD. The possible mechanism of neuroprotection of MAO B inhibitors may be related not only to MAO B inhibition but also to induction and activation of multiple factors for anti-oxidative stress and anti-apoptosis: i.e., catalase, superoxide dismutase 1 and 2, thioredoxin, Bcl-2, the cellular poly(ADP-ribosyl)ation, and binding to glyceraldehydes-3-phosphate dehydrogenase (GAPDH). Furthermore, it should be noted that selegiline increases prodn. of neurotrophins such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF), possibly from glial cells, to protect neurons from inflammatory process.

- Shibata E, Sasaki M, Tohyama K, Kanbara Y, Otsuka K, Ehara S, Sakai A.
Age-related Changes in Locus Ceruleus on Neuromelanin Magnetic Resonance Imaging at 3 Tesla. Magn Reson Med Sci. 5(4):197-200, 2006.
Purpose: To investigate age-related changes in the locus ceruleus (LC) in healthy subjects using neuromelanin magnetic resonance (MR) imaging at 3 Tesla. Methods: We examined 64 healthy volunteers (aged 23 to 80 years) using neuromelanin-sensitive T(1)-weighted images and measured the contrast of areas of high signal intensity corresponding to the LC. Results: A pair of punctate areas of high signal intensity that represented neuromelanin within the noradrenergic neurons of the LC was easily recognized in all subjects. The contrast ratio of the LC to the adjacent pontine tegmentum increased to the age of 40 to 59 years and gradually and significantly decreased in elderly

subjects. This correlates well with pathologically proven age-related changes in neuromelanin content within the LC. Conclusion: Age-related variance should be considered when determining the existence of abnormalities in the LC.

6. Genetics, molecular and developmental biology

(Dr. F. Beermann)

- April CS, Barsh GS.
  Distinct Pigmentary and Melanocortin 1 Receptor-Dependent Components of Cutaneous Defense against Ultraviolet Radiation. PLoS Genet 3: e9, 2007
  Summary: Mice without viable melanocytes ($Kit^{W\text{-}v}/Kit^{W\text{-}v}$) or animals lacking a functional Mc1r ($Mc1r^{e}/Mc1r^{e}$) were exposed to sunburn-level doses of UVB radiation, and the patterns of large-scale gene expression in the basal epidermis were compared to each other and to nonmutant animals. The analysis revealed discrete Kit- and Mc1r-dependent UVB transcriptional responses in the basal epidermis.

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  Isolation of a mesenchymal cell population from murine dermis that contains progenitors of multiple cell lineages. Faseb J, 2007 [Epub ahead of print].

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  Central Role of p53 in the Suntan Response and Pathologic Hyperpigmentation. Cell 128: 853-864, 2007.
  Abstract: UV-induced pigmentation (suntanning) requires induction of alpha-melanocyte-stimulating hormone (alpha-MSH) secretion by keratinocytes. alpha-MSH and other bioactive peptides are cleavage products of pro-opiomelanocortin (POMC). Here we provide biochemical and genetic evidence demonstrating that UV induction of POMC/MSH in skin is directly controlled by p53. Whereas p53 potently stimulates the POMC promoter in response to UV, the absence of p53, as in knockout mice, is associated with absence of the UV-tanning response. The same pathway produces beta-endorphin, another POMC derivative, which potentially contributes to sun-seeking behaviors. Furthermore, several instances of UV-independent pathologic pigmentation are shown to involve p53 "mimicking" the tanning response. p53 thus functions as a sensor/effector for UV pigmentation, which is a nearly constant environmental exposure. Moreover, this pathway is activated in numerous conditions of pathologic pigmentation and thus mimics the tanning response.

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A three-single-nucleotide polymorphism haplotype in intron 1 of OCA2 explains most human eye-color variation. Am J Hum Genet 80: 241-252, 2007.

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Schistosome egg production is dependent upon the activities of two developmentally regulated tyrosinases. Faseb J 21: 823-835, 2007.

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Pigment pattern in jaguar/obelix zebrafish is caused by a Kir7.1 mutation: implications for the regulation of melanosome movement. PLoS Genet 2: e197, 2006.
Extract: The inwardly rectifying potassium channel 7.1 (Kir7.1) gene is responsible for pigment cell distribution among jaguar/obelix mutant fish. Further observations indicate that melanophores of jaguar/obelix mutant fish have a defect in

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Shortened abstract: Embryos mutant for choker manifest a unique pigment pattern phenotype that combines a loss of lateral stripe melanophores with an ectopic melanophore; collar' at the head-trunk border. We uncover an aberrant pattern

of expression of the gene encoding the chemokine Sdf1a in choker mutant homozygotes that correlates with each aspect of the melanophore pattern defect. Using morpholino knock-down and ectopic expression experiments, we provide evidence to suggest that Sdf1a drives melanophore invasion in the choker mutant collar and normally plays an essential role in patterning the lateral stripe. We thus identify Sdf1 as a key molecule in pigment pattern formation, adding to the growing inventory of its roles in embryonic development.

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Differential oncogenic potential of activated RAS isoforms in melanocytes. Oncogene, 2007.

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Neural crest-derived cells with stem cell features can be traced back to multiple lineages in the adult skin. J Cell Biol 175: 1005-1015, 2006.
Abstract: Given their accessibility, multipotent skin-derived cells might be useful for future cell replacement therapies. We describe the isolation of multipotent stem cell-like cells from the adult trunk skin of mice and humans that express the neural crest stem cell markers p75 and Sox10 and display extensive self-renewal capacity in sphere cultures. To determine the origin of these cells, we genetically mapped the fate of neural crest cells in face and trunk skin of mouse. In whisker follicles of the face, many mesenchymal structures are neural crest derived and appear to contain cells with sphere-forming potential. In the trunk skin, however, sphere-forming neural crest-derived cells are restricted to the glial and melanocyte lineages. Thus, self-renewing cells in the adult skin can be obtained from several neural crest derivatives, and these are of distinct nature in face and trunk skin. These findings are relevant for the design of therapeutic strategies because the potential of stem and progenitor cells in vivo likely depends on their nature and origin.

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Rescue of the albino phenotype by introducing a functional tyrosinase minigene into Kunming albino mice. World J Gastroenterol 13: 244-249, 2007.

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Mcl-1, Bcl-XL and Stat3 expression are associated with progression of melanoma whereas Bcl-2, AP-2 and MITF levels decrease during progression of melanoma. Mod Pathol 20: 416-426, 2007.

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The Fugu tyrp1 promoter directs specific GFP expression in zebrafish: tools to study the RPE and the neural crest-derived melanophores. Pigment Cell Res 19: 615-627, 2006.

7. Tyrosinase, TRPs, other enzymes

(Prof. J.C. Garcia-Borron) Not available

8. Melanosomes

(Prof. J. Borovansky)

In melanoma therapy melanosomes have been exploited so far as producers of leaky cytotoxic melanin precursors or as catchers of radioactively-labelled compounds. Recently, melanosomes have been shown to contribute to drug resistance by sequestering cis-platin and hence by decreasing the possibility of chemotherapeutics to reach the cell nucleus (*Chen et al*). Series of exciting papers from the lab of prof Simon on various melanosomal aspects based on modern sophisticated techniques has continued this time with the determination of association constant of calcium ions to Sepia melanin granules (*Bush & Simon*) and with a finding that lipid moiety of ocular melanosomes depends on the embryologic origin of the cells from which they were isolated (*Ward & Simon*). *Wasmeier et al* identified a key role for the Rab38/Rab32 subfamily in the biogenesis of the melanosome. Proteomic analysis of isolated melanoliposcin granules revealed that these granules have a different chemical composition and origin in comparison to lipofuscin (*Warburton et al*). *Peters et al* announced differences in the stability of RPE melanosomes to UV irradiation in relation to their shape. Melanosome transport in melanophores was studied by *Kural et al*. Epitheloid angiomyolipoma can be added to the group of tumours containing some cells positive for melanosomal immunomarkers and with melanosome-like structures (*Meng YH et al*). Depigmenting activity of a fullerene derivative was tested by *Xiao et al*. Three reviews (*Baumann et al, Costin & Hearing, Lin & Fisher*,) make the list of recent literature devoted to melanosomes complete.

- Baumann L, Rodriguez D, Taylor SC, Wu J.
  Natural considerations for skin of color. Cutis 78(suppl.6): 2 – 20, 2006.
  Comments: A broad review devoted to various differences between the Caucasoid skin and the skin of colour. Skin structure, clinical controversies as pertain to the the skin of colour, melanin physiology, sun protection, pigmentary disorders , skin lightening, whitening and brightening have all been discussed. Specifically, in regard to melanosomes, racial differences in the melanosome size and distribution and the melanosome transfer inhibition by means of fresh soy extracts or niacinamide have been dealt with.. The ability of melanosomes in the black skin to produce larger quantity of pigment has been suggested as a factor contributing a higher prevalence of pigmentary disorders in patients of colour.

- Bush WD, Simon JD.
  Quantification of Ca^{2+} binding to melanin supports the hypothesis that melanosomes serve as a functional role in regulating calcium homeostasis.
  Pigment Cell Res 20(2): 134 – 139, 2007.
  Comments: By means of isothermal titration calorimetry the association constant for Ca^{2+} binding to Sepia melanin granules was determined to be 3.3×10^3/mol, i.e. value comparable with other intracellular calcium binding proteins, which further suggests that melanosomes serve as intracellular mediators of calcium homeostasis in melanocytes. The pK_a of carboxyl group coordinated to Ca^{2+} was calculated to be 3.1. The introduction represents a review dealing with what has been known about calcium ions in relation to pigment cells and structures.

- Chen KG, Valencia JC, Lai B, Zhang G, Paterson JK, Rouzaud F, Berens W, Wincovitch SM, Garfield SH, Leapman RD, Hearing VJ, Gottesman MM.
  Melanosomal sequestration of cytotoxic drugs contributes to the intractibility of malignant melanomas. PNAS 103(26): 9903 – 9907, 2006.
  Comments: The melanosomal sequestration of cis-platin was demonstrated by means of both the immunofluorescent confocal microscopy and the X-ray microprobe technique. The accumulated cis-platin modulated melanogenesis: tyrosinase activity rose and there was an increase both in cellular pigmentation and in extracellular export of cis-platin-containing melanosomes. This might contribute to the refractory properties of the melanoma cells to chemotherapy.

- Choi YG, Bae EJ, Kim DS, Park SH, Kwon SB, Na JI, Park KC.
  Differential regulation of melanosomal proteins after hinokitiol treatment. J Dermatological Sci 43(3): 181 – 188, 2006.

- Costin GE, Hearing VJ.
  Human skin pigmentation: melanocytes modulate skin color in response to stress. FASEB J 21(4): 976 – 994, 2007.
  Comments: A review updating our knowledge on skin structure, melanocytes, melanosomes, signalling pathways within the epidermal melanin unit; the main focus of the review is to describe importnant external and internal factors that increase pigmentation and the mechanisms by which they do so.

- Kural C, Serpinskaya AS, Chou YH, Goldman RD, Gelfand VI, Selvin PR.
  Tracking melanosomes inside a cell to study molecular motors and their interaction. PNAS 104(13): 5378 – 5382, 2007.

Comments: The bright-field imaging with a one-nanometer accuracy (bFIONA) was employed to trace the transport of melanosomes in cultured Xenopus melanophores. 8.4nm steps for dynein, 8.0nm steps for heterotrimeric kinesin-2 and 35.1nm steps for myosin were found. Myosin V steps occurred faster in the absence of intermediate filaments, thus indicating that the IF network physically hinders the organelle transport.

- Lin JY, Fisher DE.
Melanocyte biology and skin pigmentation. Nature 445(7130): 843 – 850, 2007.
Comments: This review summarizes how pigmentation is regulated at the molecular level, and how tanning response provides protection against damage and skin cancer. It also describes melanocyte – melanoblast stem cell relations. Four paragraphs are devoted to melanosomes. However, a few inaccuracies have been noted in this part of the text.

- Meng YH, Pei F, Lu P, Yu JY, Zheng J.
Epitheloid angiomyolipoma of kidney: Clinicopathologic study of two cases and review of literature. */In Chinese/* Zhongua Bing Li Xue Za Zhi 36(1): 19 – 23, 2007.
Comments: The epitheloid angiomyolipoma cells were strongly positive for HMB-45 as well as for neuron-specific enolase and focally positive for S100 and melan-pan. An ultrastructural examination revealed the presence of melanosome-like dense granules in the tumour cells. For these reasons some authors (e.g. *Mentzel T et al/Histopathology 46(5): 498-504, 2005*) speak of myomelanocytic tumour cells.

- Peters S, Lamah T, Kokkinou D, Bartz-Schmidt KU, Schraermeyer U.
Melanin protects choroidal blood vessels against light toxicity. Z. Naturforsch. 61c(5-6): 427 – 433, 2006.
Comments: Photoxic damages in retinal and choroid tissues of pigmented (Long Evans) and albino (Wistar) rats were compared in order to determine the role melanin pigmentation. Pigmented rats were characterized by significantly more surviving RPE and photoreceptor cells and by a far better perfused choriocapillaris than albino rats. As for melanosomes, irradiation of pigmented rats led to a decrease of RPE melanosomes to one half. Untreated RPE contained spindle shaped and spherical melanosomes. After irradiation, the proportion of spindle-shaped and spherical melanosomes switched significantly to a higher proportion of spherical granules due to a selective loss of spindle-shaped granules. (I do not understand why the terms melanin, melanin granule and melanosome are used *promiscue* in the text as their exact meaning is not identical.)

- Warburton S, Davis WE, Southwick K, Xin H, Woolley AT, Burton GF, Thulin CD.
Proteomic and photoxic characterization of melanolipofuscin: Correlation to disease and model for its origin. Molecular Vision 13: 318 – 329, 2007.
Comments: This is the first detailed biochemical study (including a proteomic approach) of melanolipofuscin which suggests that the melanolipofuscin and lipofuscin granules differ not only in several components but also in their origin. In contrast to lipofuscin, melanolipofuscin does not contain photoreceptor specific proteins (rhodopsin, peripherin) but it does contain RPE-specific proteins (RGR, rpe 65) and melanosome-specific proteins (23 proteins commonly present in RPE melanosomes were identified). This shows that the melanolipofuscin granules originate as a result of melanosomal autophagocytosis of the RPE cells. The melanolipofuscin granules were characterized also by means of TEM, SEM and the atomic force microscopy.

- Ward WC, Simon JD.
The differing embryonic origins oíf retinal and uveal (iris/ciliary body and choroid) melanosomes as mirrored by their phospholipid composition. Pigment Cell Res 20(1): 61-66, 2007.
Comments: The phospholipids of isolated ocular melanosomes were analyzed by means of liquid chromatography/mass spectrometry techniques. Significant differences were found between the uveal and retinal melanosomes: The uveal melanosomes (i.e. organelles from the cells of neural crest origin) contained mostly sphingomyelin and other ceramide derived lipids; the retinal pigment epithelium melanosomes (derived from forebrain) contained mostly phosphatidylethanolamine with polyunsaturated fatty acids in the *sn*-2 position. The authors concluded that lipids did not play a substantial role in keeping the organelle assembly together because the melanosomes remained intact after lipid extraction. This is in accord with our opinion that it is the melanin framework which keeps up the melanosome architecture – cf. *Borovanský et al /Cell Biol Int Reports 1: 549-555, 1977*).

- Wasmeier C, Romao M, Plowright L, Bennett DC, Raposo G, Seabra MC.
Rab38 and Rab32 control post-Golgi trafficking of melanogenic enzymes. J Cell Biol 175(2): 271 – 281, 2006.
Comments: Analysis of the mouse coat colour mutant „chocolate“ /cht/ revealed that Rab38 was inactive and that nearly normal pigmentation in cht melanocytes resulted from functional compensation by the closely related Rab32. In Rab38/Rab32 deficient cells tyrosinase and Tyrp-1 trafficking to the melanosome was blocked and only Stage II melanosomes could be seen. Hence, the key role of Rab38/Rab32 in the biogenesis of melanosomes was identified.

- Xiao L, Matsubayashi K, Miwa N.

Inhibitory effect of the water-soluble polymer-wrapped derivative of fullerene on UVA-induced melanogenesis via downregulation of tyrosinase expression in human melanocytes and skin tissues. Arch Dermatol 2007, E-pub ahead of print.

Comments: The water soluble polyvinylpyrrolidone-wrapped fullerene derivative, called „Radical Sponge“ was tested for its expected antioxidant activity and for a depigmenting action. The Radical Sponge exerted excellent inhibitory action on the UVA-induced melanogenesis in normal human epidermal melanocytes and in human melanoma HMVII cell cultures.The TEM study proved that the UVA-enhanced melanosome production and melanin migration were reduced by the Radical Sponge application.

9. Melanoma experimental, Cell culture

(Dr R. Morandini)

The 3D cell culture model is a potent method to study therapeutic potential of new drugs and mimic what happens in vivo but in a controlled environment. In a collagen-constructed fibroblast matrix, Roscovitine (a cyclin-dependent kinase inhibitor) regulates the growth and the differentiation of metastatic melanoma cell line and is able to inhibit invasion. The difference found between 2D and 3D cell growth as shown in three-dimensional artchitectures promotes resistance to drugs, cytokines or irradiation (Mohapatra et al.).
Expression of some melanoma differentiation antigens are downregulated in 3D cultures as compared with monolayers. It seems that the mechanism is related to a decrease in MITF gene expression and to a high cell density. HLA class I molecules might also be downregulated. These features have been detected frequently in clinical melanoma (Feder-Mengus et al.).
A 3D model may also be used to investigate and quantify the possibility for a cell line to have metastatic abilities. Ghajan et al. have developed a model for the discovery of new chemotherapeutic drugs.

- April CS, Barsh GS.
  Distinct Pigmentary and Melanocortin 1 Receptor-Dependent Components of Cutaneous Defense against Ultraviolet Radiation. PLoS Genet. 3(1):e9 [Epub ahead of print], 2007.

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  The density and distribution of melanocytes adjacent to melanoma and nonmelanoma skin cancers. Dermatol Surg. 33(2):199-207, 2007.

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  Effects of the COOH-terminal tripeptide alpha-MSH(11-13) on corneal epithelial wound healing: role of nitric oxide. Exp Eye Res. 83(6):1366-72, 2006. Epub 2006 Sep 11.

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  Long-lived antitumor CD8+ lymphocytes for adoptive therapy generated using an artificial antigen-presenting cell. Clin Cancer Res. 13(6):1857-67, 2007.

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  New insight into BRAF mutations in cancer. Curr Opin Genet Dev. 17(1):31-9, 2007. Review.

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  Platelet-activating factor (PAF) is the effector of IFN gamma-stimulated invasiveness and motility in a B16 melanoma line. Prostaglandins Other Lipid Mediat. 81(3-4):171-7, 2006. Epub 2006 Oct 18.

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A novel three-dimensional model to quantify metastatic melanoma invasion. Mol Cancer Ther. 6(2):552-61, 2007. Epub 2007 Jan 31.

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Melanocytes: the new Black. Int J Biochem Cell Biol. 39(2):275-9, 2007. Epub 2006 Oct 7.

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Melanoma biology and new targeted therapy. Nature. 445(7130):851-7, 2007. Review.

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Endothelin-1 combined with extracellular matrix proteins promotes the adhesion and chemotaxis of amelanotic melanocytes from human hair follicles in vitro. Cell Biol Int. 30(12):999-1006, 2006. Epub 2006 Aug 14.

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ANNOUNCEMENTS & RELATED ACTIVITIES

Calendar of events

2007 68th Annual Meeting for the Society for Investigative Dermatology

May 9-12, Los Angeles, California

Contact: Carolyn Slade
Meetings Coordinator
Tel: 216-589-0917 Fax: 216-579-9333
E-mail: slade@sidnet.org

2007 4th Research Meeting on Melanoma

May 10-11, Milan, Italy

Contact: CQ Travel srl
Via Pagliano 3
I- 20149 Milano
Fax: 39-02-43911650
E-mail: infoeventi@ieo.it

2007 16th Congress of the European Academy of Dermatology and Venereology

May 16-20, Vienna, Austria

Contact: Prof. Erwin Tschachler
Congress President
16th EADV Congress
E-mail: info@eadvvienna2007.com
Web site : www.eadvvienna2007.com ; www.eadv.org/

2007 1st Bosnia and Herzegovina International Dermato-Venereology Conference

May 23-26, Sarajevo, Bosnia and Herzegovina

Contact: Dr. Alendar Faruk, Dr. Hana Helppikangas
Clinical Center University of Sarajevo,
Department of Dermatology
Bolnicka 25
71000 Sarajevo - Bosnia and Herzegovina
Tel: +387 33 297 626
Fax: +387 33 213 490
Web site: www.udvbih.ba

2007 11th World Congress on Cancers of the skin

June 8-11, Amsterdam, The Netherlands

Contact: Congress Secretariat 11th World Congress on Cancers of the Skin 2007
International Conference Services BV
P.O. Box 83005

NL - 1080 AA Amsterdam
Tel: +31 (0)20 679 32 18
Fax: +31 (0)20 675 82 36
Email: wccs2007@nl.ics-online.com

2007 Pigment Cell Development Meeting

June 14-15, Reykjavik, Iceland

Contact: University of Iceland
Web site: http://www.genome.gov/20519498

2007 12th Congress of the European Society for Dermatology and Psychiatry

June 14-17, Wroclaw, Poland

Contact: Congress Care
P.O. Box 440
5201 AK 's-Hertogenbosch
The Netherlands
Tel: +31-73-690 1415
Fax: +31-73-690 1417
Email: info@congresscare.com
Web site: www.esdap2007.org

2007 Dermatopathology and Beyond It

June 29 - July 1, Eisenach, Germany

Contact: Dr. Mirjana Ziemer
Tel.: 0049 -(0)3641 937 441
e-mail: mirjana.ziemer@derma.uni-jena.de
Web site: www.derma.uni-jena.de/00englisch/04tagung/dermapatho.pdf

2007 2nd Conference of the Asian Society for Pigment Cell Research (ASPCR)

Incorporating :

20th Annual Scientific Meeting of the Dermatological Society of Singapore

July 6-8, Singapore

Contact: Conference Secretariat, Mrs Alice Chew
National Skin Centre
1 Mandalay Road
Singapore 308205
Tel: (65) 6350 8405; Fax: (65) 6253 3225
E-mail: training@nsc.gov.sg
Web site: http://www.aspcr.org/ASPCR2007

2007 16th Annual Growth Factor and Signal Transduction Symposium. Senescence, Aging and Cancer

July 26–29, Ames, Iowa, USA

Contact: Symposium Office,
3208 Molecular Biology Building,
Iowa State University, Ames, IA 50011-3260, USA
Phone: +1 515 294 7978
Fax: +1 515 294 2244
E-mail: gfst@iastate.edu
Web site: http://www.bb.iastate.edu/~gfst/homepg.html

2007 First World Meeting of Interdisciplinary Melanoma Centers

September 5–8, Barcelona, Spain

Contact: Apartado Correos 14.040
08080 Barcelona, Spain
Tel. +34 690 846097
Fax +34 932 057230
Email: sbc@sbc-congresos.com
Web site: www.melanomacentersmeeting.com

2007 7th Congress of the BADV

September 6-8, Riga, Latvia

Contact: Professor Andris Rubins
Tel: +371 2948 1725
Fax: +371 736 1615
E-mail: info@badv.lv
Web site: www.badv.lv

2007 14th Annual meeting of the PanAmerican Society for Pigment Cell Research

September 13-16, Chicago, IL, USA

Contact: Caroline LePoole
E-mail: ilepool@lumc.edu
Web site: paspcr.med.umn.edu/ ; www.paspcr2007.org

2007 21st World Congress of Dermatology

October 1-5, Buenos Aires, Argentina

Contact: E-mail: info@dermato2007.org
Web site: www.dermato2007.org

2007 The 23rd IUSTI-Europe Conference on Sexually Transmitted Infections and HIV/AIDS

October 11-14, Cavtat/Dubrovnik, Croatia

Contact: Spektar Putovanja
Tkalciceva 15
HR-10000 Zagreb
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Tel: 385 1 4862 600, 4862 607
Fax: 385 1 4862 622
Email: kongres-derma@mef.hr
Web site: www.iustieurope2007.org

2007 XIVth Meeting of the European Society for Pigment Cell Research

October 14-17, Bari, Italy "Pigment Cells and their environment"

Contact: Prof Rosa Cicero
E-mail : r.cicero@biolgene.uniba.it
E-mail : espcr@gruppotriumph.it
Web site: www.espcr.org/espcr/meetings/

2007 The IV International Melanoma Congress

November 1-4, NY City, USA

Contact: Justina Treventi
E-mail: justina@sitesolutionsworldwide.com

Web site: www.melanomacongress07.net

2007 XXVII Symposium of the ISDP

November 9-11, Malaga, Spain

Contact: E-mail: intsocdermpath@aol.com
Web site: www.intsocdermpath.org

2007 26th PAD & 5th SARAD Conference of Dermatology

November 15-18, Lahore, Pakistan

Contact: Professor Atif Kazmi
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Mayo Hospital, Lahore, Palistan
Tel: +92 42 735 4094
Fax + 92 42 735 3043
E-mail: atifkazmi80@yahoo.com
Web site: www.padsarad2007.com

2007 20th Annual Meeting of the Japanese Society for Pigment Cell Research (JSPCR)

November 25-26, Matsumoto City, Japan

Contact: Prof. Toshiaki Saita, Shinsyu University
Web site: wwwsoc.nii.ac.jp/jspcr/

2007 21th Annual Meeting of the Japanese Society for Pigment Cell Research (JSPCR)

December 8-9, Toyoake City, Japan

Contact: Prof. Kazumasa Wakamatsu
E-mail: kwaka@fujita-hu.ac.jp
Web site: wwwsoc.nii.ac.jp/jspcr/

2008 66th Annual Meeting AAD

February 1-5, San Antonio (TX), USA

2008 20th International Pigment Cell Conference (IPCC)

conjoined with

2008 Vth International Melanoma Research Congress

May 7–12 Sapporo, Japan

Contact: Secretariate Office
Toshiharu YAMASHITA (Sapporo Medical University, Japan)
Minami 1-jo, Nishi 16-chome Chuo-ku, Sapporo, Japan 060-8543
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Web site: www.e-convention.org/ipcc-imrc2008

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

May 14-17 , Kyoto, Japan

Contact: E-mail: office@esdr.org
Web site: www.esdr.ch

2008 9th Congress of the European Society for Pediatric Dermatology

May 15-17, Athens, Greece

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

2008 5th EADV Spring Symposium

May 22-25 , Istanbul, Turkey

Contact: Professor Mehmet Ali Gürer
Ayazmaderesi Cad. Karadut Sok. No:7
34394 Dikilitas - Istanbul, Turkey
Tel: +90 212 258 60 20 pbx
Fax: +90 212 258 60 78
E-mail: info@eadvistanbul2008.com or president@eadvistanbul2008.com
Web site: www.eadv.org/istanbul2008

2008 17th Annual Congress of the EADV

September 17-21, Paris, France

Contact: EADV PARIS 2008 CONGRESS OFFICE :
EADV 2008 MCI - 24, rue Chauchat
FR - 75009 Paris - France
Tel. : + 33 (0)1 53 85 82 70
Fax.: + 33 (0)1 53 85 82 83
E-mail: www.eadvparis2008.com

2009 6th EADV Spring Symposium

April 23 – 26, Bucharest, Romania

2009 Annual Meeting for the Society for Investigative Dermatology

May 6-9, Montreal, Quebec, Canada

Contact: Web site: www.sidnet.org

2009 39th Annual ESDR Meeting

September 9-12, Budapest, Hungary

2009 18th EADV Congress

October 7-11, Berlin, Germany

2010 40th Annual ESDR Meeting

September 8-11, Helsinski, Finland

NEW MEMBERS

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

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IN MEMORIAM

Aaron B. Lerner, M.D., Ph.D.

By Richard L. Edelson
Professor and Chair, Department of Dermatology
Director, Yale Cancer Center

Aaron B. Lerner, M.D., Ph.D., guided dermatology at Yale from its inception in 1956 as a small new section within the Department of Internal Medicine under Paul Beeson to its later status as a free-standing department in 1971. He is largely responsible for the department's broad recognition as one of the world's foremost intellectual centers of cutaneous biology and medicine. Dr. Lerner was the first dermatologist elected a member of the National Academy of Sciences and was widely considered to be the leading fundamental scientist in the specialty during the early stages of the modern era of biomedical research. In his 30 years as chair at Yale, he attracted a highly talented young faculty, which he weaved into a tightly knit group of outstanding clinical scholars and investigators.

A native of Minneapolis, he received his undergraduate, medical and doctoral degrees from the University of Minnesota. Before coming to Yale, he was a faculty member at the universities of Michigan and Oregon. Dr. Lerner's scientific accomplishments are legion. He is well known as the discoverer, in 1958, of melatonin, a hormone secreted by the pineal gland, and of melanocyte stimulating hormone-work (MSH) he completed with colleagues at Yale and elsewhere. Previously he and a fellow graduate student, G. Robert Greenberg, isolated the first monoclonal antibody, cryoglobulin, a protein that precipitates in the blood and tissues at low temperature. Dr. Lerner also led the group that demonstrated the central role of tyrosinase in melanin synthesis, and he performed the critical experiments demonstrating that 8-methoxy-psoralen (8-MOP), a DNA-crosslinking agent which can essentially be turned on by long wave ultraviolet energy, can be safely administered to humans, paving the way for its wide use in the treatment of psoriasis, vitiligo and cutaneous lymphoma. He was the preeminent clinical expert in melanocytic diseases, ranging from depigmenting to hyperpigmenting to malignant diseases, all stemming from aberrant melanocyte behavior. As such, he was a high impact pioneer "translational scientist," tightly coupling scientific insights with clinical advances, literally decades before the term was introduced. Among his most treasured honors, was his acknowledgement as the first recipient of the Dermatology Foundation's Discovery Award for his extraordinary seminal scientific contributions.

Aaron took special pride in the abundant number of Yale medical students who now prominently populate the field throughout the country and the world. Two of them are his sons, Ethan and Michael, as well as several of our own faculty. Dr. Lerner's scientific progeny, both at Yale and beyond, have shaped the field of melanocyte biology and continue to play prominent roles in that field.

The dermatology community will sorely miss this iconic figure and mentor to many. More than anyone else of his era, he is responsible for the intellectual roots of the specialty and took enormous pride in how the discipline has blossomed. I join my Yale colleagues in both the sense of awe of his legacy and the extreme personal loss. His many, many Yale friends, colleagues and disciples will miss Aaron deeply, but will hold his memory and example tightly to their hearts and aspirations.

Transmitted by:
Dr. Mats J. Olsson, Dept of Medical Sciences, Dermatology, University of Uppsala, SWEDEN