Issue n° 31 - August 1998

ESPCR BULLETIN

PUBLISHED BY THE EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH

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EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH BULLETIN

N° 31 - August 1998

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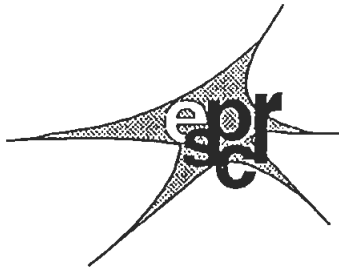

LETTER TO THE EDITOR
DISCUSSION, REVIEW, SHORT COMMUNICATION, ...

MEETING REPORT

Iris Pigment Epithelium (IPE) Transplantation
Fort Lauderdale, FL. 12 May 1998
by Dr Dan-Ning Hu

The symposium " IPE Transplantation: Theoretical and Practical Considerations" was held in the Fort Lauderdale Convention Center, (Florida, USA) on May 12, 1998 during the 1998 Annual Meeting of The Association for Research in Vision and Ophthalmology. This meeting was organized by the Ocular/Extracutaneous Pigmentation Expert Group of the International Federation of Pigment Cell Societies. This symposium was composed of 2 sessions, which included 7 presentations. More than 150 ophthalmologists and basic scientists from all over the world joined this meeting. Dr. Uri Shabto of The New York Eye & Ear Infirmary (USA) gave the introduction, "Why IPE transplantation?". He mentioned that subretinal neovascular membranes associated with age-related macular degeneration are a major cause of legal blindness. Surgical excision of these membranes always leaves a retinal pigment epithelium (RPE) defect, which may lead to further damage to the neural retina and the visual function. RPE transplantation usually fails because of rejection of the RPE allograft. It is easy to obtain autologous IPE from iridectomy specimens. Therefore, it is worthy to study subretinal IPE transplantation as a substitute for RPE in various retinal degeneration diseases related to RPE defects. The first session, "Comparison of physiology and cell biology of IPE and RPE" was chaired by Dr. Dean Bok of University of California Los Angeles (USA). Dr. Ulrich Schraermeyer of the University of Cologne (Germany) presented on "Phagocytosis of photoreceptor outer segments by IPE". They found that the IPE possess phagocytic capacity in vivo and in vitro, which is one of the important function of the RPE. Dr. Dan-Ning Hu of The New York Eye & Ear Infirmary (USA), presented "Comparison of IPE and RPE in vitro". He showed that adult human IPE and RPE contain melanin that is similar in amount and nature. Both do not demonstrate any melanogenesis in vitro. Both cells reduced exogenous NO in the culture medium, and each responded similarly to various growth factors and cytokines and produced similar growth factors and neurotrophic factors. Drs. Dean Bok of UCLA and Ron P. Gallemore of Duke University (USA) presented "Retinoid metabolism of RPE" and "Water and ion transport by RPE", respectively. They discussed these two important functions of RPE, which have not yet been studied thoroughly on the IPE.
The second session "Animal models and clinical experience" was chaired by Dr. Jason S. Slakter of Columbia University (USA). Dr. Kouros A. Rezai of Chicago University (USA) presented "IPE transplantation". He reported the studies on IPE transplantation in vitro and in vivo and documented that IPE have phagocytic activity and can form a blood-retinal barrier. Dr. Schraermeyer presented "IPE transplantation in rabbits and RCS rats". He reported that transplanted IPE could survive in subretinal space in both rats and rabbits. They took up photoreceptor outer segments and had a beneficial influence on photoreceptors of RCS rats. Dr. Amparo Navea of the University of LA FE (Spain) presented "Autologous transplantation of IPE into the subretinal space in humans". She reported 6 cases of IPE transplantation in age-related macular degeneration patients. IPE transplantation seems to be well tolerated. Three cases showed improvement of vision.

Based on this meeting, it is clear that much work has been done in the study on IPE transplantation, both in vitro and in experimental animals; preliminary clinical experiences have obtained encouraging results. However, many problems still exist and require further investigation in this exciting, nascent field.

1. Melanins and other pigments chemistry

(Prof. M. Peter)

The marine melanogenic bacterium MMB-1 contains a polyphenol oxidase (PPO) showing cresolase, catechol oxidase and laccase activities which catalyzes the oxidation of a very wide range of substrates (Sanchez-Amat and Solano). This range includes monophenols such as L-tyrosine, o-diphenols such as L-dopa, p-diphenols such as hydroquinone, o- aminophenols such as 3-hydroxyanthranilic acid, activated monophenols such as 2,6-dimethoxyphenol and syringaldazine, and chromophores such as ABTS. Such PPO could be a very useful model to study the structural requirements, catalytic mechanisms and involvement of the copper sites existing in non- blue and blue copper-oxidases.
Inhibition of mushroom tyrosinase 4-substituted resorcinols was studied (Jimenez and Garcia-Carmona) The inhibition is characterized by a long transient phase with a progressive decrease in initial velocity followed by a constant steady-state rate, both decreased with increasing concentrations of inhibitor. Kinetic data suggest a rapid formation of an enzyme-inhibitor complex that subsequently undergoes a relatively slow reversible reaction. Thiourea was mentioned repeatedly as a melanoma seeker. The mechanism of selective incorporation of thiourea into melanotic melanoma was now investigated in vitro (Palumbo et al.). It was found that thiourea is incorporated during the early stages of melanogenesis by formation of a 1:1 dopa-thiourea adduct with concomitant inhibition of dopachrome formation. A less remarkable effect of thiourea was observed on the oxidative polymerization DHI and DHICA. These results provide a chemical basis for the interpretation of the selective accumulation of thiourea in those melanoma areas with high rates of melanin synthesis seen in autoradiographic experiments.

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2. Biology of pigment cells and pigmentary disorders

(Dr M. Picardo)

Coleman and Lugo have examined the effects of constitutive basic fibroblast growth factor (bFGF) expression on the in vitro growth requirements of normal human melanocytes. bFGF was overexpressed in normal human epidermal melanocytes through genomic insertion of a human bFGF cDNA in a retroviral vector. The bFGF produced by these cells was mitogenic for 3T3 fibroblasts and therefore possessed functional activity; however, melanocytes producing bFGF had the same appearance and growth patterns as those infected with control virus or uninfected melanocytes These results indicate that expression of bFGF alone is not enough to cause aberrant growth of normal human melanocytes. Hedley et al. identified the media conditions in which to obtain a reproducible melanogenic response to alpha MSH in normal human adult melanocytes. Under the majority of media conditions that supported melanocyte survival and proliferation, cells did not respond to alpha MSH with any consistent increase in dopa oxidase activity or melanin content. In only one medium condition, where basic fibroblast growth factor (bFGF) was the sole mitogen present, alpha MSH induced both an increase in dopa oxidase activity and in melanin content. In an other work, the same authors illustrate that α-MSH was found significantly to reduce TNF-α stimulated upregulation of ICAM-1 in normal adult melanocytes. Preliminary data in three human melanoma cell lines also showed α-MSH and forskolin to be effective in reducing TNF-α stimulated ICAM-1 expression over 24 h. The extent of the inhibition varied from cell line to cell line and was greatest in those cells with the highest number of α-MSH receptors. These data suggest that α-MSH has the ability to oppose the action of the pro-inflammatory cytokine TNF-α on melanocytes and melanoma cells. Morandini et al. have conducted a study in order to evaluate the possible effect of MSH on ICAM-1 expression in human cultured malignant and normal melanocytes. The authors conclude that theirs data strongly suggest alpha-MSH as a potent inhibitor of ICAM-1 expression in malignant melanocytes acting through MSH receptor and subsequent cAMP increase. Imokawa and co-worker have investigated the effects of human fibroblast-derived factors on the proliferation of human melanocytes and, measuring the levels of these factors after cytokine application, they suggest that stem cell factor (SCF) and hepatocyte growth factor (HGF) derived

from human fibroblasts may play a part in regulating cutaneous pigmentation during inflammation and aging. Shoji et al. have studied the expression, in situ and in vitro, of protein kinase C alpha in human melanocytes. Northern blot analysis with a specific cDNA probe for PKC-alpha showed strong PKC-alpha mRNA in cultured melanocytes, whereas PKC-alpha mRNA in cultured non-stratifying keratinocytes was expressed at low levels. The marked difference in melanocytes and keratincytes expression of PKC-alpha provides further evidence for cell type specificity in the balance of PKC-alpha expression and may implicate differential PKC isoform signaling pathways in neuro-ectodermally derived cells. Boni and co-worker, using the microdissection technique, ware able to determine the loss of heterozygosity in primary cutaneous melanomas and to relate chromosomal alterations with cell morphology and proliferation of the tumor. Neither melanization of tumor cells nor the presence of inflammation had an influence on the frequency of loss of heterozygosity. Primary cutaneous melanomas show intratumoral morphologic and chromosomal heterogeneity. Loss of heterozygosity on chromosomes 1p and 9q correlated with cell proliferation, suggesting that selected cell clones are responsible for tumor progression. Grin et al. have described several melanocytic lesions of the eye. Benign and malignant lesions were presented as well as a review of the dysplastic nevus syndrome and its proposed association with ocular melanoma. The authors propose that knowledge of melanocytic lesions will aid the dermatologist in detection and in proper referral of these patients. Manenti and co-worker have compared the expression of myristoylated alanine-rich C kinase substrate (MARCKS) in human tumor-derived choroidal melanoma cells (OCM-1) and in primary cultures of normal choroidal melanocytes. They have found an important down-regulation of the protein in the melanoma cell line. Stable transfection of these cells with the cDNA coding for MARCKS led to the selection of several clones expressing variable levels of the protein. Proliferation experiments performed with four of these clones revealed that cell growth was reduced by 35-40% when compared with control cells. These data suggest that the expression of this protein kinase C substrate affects the proliferation and partially reverts the transformed phenotype of the OCM-1 cells. Kippenberger et al. have tested different culture systems in order to observe the mechanism of melanocyte dendrite formation. In particular, they focused on the role of keratinocytes in this process. Time lapse studies revealed that only differentiated keratinocytes enhance melanocyte dendricity. Kahn and Cohen have investigated results of dermabrasion with melanocyte transplantation using new modifications of the technique in patients with stable vitiligo. The epithelium of vitiliginous areas was removed by dermabrasion and the dermabraded area was then reepithelialized with ultra-thin sheet grafts. Good to excellent repigmentation was observed in 88% of the procedures and the authors conclude that this technique provides a valuable treatment option in patients who have failed medical management. Kunisada et al. in order to examine both the potential of stem cell factor (SCF) to cause mastocytosis and its role in epidermal melanocyte homeostasis, have targeted the expression of SCF to epidermal keratinocytes in mice with two different transgenes controlled by the human keratin 14 promoter. The transgenes contained cDNAs that either produced SCF, which can exist in both membrane-bound and soluble forms, or SCF, which remains essentially membrane-bound. Murine epidermal keratinocyte expression of membrane-bound/soluble SCF reproduced the phenotype of human cutaneous mastocytosis. The authors conclude that a phenotype matching that of human mastocytosis can be produced in mice by keratinocyte overproduction of soluble SCF, suggesting a potential cause of this disease; they also conclude that keratinocyte expression of membrane-bound SCF results in the postnatal maintenance of epidermal melanocytes in mice. Brown et al. have found that several aliphatic and alicyclic diols induce melanogenesis in cultured S91 mouse melanoma cells and normal human epidermal melanocytes (NHEM). In addition these compounds induce melanogenesis when applied to guinea pig skin, with transfer of melanin to keratinocytes and formation of supernuclear caps, as occurs in naturally pigmented skin. The results of this study indicate that cultured NHEM treated with diols export melanosomes in a fashion that is commensurate with natural melanogenic process. The authors suggest that the diols described in this report are candidates for use as cosmetical tanning agents. Nakajima and co-worker assessed the effects of arbutin on the pigmentation of cultured human melanocytes. As indicate by a cell-blotting assay, arbutin at concentrations in the range of 0.5-8 mM increased the pigmentation of the cultured melanocytes. The pigmentation-augmenting effect of arbutin was further confirmed by the results of a cell-pelleting assay. These results demonstrate that arbutin promotes an increase in pigmentation of cultured human melanocytes that in not mediated by augmented. Schallreuter et al. have investigated 6-Tetrahydrobiopterin (6-BH4) functions in UVB-light melanogenesis. 6-BH4 and its 7-isomer function as uncompetitive inhibitors of human and mushroom tyrosinases. Photo-oxidation by UVB-light and O_2 reverses the inhibition of tyrosinase by 6-BH4 and 7-BH4 with the 6-BH4/tyrosinase complex being four-fold more photolabile than 7-BH4/tyrosinase. By contrast, UVA light does not catalyze the photodegradation of 6-BH4. The authors postulate that their results indicate that the photo-oxidation of the tetrahydrobiopterins by UVB may represent a photo-switch in the regulation of tyrosinase activity to promote de novo melanogenesis. Iyengar, in a study conducted with irradiation of whole skin organ cultures from the marginal zone skin in vitiligo, demonstrated that the differentiating keratinocytes in skin do not express PCNA but appear to be dependent on active UV responding melanocytes for DNA repair. The author concludes that this factor could play an important role in the occurrence of UV-related skin tumors. Atillasoy et al. have conduced a study to establish the causality of relationship between UVB-light and human melanoma development. A total of 158 RAG-1 mice, grafted with human newborn foreskin, were separated into four groups and observed for a median of 10 months: 1) no treatment; 2) a single treatment with 7, 12-dimethyl (a) benzanthracene (DMBA); 3) UVB irradiation at 500 J/m2 , alone, three times weekly, and 4) a combination of DMBA and UVB. The authors affirm that this experimental system demonstrates that chronic UVB irradiation with or without an initiating carcinogen can induce human melanocytic lesions, including melanoma. Nakazawa and co-worker have compared the effects of heat and UVB on normal human melanocytes functions. The experiments conduced on monolayer culture suggest that heat shares significant biologic activities with UVB in melanocyte functions. These results could be considered as one of the protective or adaptive responses of the skin pigmentary system to the environment.

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In situ and in vitro expression of protein kinase alpha in human melanocytes. Pigment Cell Res. 11(1):18-23, 1998.

Melanocyte cultures
(Dr N. Smit)

In the paper by Bessou et al an interesting model to study vitiligo melanocytes is described in epidermal reconstructs on dead de-epidermized dermis. Combinations were studied of melanocytes and keratinocytes of normal and vitiligo skin. So far no differences in the histology and ultrastructure of the heterologous and autologous reconstructs from the vitiligo patients have been found. The model seems however promising for further study of the factors responsible for the pathophysiology of the disease. Venneker et al studied the expression of complement regulatory proteins like decay accelerating factor (DAF), membrane cofactor protein (MCP) and CD59. The protective effects of these molecules against complement mediated lysis using vitiligo sera were investigated. In the cultured melanocytes the strongest protective contribution was found for the DAF.
Halaban et al have studied the roles of E2F, p16 and p21 in mouse melanocytes. TPA-independent growth was not found for the melanocytes from the p16 or p21 null-mice. Overexpression of the DNA-binding-defective E2F1 mutant in the melanocytes did result in TPA-independent growth. An important role for the activation of E2F1 in melanomas is suggested. In the Biochemical Journal Imokawa et al demonstrate the importance of hepatocyte growth factor and stem cell factor in fibroblast conditioned medium for the stimulation of DNA synthesis in human melanocytes. A striking difference is found between fibroblasts from aged skin (61 years or older) and young skin (10 years or younger). The mechanism of activation by the factors released from the (old) fibroblasts was studied using inhibitors of tyrosine kinase and protein kinases C and A. The results suggest a tyrosine kinase ligand-receptor mediated stimulation of DNA-synthesis. Unfortunately, the paper does not describe at what age of "adult" fibroblasts (between 10 and 61 years) the optimal secretion of these factors is reached. Kunisada et al describe a model of transgenic mice with keratinocytes producing either soluble (S) or membrane bound (MB) stem cell factor. The animals with keratinocytes producing MB-SCF showed epidermal melanocytosis and melanin production. Since this approximates the situation in human skin these animals may be relevant for the study of human melanocyte biology.
In the paper by Rosemblat the effects of l-tyrosine supplementation of culture medium on melanosomal maturation are nicely demonstrated. In mouse melanocytes lacking the pink-eyed dilution gene a strong increase in expression of the tyrosinase protein and the TRP-1 were found with increased levels of l-tyrosine, especially in the Ham's F-10 culture medium.

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Commentary: The potential role of this melanoma-associated retrovirus (MelARV) in melanoma formation remains unknown and has not been previously investigated. To test this, normal melanocyte lines (melan-a and C57M) of C57BL/6 mice were infected with the MelARV produced by B16BL6 melanoma. Infection of these melanocytes with the MelARV was associated with the appearance of the MAA recognized by MM2-9B6 MAb. Most of the infected melanocyte sublines were able to grow only in the presence of 12-O- tetradecanoylphorbol-13-acetate (TPA). Two infected melanocyte sublines showed morphological changes, were able to grow in the absence of TPA and, after inoculation into C57BL/6 mice, produced rapidly growing, highly pigmented tumors.

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Expression of bcl-2 and bax in cultured normal human keratinocytes and melanocytes: relationship to differentiation and melanogenesis. Br J Dermatol 137(6):883-889, 1997.
Commentary: Quantification of Bcl-2 antigen sites per cell showed that Bcl-2 expression is higher in keratinocytes than in melanocytes. An increase in transglutaminase activity, a marker of keratinocyte terminal differentiation initiating cornified envelope formation, was accompanied by a decrease in Bcl-2 levels without significant modification of Bax expression. In melanocyte cultures, stimulation of the dopa-oxidase pool, a key enzyme in melanin synthesis, paralleled Bcl- 2 down-regulation and Bax-up-regulation, This led us to conclude that the expression of these two oncogenes and their cellular ratio are closely involved in keratinocyte differentiation and melanogenesis.

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3. MSH, MCH, other hormones, differentiation

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5. Neuromelanins

(Prof. M. d'Ischia)

A large amount of work continues to be carried out on the structure and properties of dopamine melanin, as a model for the human brain pigment. Ito and Wakamatsu (Pigment Cell Res., 11, 120-126, 1998) revisited the alkaline H2O2 degradation method of Napolitano et al.(Tetrahedron, 51, 5913, 1995) and the HI hydrolysis method of Wakamatsu et al. (Neurosci. Lett. 131, 57-60, 1991), and applied them to the analysis of diverse types of melanins, including chiefly dopamine melanins. Of particular interest was the finding that HI hydrolysis of melanins prepared by oxidation of dopamine with different amounts of cysteine gave 3-amino and 4-amino isomers of aminohydroxyphenylethylamine (AHPEA) in a ratio that varied significantly with the sulfur content. This and other results highlight the potential of HI hydrolysis for studies of the chemical composition of melanins from catecholamine oxidation, including neuromelanin.
Stepien et al. (Biochem. Biophys. Res. Commun., 244, 781-784, 1998) reported experimental evidence indicating that dopamine melanin has the ability to reduce 13-hydroperoxyoctadecadienoic acid (13-HPODE) into the corresponding alcohol both in the presence and in the absence of ferrous ions. This finding has been taken to suggest an important specific role of neuromelanin as an antioxidant in lipid peroxidation processes.
In a reviewing article, Smythies and Galzigna (Biochim. Biophys. Acta, 1380, 159-162, 1998) summarize available evidence for the occurrence of aberrant oxidative pathways of dopamine and related catecholamines via their corresponding o-quinones and provide suggestions for the possible significance of these pathways in the biogenesis of neuromelanin and in neuron functioning.
Using immunohistochemical techniques, Schipper et al. (Exp Neurol 150, 60-68, 1998) assessed expression of heme oxygenase-1 (HO-1), a cellular stress protein expressed in brain and other tissues in response to oxidative challenge, in various postmortem human brain specimens derived from PD and control subjects. In the substantia nigra of both PD and control specimens, moderate HO-1 immunoreactivity was observed in neuromelanin-containing (dopaminergic) neurons. Lewy bodies in PD nigra neurons, however, exhibited intense HO-1 immunostaining in their peripheries. The authors suggested that upregulation of HO-1 in the substantia nigra of PD subjects is an indirect index of chronic oxidative stress, and that excessive cellular levels of heme-derived free iron and carbon monoxide resulting from HO-1 overactivity may contribute to the pathogenesis of PD.
Finally, Lack et al. (Am J Surg Pathol 22:265-269, 1998) reported the putative occurrence of neuromelanin in a pigmented ("black") extraadrenal paraganglioma in the retroperitoneum near the superior border of the right kidney of a 57-year-old woman.

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6. Genetics, molecular biology

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7. Tyrosinase, TRP1, TRP2 and other enzymes

(Prof. J.C. Garcia-Borron)

The current interest in immunological aspects of melanoma is prompting a series of relevant studies aiming at the characterization of melanocyte-specific differentiation proteins and their intracellular processing. These studies are highlighting the somehow unexpected complexity of the post-translational events leading to mature melanosomal proteins. Mosse et al. (J. Exp. Med., 187, 37-48) present evidence for the involvement of proteasomes in tyrosinase processing and in the presentation of tyrosinase-derived antigenic peptides. Their data suggest the possibility that full-length tyrosinase might reside transiently in the cytosol, a possibility that correlates with the presence of enzymatically active tyrosinase in the cytosolic fraction of melanoma cell homogenates. The involvement of the proteasome in tyrosinase processing has been already suggested by others (Halaban et al., Proc. Natl. Acad. Sci, USA, 94, 6210-6215). Since degradation by the proteasome can be a tightly regulated process, these observations open new perspectives for the study of the regulation of tyrosinase levels, specially in those cases where the levels of the protein change, without parallel variations in mRNA (see, for example, Rosemblat et al., Exp. Cell Res. 239, 344-352).
Another paper deals with the sorting of TRP-1 (Xu et al., J. Invest. Dermatol. 109, 788-795), and describes the occurrence of a post-translationally generated, truncated form of the protein which is secreted to the medium by human melanoma cells. Moreover, full-length TRP-1 is also present at the plasma membrane. These non-melanosomal forms of the melanogenic enzymes are more likely to generate immune responses and, as pointed out by the authors, may explain the presence of autoantibodies in a variety of diseases.
Furumara et al. (Biochem. Biophys. Res. Commun. 242, 579-585) provide a structural basis for the different enzymatic activities of tyrosinase and the TRPs by showing a different specifity for the binding of the metal ion cofactor. By means of radioactive tracers and reconstitution experiments, the authors show that tyrosinase binds copper whereas TRP-2 binds zinc, i.e. an ion that does not participate in redox reactions. Thus, the basic chemistry of the ion cofactors present in both proteins fits perfectly with the observed reaction specificity of the corresponding holoenzymes.

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8. Melanoma and other pigmented tumours

Experimental melanoma therapy (Dr. N. Smit)

In the immuno and genetherapy treatment of melanoma the importance of expression of b7.1 (and b7.2) is mentioned in the papers by Chong et al, Dummer et al and Fujii et al. Chong et al studied the effects of co-expression of b7.1 and b7.2 with GM-CSF or Il-12 in murine colorectal and melanoma tumours. Dummer et al show that b7.1 and b7.2 transduced melanoma cells induce proliferation of PBMCs and transcription of Il-10, Il-2 and IFN-gamma. An adverse effect of IL-10 was shown and should be considered in these gene therapy tumour cell vaccination approaches. Fujii et al describe the antimetastatic effects of vaccination with b7.1 transfected B16-BL6 melanoma cells. In combination with anti-adhesive therapy using a pseudo-peptide FC-336 the antimetastatic effect could be augmented.
Soncin et al studied the photosensitizing effects of two far-red absorbing naphtalocyanines . The compounds were more efficient in B16-amelanotic melanoma than in highly pigmented B16 cells as a result of the protective action of melanin, filtering the 776 nm light. The photosensitization of the compounds was mainly correlated with the damage to cell membranes and a reduction in a lysosomal maker enzyme. For photodynamic therapy also lutetium texaphyrin (PCI-0123) with strong absorbance in the near infrared (700-760 nm) was examined in the study by Woodburn et al. In this case, the predominant site of photosensitizer binding was to melanosomes. A good tissue penetration depth using the PCI-0123 and the correlation with melanosomes could make this drug usefull for the PDT of pigmented melanomas.

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

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