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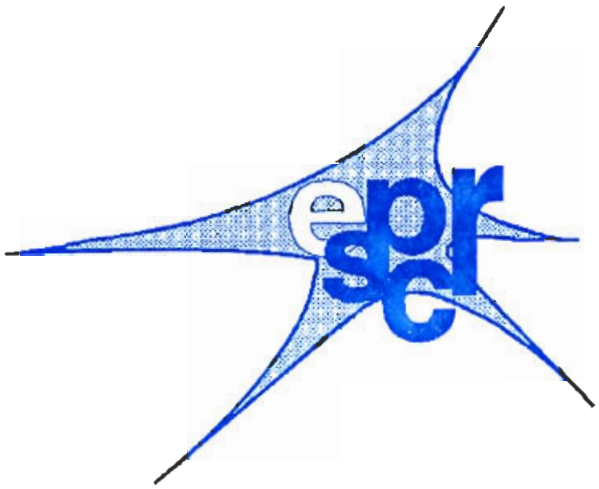

EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH BULLETIN

N° 23 - October 1995

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DISCUSSION

Has melanin a photoprotective role ?

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It is currently believed that melanogenesis is a natural, protective response to solar irradiation in the course of which melanin is synthesized in the melanocytes and transferred to the keratinocytes. If no one questions the fact that the process is a natural one, the question can be asked about the protecties against sunlight (if any) of melanin inside the keratinocytes.

What makes us think that melanin is protective?

Nordlund and co-workers (1) reports that the idea that melanin is protective has an history, the origin of which has been pinpointed down to Benjamin Franklin. As a matter of fact. Franklin observed that "*dark coloured cloths laid upon fresh snow on a bright sunny day melted the underlying ice cristals more rapidly than light colored cloth*" in agrement with the observation that, all the rest being equal, black objects exposed to sunlight reach higher temperatures than white ones. "*It was known that black-skinned individuals normally inhabited tropical regions and that white individuals came from the north. It seemed perverse to Franklin that nature would endow individuals living in the tropics with a type of skin which was inappropriate for the environment. Everard Home resolved this enigma ... He exposed both his hands to the sun. One was covered with a black cloth, and the other was left bare. He measured the temperature of his skin. He found that the black cloth did indeed elevate the temperature of his skin a few degrees. However, the exposed hand became sunburned. He concluded that pigment did indeed cause a slight warming of the skin but protected it from the nonthermal, i.e., scorching, effects of the sunlight. Thus was born the idea that melanin was a sunscreen which prevented sunburn, a concept which persists to modern age and is only now undergoing reconsideration*".

An obvious comment to Home's experiment is that it would have been better to cover both hands with cloths of identical manufacture, the only difference being the colour. An obvious comment to Home's conclusion is that the experiment proves protective properties for topically applied dark coloured molecules, and that nothing can be said about the role of endogenous pigmented granules.

Apparently this is the historical reason for believing that melanin is a natural against sunlight, possibly conforted by the observation that melanin production is a painless consequence of exposure to sunlight.

Upon learning more about the physiology of black skin, it was realized that black-skinned individuals exposed to sunlight experience sunburn as well. Someone also realized that prehistorical men used not to live in the sun-exposed savannah but in the sun-protected rainforest and scientists started wondering about the selective advantage of being black in such an environment. It was pointed out that in a forest environment, some sort of camouflage would be essential and black skin, reflecting only 16% of visible light, could be very effective for this purpose, much more effective than white skin which reflects 45% of visible light. Another selective advantage comes from the fact that radiant energy from sunlight can be absorbed by melanin and converted to heat. As a matter of fact, pigmentation can thus contribute to the maintainance of body temperature and to the conservation of metabolic heat, and be very important for prehumans, who slept without the benefit of fire or clothing and were not always successful in hunting (2).

Of course these discussions did not answer the question about photoprotective properties of melanin inside the keratinocytes and a number of experiments were designed in order to contribute to the advancement of knowledge.

Once it is made clear that the biological properties of melanin depend on its chemical structure (there is not one melanin, there are many different melanins, grouped in the categories of eumelanins and phaemelanins), one of the first questions which can be asked, when the role of melanin is questioned, concerns cell survival after UV irradiation.

Brian Johnson and coworkers observed that sunburn cells contained granules which appeared to be similar to those, known to be melanin, in basal layer cells. They also observed that in biopsies from normal human volounteers, the fraction of sunburn cells in lightly pigmented skin increased linearly with the dose up to nearly 90 per thousand malpighian cells for 8 Minimal Erythemal Doses (MED), while in vitiligo skin, in which no melanocytes are present, the fraction of sunburn cells remained nearly constant ($\sim$ 5 per thousand) with doses up to 16 MED. (It has to be noted that Brian Johnson used to work in Dundee, so that if the volounteers were autochtonous there are chances for their epidermis to contain phaeomelanin).

Taking advantage of the fact that macrophages can phagocytose melanin from the environment, Brian Johnson and coworkers exposed to UV from FS 20 fluorescent tubes, macrophages from mouse peritoneum which had been incubated with squid ink melanin. They observed that macrophages incubated for 24 hours with melanin were slightly more sensitive to UV than macrophages which did not take up melanin (3).

Another question which can be asked concerns the formation of UV-induced DNA damage in cells containing or not containing melanin. Schothorst and coworkers (4) undertook to expose cultured human keratinocytes and melanocytes to monochromatic radiation in the UV range and measured the amount of Endonuclease Sensitive Sites (ESS) versus the dose at different wavelengths. Melanocytes were grown in a medium containing isobuthyl-methyl-xanthine, so it is reasonable to believe that they were pigmented, even though the authors did not present the reader with figures relative to the amount of melanin per cell. The outcome of this experiment is particularly interesting: no difference can be pointed out in the dose- and wavelength- dependence of ESS formation in keratinocytes or in melanocytes in the UV-C and UV-B regions, except for a small

difference when 297 nm radiation is utilized, in this case melanocyte DNA is slightly more damaged than is keratinocyte DNA. An analogous experiment was performed by De Leeuw and coworkers, who measured the residual clone-forming ability of cultured human melanocytes and keratinocytes after monochromatic UV irradiation. They found that melanocytes are slightly less sensitive than keratinocytes to UVB and more resistant to UVA than keratinocytes (5).

Of course, cultured melanocytes are not melanocytes in the epidermis, moreover their melanin is distributed in melanosomes within the dendrites and only occasionally is interposed between the cell's nucleus and the source of UV light. Therefore it seemed necessary to measure the protection against radiation of cells having ingested different amounts of melanin, making sure that these cells could not be suspected of digesting melanin as it could have been the case in the experiment with macrophages.

Cell biology offers tools and methods for tackling this kind of problems. Ideally one should grow two samples of keratinocytes in the presence of homologous melanocytes, stimulate the first sample with UV light in order to include melanin synthesis and transfer of the pigment from the melanocytes to the keratinocytes, and treat the second sample according to a mock-irradiation protocol. After the transfer, which could be monitored by observation under the microscope, keratinocytes and melanocytes should be separated, the keratinocytes seeded, exposed to UV and checked for some physiological parameters (growth, DNA damage, loss of cytoplasmic enzymes, cell morphology and so forth).

If melanin is photoprotective one expects sample one to be in a better shape after UV xposure than sample two.

Of course such an experiments is extremely difficult to be carried out and some simplified protocols have been designed.

Hill and Hill induced B16 CL 4 mouse melanoma cells in culture to phagocytose melanin particles dispersed in the growth medium and subjected them to ionizing radiation.

The result of the non-irradiated control was that after the incubation in the presence of melanin, the alkaline elution of labelled DNA reveals conspicous nicking, the amount of which is dependent on the concentration of melanin to which cells were exposed. When cells preincubated with melanin are exposed to ionizing radiation, the results indicate that the nicking of DNA provoked by the two agents are additive (6).

In another experiment, Hill and coworkers undertook to measure the survival of three Cloudman S 91 mouse melanoma cell lines after exposure to 137 Cs radiation (7). The three cell lines contain different amount of melanin (respectively 1.2, 1.8 and 3.6 pg/cell) and, all the rest being equal, can be assumed to give responses to insults, which are dependent on the content of melanin. For low irradiation doses (below 5 Grays) there is a direct correlation between survival and melanin content. At 5 Grays, for instance, the surviving fractions for the three cell lines are 0.02, 0.09 and 0.3, respectively.

Of course this result gives informations about the physico-chemical properties of irradiated melanin, but the phagocytosis of melanin particles is not equatable to the melanosomal transfer from cell to cell and it is not sure that, within a melanoma cell, melanin forms a cap around the nucleus as it forms in keratinocytes.

Because of the difficulty to learn in cultured cells about the role of melanin in human epidermis, Young and co-workers designed a clever experiment with human volounteers. In order to have cells containing more or less melanin, all the rest being equal, they exposed the volounteers to a series of suberythemal UV irradiations from a solar simulator, either in the presence of a conventional sunscreen, in order to maintain an "*amelanotic*" status, or in the presence of the same sunscreen added with trace amounts of 5 methoxypsoralen, in order to obtain an artificially generated "*highly pigmented*"

status, or without xenobiotics in order to obtain a naturally "*melanin enriched*" status. One week after the end of the series of the suberythemal irradiations, the volounteers where exposed to an erythemal dose of UV and checked for several parameters, such as melanin content and stratum corneum thickness (taken as two possible natural sunscreens) and the extent of Unscheduled DNA Synthesis (UDS or DNA repair), taken as an indicator of the extent of DNA damage, which is a major target of sunlight (8). The results seem to indicate that acquired pigmentation affords better protection against DNA damage, at least in phototypes III, IV and V. Yet the authors conclude that "*Photoprotection is often explained by induction of melaninization and/or stratum corneum thickening. As such induction was independent of skin type and similar for the three types of treatment, there is no overall correlation between either or both these parameters with UDS levels, which indicates that photoprotection is more complex than previously thought*".

A Symposium on "Melanin: Its Role in Human Photoprotection" was held in March 1994 in Washington, D.C. and the discussions pointed out that the consensus about the role of melanin is far from being reached. The major clinical observation, pointed out by Helen Hill as well as by Albert Kligman, John Pawelek and James Nordlund, that skin cancer rates correlate inversely with skin pigmentation, is the only major evidence in favour of a protective effect of melanin. Yet this protective effect does not necessarily imply that it is exerted *via* the sunscreen properties of melanin itself.

One could for instance imagine that the vigourous activity of the melanocyte as a modulator of inflammation, manifested as dark or tanned skin, protects the individuals against skin cancers (Nordlund).

One can also surmise that melanin can play several roles in oxido-reduction reactions triggered by UV radiation within exposed cells, and that the end result will depend on the initial oxidation status of the cell, that is to say, to every experiment a different result (Menter & Willis).

As a matter of fact the photochemical, photophysical and physico-chemical properties of melanins have been discussed by Miles Chedekel who stated that" *melanin can contribute to photoprotection by directly scavenging free radicals, especially active oxygen species*". On the other hand Menter and Willis wrote:" *depending on the reductant, melanin either retards or accelerates ferricyanide reduction. Melanin also acts as an electron conduit in markedly accelerating the tyrosinase catalyzed oxygenation of p-hydroxyanisole...The net result of such melanin mediated processes, if they occur in vivo, could be either beneficial or deleterious to the organism*"

The outcome of the meeting was brilliantly expressed by the title of Kligman's abstract: Is melanin photoprotective? Answer: sometimes yes, sometimes no"

Some authors are considering the possibility that the properties of melanin might depend on its chemical and stereochemical properties. Melvin Eisner suggested that "*the protective capabilities of melanin may be influenced strongly by the morphology of the melanin granule. The layered structures found in vivo do not seem to make full use of the optical absorptivity of the interior melanin, suggesting perhaps a separate quenching or sequestering role*".

On the basis of all these consideration, an observation made in our laboratory might help in designing new experiments. We have indeed observed that in the presence of metal chelators such as ~ 1 millimolar EDTA or ~ 10 millimolar citrate or ~ 100 millimolar histidine, some melanins become water soluble at neutral pH and can be re-precipitated by the addition of millimolar amounts of di-valent cations such as calcium, magnesium, iron, copper and so forth (10,11).

The interesting aspects of the phenomenon is that:
i) divalent cations can also precipitate eumelanin dissolved in sodium hydroxide
ii) the precipitate forms particles the diameter of which can be submicrometric
iii) conditions can be found in which the diameter increases slowly with time.

These findings make it possible to prepare melanins with different physico-chemical properties in oreder to check Eisner's hypothesis. They also bring circumstantial evidence in favour of the model which suggests that some of the protective properties of melanin are linked to its capability to bind iron and other transition elements which might play a role in photofenton phenomena or in metal catalyzed oxidations.

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1. Melanins and other pigments chemistry

(Comments by Prof. M. Peter)

The melanins of various gastrointestinal tract melanoses have been investigated by application of Electron microscopy (EM) and electron-probe energy dispersive x-ray analysis (*Ghadially and Walley*). It was shown that the pigments contain either lipofuscin, silicates and titanium or hemosiderin, or iron sulfide. The pigment melanosis oesophagi could be melanin or lipofuscin. HPLC separation of dopa and dopachrome on C-18 reversed-phase at various pH was described by *Kagedal et al.*. An advantage of the method is that the measurements of dopachrome are uninfluenced by concomitant formation of melanochromes. The procedure was used to follow disappearance of dopachrome as a measure of dopachrome tautomerase activity.

Several papers dealt with aspects of melanin biosynthesis and with the redox chemistry of the pigments or their precursors. *Mimaki et al.* isolated (5aR*,6R*,9R*,9aS*)-4-cinnamoyl-3,6-dihydroxy-1-methoxy-6-methyl-9-(1-methylethyl)-5a,6,7,8,9,9a-hexahydrodibenzofuran from the bark of Lindera umbellata as a novel inhibitor of melanin biosynthesis. It does not cause any cytotoxicity in cultured cells or skin irritation in guinea pig. *Napolitano et al.* described a mechanistic route for the degradation of 2-substituted DHI-units in melanin polymer to pyrrole-2,3,5-tricarboxylic acid (PTCA). Synthetic pigments prepared from 5,6-dihydroxyindole (DHI) or 5,6-dihydroxyindole 2-carboxylic acid (DHICA) were also subjected to degradation with alkaline hydrogen peroxide which gives improved yields as compared to conventional prodecures. PTCA may originate from 2-linked DHI-units in the pigment polymer as well as from DHICA-derived units, whereas PDCA arises from DHI-units not substituted at 2-position. *Bertazzo et al.* have detected oligomers of dopamine during oxidation with mushroom tyrosinase, using matrix-assisted laser desorption/ionization (MALDI) and fast-atom bombardment (FAB) mass spectrometry. Oxidation of 2,4,5-Trihydroxyphenylalanine (TOPA) gives a quinone derivative that is a non-NMDA glutamatergic agonist and neurotoxin (*Newcomer et al.*). DOPA can autoxidize in physiological solutions to form small amounts of both TOPA and TOPA quinone. This conversion can be dramatically enhanced by iron (II) alone, but more so by iron (II) in the presence of hydrogen peroxide. This finding suggests that TOPA quinone may play a role in pathological processes involving abnormal iron metabolism in catecholaminergic neurons.

A number of publications on melanins of microorganisms have appeared. *Elliot* reported that melanin biosynthesis in the fungus Gaeumannomyces is inhibited by dihydroxynaphthalene (DHN) melanin inhibiting compounds (tricyclazole, pyroquilon, phthalide and chlobenthiazone) but not with DOPA-melanin inhibiting compounds (tropolone, kojic acid, 2-mercaptobenz-imidazole and diethyldithiocarbamate). Intact melanin biosynthesis is not necessary for fugal growth or infectivity. *Wheeler and Klich* have investigated pigment formation in various Aspergillus and Penicillium spp. in a similar approach, and concluded that a number of brown to black fungi biosynthesize melanin from DHN which is formed in the poleketide pathway. Electron microscopy, atomic absorption spectroscopy, and inhibition tricyclazole were used to investigate the pigment of Gaeumannomyces graminis, grown in the presence of copper ions (Caesartonthat et al.). CuS associated with the melanin layer was present in cell walls and septa of copper grown hyphae. *Rakoczy and Panz* employed ESR in order to characterize the type of pigment present in the spore wall and black pigment isolated from the spores of Physarum polycephalum, Physarum nudum, and Fuligo septica using ESR) method. The paper contains little information on the chemical nature of the pigments. Melanins of fungi forming of black stains on monuments were analyzed by analytical pyrolysis and found to be complex mixtures of polysaccharides, proteins, lipids, nucleic acid derivatives and aromatic compounds (*Saizjimenez et al.*).

Two papers dealt with aspects of biosynthesis of melanins in microorganisms. Pyomelanin formation is correlated with homogentisic acid production and p-hydroxyphenylpyruvate hydroxylase expression in three disparate marine species (*Kotob et al.*). *Pierce and Rast* conclude from results of a detailed study employing Fourier-transform infrared spectroscopy of the spore of Agaricus bisporus, of the melanin isolated therefrom and of various synthetic melanins prepared from g-glutaminyl-4-hydroxybenzene (GBH) or from simple phenol analogues of GHB, that the pigment is biosynthesized from 4-aminocatechol rather than 4-aminophenol or directly GBH.

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The Effects of Tricyclazole, Pyroquilon, Phthalide, and Related Fungicides on the Production of Conidial Wall Pigments by *Penicillium* and *Aspergillus* Species. Pestic. Biochem. Physiol. 52:125-136, 1995.

2. Biology of pigment cells and pigmentary disorders

(Comments by Dr M. Picardo)

- Alena F, Dixon W, Thomas P, Jimbow K.
Glutathione plays a key role in the depigmenting and melanocytotoxic action of N-acetyl-4-S-cysteaminylphenol in black and yellow hair follicles. J Invest Dermatol. 104(5):792-7, 1995.

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Isolation of a unique melanogenic inhibitor from human skin xenografts: initial in vitro and in vivo characterization. J Invest Dermatol. 104(5):739-43, 1995.
Commentary: The relationship between melanocytes and the other epidermal and dermal cells is an essential point to understand the pigmentation process. Recent studies have defined the paracrine effects of keratinocytes and fibroblasts and the use of Human Skin Equivalent and conditioned media has provided new models to study this effect and has opened a new view to evaluate the pigmentation process. The group of Barbara Gilchrest now report that co-culture with keratinocytes and fibroblasts enhance the survival of melanocytes and melanin synthesis following UVB exposure. Several hypothesis can be performed on the possible factors secreted or produced by neighboring cells which affect melanocyte activities and among these leukotrienes and cytokines have to be considered. In this connection Imokawa and co-workers have reported that UVB irradiation of keratinocytes induce the expression of Endothelin 1 gene and its secretion. Endothelin 1 is a potent vasoconstrictor peptide which stimulate melanocyte proliferation via receptor-mediated signal transduction pathway. With their experiments, the authors were able to conclude that Endothelin 1 could be one of the mediators for UVB-induced pigmentation of human skin. The group of Nordlund looking for the identification of a melanogenic stimulator in human skin xenograft to explain the marked iperpigmentation observed following skin grafting onto athymic mice, have found and partially characterized a 14kD protein which inhibits tyrosinase synthesis and melanocyte proliferation. Injections of the inhibitor induced a delay and reduction in pigmentation in skin grafting. Interestingly the authors speculate that this inhibitor may function as a feed-back control in heavily melanized skin and that the relative ratios between inhibitors and stimulators can determine the ultimate melanogenic outcome.
The view of the skin of unique organ and that all the cells present can participate and co-operate in the response to

external stimuli is certainly a more complete way to define the mechanisms of pigmentation.

- Orlow S.
  Melanosomes are specialized members of the lysosomal lineage of organelles. J. Invest. Dermatol. 105:3-7, 1995. (Review)
  Commentary: Melanosomes are specialised subcellular organelles in which melanin is synthesised and deposited. in this paper Seth Orlow review the evidences in support of a common biogenesis between melanosomes and lisosomes. The reader is accompanied in a journey through the biogenesis of melanosomes, the distribution and the activity of the melanosome enzymes other than tyrosinase, the trafficking to melanosomes and the evidences of genetic lysosomal-melanosomal pathologies. The definition of the biogenesis of melanosomes may be useful in studies on different aspects of pigmentation. It is known more about the biological properties, protein traffic and enzyme activities in lysosomes than in melanosome and these data could be the basis for further development on pigmentation and pigmentary disease.

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  Investigation of the personality structure in patients with vitiligo and a possible association with impaired catecholamine metabolism. Dermatology. 190(2): 109-15, 1995.
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  Some aspects of melanin formation of melanocytes cultured on collagen coated microcarrier beads. Pigment Cell Research. 8:89-96, 1995.

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  Reduced growth factor requirements and accelerated cell-cycle kinetics in adult human melanocytes transformed with SV40 large T antigen. J Invest Dermatol. 104(5):755-62, 1995.

Melanocyte cultures
(Comments by Dr N. Smit)

Abdel-Malek et al describe the effects of UV irradiation on melanocytes from different skintypes. The effects on melanogenesis as described could lead to better understanding of how the different types of melanin are produced. In this respect the study of *Kobayashi et al* towards the expression of the different melanogenic proteins in melanocytes from hair bulbs in mice is also of interest. Their results indicate that TRP-1, TRP-2 and the silver protein are all eumelanogenesis specific. The system of uveal melanocytes as described by Hu et al could also serve as an interesting model to study differences in melanogenesis since these cells maintained their inherent capacity for melanogenesis in culture.

Different systems are described in which melanocytes are used originating from different disorders such as neurofibromatosis 1/cafe au lait macules (*Griesser et al, Eisenbarth et al*), oculocutaneous albinism and Chediak Higashi Syndrome (*Zhao and Boissy*) or mutants from the White Leghorn (*Bowers et al*). *Zhao and Boissy* show differences in the tyrosinase enzymes of these cells whereas *Bowers et al* show that reduced levels of GSH and superoxide dismutase may cause low antioxidant levels and cause premature death of the mutant melanocytes.

Ponec points out that reconstructed human epidermal cultures populated with melanocytes can be of great use for studying interaction of melanocytes and keratinocytes. Examples of this approach are given in the studies by *Archambault et al, Franchi et al, Harriger at al* and *Nakazawa et al. Archambauld et al* show that melanocytes survive better on a dermal equivalent after UV irradiation as compared to melanocyte monolayers. *Franchi et al* describe a model in which melanocytes and keratinocytes are grown on human de-epidermized dermis which forms an epidermal equivalent resembling native epidermis. *Harriger* describes the study of repigmentation of burn wounds treated with cultured skin substitutes on a biopolymer material. *Nakazawa et al* nicely show the effects of the keratinocyte extracellular matrix on melanocyte morphology and proliferation.

The paper by *Carsberg et al* shows that diacylglycerol (DAG) is increased in both keratinocytes and melanocytes after a single UV-exposure. Since DAG has been shown previously to stimulate melanogenesis in cultured melanocytes (*Gordon and Gilchrest*, 1989) DAGs may be involved in the UVR-induced responses on pigmentation.

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Commentary - Agouti in transgenic mice: Expression of a gene in transgenic mice, driven by its own or a heterologous promoter, allows to prove and understand gene function and to analyse mutations of the gene in vivo. In the pigment field, such experiments have been helpful in analysing the mouse tyrosinase gene and its regulation. This year, similar experiments have been performed with the agouti gene with the intention to obtain an assay for the activity of the protein. When regulated by the §-actin promoter, the agouti transgene led to yellow pigmentation on an otherwise agouti or nonagouti coat (see also Perry et al., 1995). Similar results were obtained with the human homolog of agouti, Asp (Wilson et al., Human Molecular Genetics 4, 223-230, 1995). Mice overexpressing the agouti protein result in phenotypes which are similar to mice carrying dominant agouti mutations like *lethal yellow* or *viable yellow* (Manne et al., 1995).

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Summary: The mutated T24Ha-ras oncogene was targeted to pigment cells in transgenic mice using mouse tyrosinase 5' sequences. Mice were deeply pigmented in the skin with multiple nevi, and hyperplasia and/or hyperpigmentation was observed in skin, eyes, inner ear and meningeal membranes of the brain.

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Summary: A description of 3 alleles of the bovine E locus, coding for MSH-receptor, which was localized to bovine Chromosome 18.

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Intracellular sorting and targeting of melanosomal membrane proteins - identification of signals for sorting of the human brown locus protein, gp75. Journal of Cell Biology 130(4):807-820, 1995.
Summary: The authors used fusions to the T lymphocyte surface protein CD8 to analyse deletions of the C terminus of gp75 (TRP1). Deletion of up to 20 aminoacids did not affect intracellular retention and sorting, whereas mutants lacking the c terminal 27 aminoacids were transported to the cell surface. This region contains a conserved hexapeptide (NQPLLTD) which may function as signal for intracellular sorting.

7. Tyrosinase, TRP1, TRP2 and other enzymes

(Comments by Prof. J.C. Garcia-Borron)

Two of the papers presented in this issue raise an interesting, yet often overlooked aspect of the regulation of melanogenesis, namely the importance of post-translational events as determinants of the levels and activity of the melanogenic enzymes. *Ando et al.* (J. Cell. physiol. 163:608-614) present evidence suggesting that tyrosinase mRNA levels not always correlate with enzymatic activity. Certain treatments, either increasing of decreasing tyrosinase activity, have no effect on mRNA accumulation within the melanocyte. *Abdel-Malek and coworkers* (Proc. Natl. Acad. Sci. U.S.A. 92:1789-93) prove, in a most interesting paper on the mitogenic and melanogenic effects of melanotropic peptides, that MSH treatment of normal human melanocytes results in increased tyrosinase, TRP-1 and TRP-2 activity and protein levels, without noticeable changes in the corresponding mRNA. Taken together, these two independent papers suggest that post-translational events appear at least as important as translational control in the regulation of melanogenesis. The need for further work on the processing and intracellular stability of the melanogenic proteins is therefore clear, and research in this area will surly become very active in the near future.

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8. Melanoma and other pigmented tumours

Melanoma therapy I
(Comments by Dr M. Picardo)

- Schandendorf D, Jurgovsky K, Kohlmus C, Czarneski BM.
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Commentary: The results of these paper underlined the role of the reducing agents in the melanogenesis process and the involvement of glutathione in the mechanisms of action of different anti-tumoral agents. From a general point of view the studies on possible correlations among the intracellular levels of antioxidants and reducing agents, the biology of neoplastic cells, the tumor progression and the response to chemiotherapetic agents seem to be a new tolls for the evaluation of tumorogenesis.

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Melanoma therapy II
(Comments by Dr N. Smit)

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Melanoma-experimental therapy
(Comments by Dr N. Smit)

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Melanoma cytotoxicity, experimental.
(Comments by Dr N. Smit)

Many examples of combinations of immuno- and chemotherapy treatments can be found in the literature on melanoma therapy. Keilholz questions wether it is time for phase III trials with chemoimmunotherapy. Examples are given in the papers by *Buzaid et al*, *Dummer et al* and *Fierlbeck et al.* In experimental models using MmB16 melanoma cells grown in mice (*Feleszko et al*) and SK-Mel 28 melanoma cells (*Hubner et al*) synergistic effects of TNF-α/lovostatin and IFN-ß/carboplatin have been described. On the other hand also antisynergistic combinations are possible (*Palomares et al*).

Cooksey et al describe the reactivity of 4-substituted phenols with cysteine and glutathione. This may indeed be of significant importance for the tyrosinase mediated anti-melanoma cytotoxicity of these agents. The use of tyrosinase for induction of specific cytotoxicity in melanoma is also the aim of the study of Inoue et al using cysteaminylcatechol as an activated form of cysteaminylphenol.

Daoud et al used liposome incorporated camptothecin for drug targeting on breast carcinoma and melanoma tumors. Successful use of liposomes containing Il-1α and TNFα is also reported by *Saito et al. Sharma et al* describe a class of multivalent fluorescent melanotropin-macromolecular conjugates which detect melanotropin receptors on all melanoma lines tested. It is suggested by the authors that substitution of the fluorophore by a chemotherapeutic agent could be a useful tool for melanoma drug targeting. Targeted delivery of doxorubicin (DOX) is described by Sivam et al using an immunoconjugate of DOX with a MoAb directed against the epidermal growth factor receptor (mAb 425). The immunoconjugate showed strong antitumar activity whereas free DOX was ineffective.

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ANNOUNCEMENTS & RELATED ACTIVITIES

1995 **Meeting of the Japanese Society for Pigment Cell Research**
Osaka, Japan, 2 - 3 December
Contact: Prof. Toshiteru Morita
Dept of Biology, Osaka University, 560 Osaka, Japan
FAX: +81 6/850-5613

1996 **XVIth International Pigment Cell Conference**
Anaheim, California, 29 October - 3 November
Contact: MMC/UCI Center for Health Education
PO Box 1428, Long Beach, CA 90801-1428
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1997 **VIIth PASPCR Annual Meeting RI**
Providence, 15 - 18 June
Contact: Dr. Walter C Quevedo, Jr.
Brown University, Division of Biology and Medicine
Providence, RI 02912
FAX: 401/863-1971

1997 **ESPCR Meeting: Krakow** - Dr T. Sarna

1998 **ESPCR Meeting: Bordeaux** - Dr A. Taieb

Bengt Lagerlöf

1930 - September 1, 1995

The ESPCR has lost a most active and respected member with the untimely passing of Professor Bengt Laferlöf. He recently retired from a professorship in pathology at the Karolinska Institute in Stockholm, where he had been working for 40 years. He gave important scientific and clinical contributions during the years within the pathology of malignant melanoma, especially as regards the identification of the preliminary stages of the disease. Bengt Lagerlöf usually attended the ESPCR and IFPCS meetings, and he was well known and appreciated by our members.

Dr B. Larsson
President

Meeting Report

6th MEETING OF THE EUROPEAN SOCIETY FOR PIGMENT CELL RESEARCH

(Lausanne 19th-21st October 1995)

By Dr Sheila MacNeil

As a new Council Member I have been asked to write a report of this Meeting which I am very pleased to do. What follows is a highly personal view of this meeting and I would like to apologise in advance to all those whose work I may misrepresent, offend or in any way overlook. As always with the ESPCR Meetings, there was an atmosphere of much enthusiasm, goodwill and considerable alcohol which promoted the multi-disciplinary approach to understanding the melanocyte. It is no coincidence that year after year people find time for this multi-disciplinary friendly event in their busy conference schedule. This year there were some very nice developments and some coming together of previously separate areas and hints of new and broader vistas of what the melanocyte may be up to.

One common unifying theme which has been growing steadily relates to the role of the melanocyte in stress management in the broader sense. Everyone has their own personal portrait of the melanocyte - however, these are not always recognisable to our colleagues - to the chemist the melanocyte may be palate of complex indole-quinones which challenge the very limits of quantitative analysis techniques - to the biochemist the regulation of tyrosinase may be a complex kinetic problem involving some uncalled for and complex hormones - the developmental and cell biologists will admire the apparent range of behaviour and roles of this energetic little cell - the immunologist will ask personal questions of the melanocyte concerning its relationship with T lymphocytes and macrophages - the oncologist, meanwhile, may view the transformed melanocyte with considerable respect and horror.

In the format of this meeting (for which the organisers should be warmly congratulated) we are positively discouraged from taking home, our own family snapshots of the melanocyte - what was particularly exciting about this meeting was some of the links being made between these previously disparate views of this cell.

There are still an embarrassingly large number of questions you can ask about the melanocyte most of which for me personally can be summed up under the two big questions - "why do we have melanin at all?" and "is alpha MSH important in man?" (I think all the other questions hang from these).

In a meeting of 51 oral presentations and 48 posters, it is possible to weave together some of the well established data with some of the newer findings to present a story of the melanocyte occupying a stress/defence role in the skin (not a new idea) but also to begin to see, at this meeting, how it relates to an overall stress management strategy for mammals. With a total disregard for the programme I am going to begin with an excellent presentation by Vaudry detailing how the expression of the propiomelanocortin (POMC) gene in the pituitary is under complex neuro-endocrine control. Working on frog pars intemedia he reported that the processing of POMC and the release of αMSH is under multifunctional control by neuronal and peptidergic factors. In particular, he described a 36

amino acid peptide, melanostatin which belongs to a highly conserved family of peptides of which NPY (found in high abundance in vitiligo) is the most well known. Melanostatin can completely block the release of α-MSH. The intracellular mechanisms of its action were discussed and this talk was a very timely reminder that neuroendocrine factors affect the expression of the POMC gene, processing of POMC proteins and the release of αMSH in a coordinate manner.

Is αMSH important in man? An exciting shaft of light has broken through on this question. Previous studies in mice have shown that mutations in the MSH receptor (MCIR) gene affects the synthesis of eumelanin or phaeomelanin resulting in coat colour changes in mice. Valverde et al., reported at this meeting that variations in the MCIR gene were found in 21 out of 30 red haired individuals who tanned poorly but in none out of 30 dark haired individuals who tanned well. Individuals with red hair have a predominance of phaeomelanin in hair and skin and are well known for their failure to tan well and for their susceptibility to melanoma. (This oral presentation received the award of the Golden Melanocyte). The significance of this work is that it restores the status of the MSH receptor (and of MSH) to an important control point in the regulation of skin pigmentation in man as well as in mice.

Are melanocytes entirely dependent on delivery of MSH from the pituitary? For a number of years there has been considerable debate on whether malignant melanocytes can produce their own MSH- a presentation by Loir et al., confirmed the presence of the full-lenght POMC transcripts in 8 human and mouse melanoma cell lines. αMSH cell content was detectable in 5 out of these 8 lines while the αMSH receptor was present in 6. The authors suggest that taken together this data strongly supports an auto-paracrine MSH/MSH-receptor loop active within the malignant melanocyte.

Are there other factors which control the response to MSH? - A protein encoded by the agouti locus in mice has been found to antagonise the ability of MSH to stimulate melanogenesis in cultured cells. However, the mechanism of the agouti protein action is not clear. Several presentations addressed this point (Sakai et al., Hunt & Thody and Siegrist & Eberle). The protein appears to be able to inhibit melanogenesis both independent of any actions on the MSH receptor but also has the ability to induce down regulation of the MSH receptor. Thus, although its mechanism of action does not appear to be dependent on the presence of the MSH receptor, it would clearly influence and down-regulate the ability of MSH to induce pigmentation. A further factor-melanocyte concentrating hormone (Drozdz and Eberle) has also been found to have receptors on melanoma cells. As with the agouti factor, the expression of these receptors is not dependent on the simultaneous presence of MSH receptors. This factor causes skin paling in bony fishes and authors pointed out that it has been proposed to function as a stress related neuropeptide.

What is the role of alpha MSH in man? It appears to regulate eumelanin but not phaeomelanin synthesis. Put simply, in response to a pituitary release of αMSH one would expect the ratio of eumelanin to phaeomelanin to increase. Three structurely related enzymes - tyrosinase, TRP1 and TRP-2 - are responsible for eumelanin production via DHI and DHICA metabolytes in mamalian skin and hair and these enzyme activities can be regulated by hormones derived from the POMC peptide. However, there is strong evidence emerging from studies on extracutaneous melanogenesis that eumelanin can be formed by tyrosinase independent routes and there are many different precursors to melanin and many different routes (enzyme dependent and independent) to this synthesis of coloured melanin. Why are there so many different precursors and do they all have biological significance and where does phaeomelanin fit in? In the chemistry/biochemistry of melanins Marco d'Ischia made a very strong case for the biological importance of the **colourless melanins** (such as 5-S-Cysteinyldopa, 5-S-CD) and 5,6- (DHI) rather than for the coloured pigments we see. The latter may be equivalent to the discarded kitchen garbage which indicates that a good meal was prepared and eaten sometime earlier. d'Ischia further proposed a very attractive theory that melanocytes may act as a outpost of the

skin's immune defence system by activating macrophages. He reported that DHI is capable of inhibiting the oxydation of arachidonic acid (and thus blocking leukotriene synthesis). Further DHICA was found to be capable of stimulating nitric oxide production by macrophages. Both actions would be consistent with the role of the melanocyte responding to local skin injury (e.g. inflammation). Nitric oxide was found to simulate melanogenesis in a human melanoma cell line (d'Acquisto and d'Ischia) thus completing the loop in that the macrophage-induced nitric oxide production would stimulate a melanocyte to produce the colourless melanin precursor DHICA which can stimulate nitric oxide production in murine macrophages. The idea proposed was that DHICA serves a protective function in acute and chronic skin inflammation.

What other factors are relevant to the production of the various colourless and coloured melanins? Well, basically oxidative stress as perceived and responded to by the melanocyte. There is now a great volume of work which shows that melanocytes (as with other cells) have a range of strategies for coping with oxidative stress. To over simplify vastly, anything that affects oxidative stress management in the melanocyte will probably affect pigmentation and vice versa. The process of pigmentation will at some stages generate free radicals, at others "mop up" free radicals. An example of this was given in a presentation by Benathan. 5-S-CD levels were correlated with tyrosinase activity in normal and malignant melanocytes and thiolcysteine was found to be a major player in the biosynthesis of 5-S-CD. But before talking further of the role of the melanocyte in coping with oxidative stress in the skin, one of the vexed questions regularly posed by Guiseppe Prota is **what controls the production of phaeomelanins and why do we have them?** For sometime now production of melanins via non-tyrosinase routes has been acknowledged and Rosei et al., reported on a lipoxygenase peroxidation of catecholamines and 5-S-catecholamines to give rise to eumelanin and phaeomelanin pigments. Also when H_2O_2 is high then another oxidative enzyme, zanthine oxidase can also behave as a peroxidase. Several talks confirm that the oxidative status of the cell has a profound influence on tyrosinase versus nono-tyrosinase. Tyrosinase activity has been reported to be inhibited by tetrahydrobiopterins (Wood et al.) when these are in a reduced configuration. In an oxidised form these pterins will not bind or inhibits tyrosinase. thus, put far too simply, there are several enzymes in pigment cells which can process melanin precursors (L-tyrosine or L-dopa or catecholamines); which enzymes are active will depend to a large extent on the oxidative status of the cell which ultimately will determine the range of colourless and pigmented melanin precursors and melanins.

This undoubtedly complex area, nevertheless, seems to be the raison d'etre for the melanocyte and defects in the vitiligo melanocyte and melanoma cell ability to respond to oxidative stress have been studied intensively for a number of years. Major contributions by the groups of Piccardo and Schallreuter and Wood have been made over the years and in this meeting we heard of two approaches to **treating vitiligo** which have arisen from these lines of investigation. Piccardo et al., reported that systemic administration of antioxidants in 112 patients with active vitiligo gave extremely encouraging results in arresting the progression of depigmentation in the majority of patients with some improvement in repigmentation in some patients. An alternative approach of twice daily topical application of a pseudocatalase and extracellular calcium combined with UVB short-term exposure twice a week has been used by Shallreuter and Wood who similary reported very encouraging results in the treatment of vitiligo.

What of relationships between the melanocyte and the immune system? We heard in this meeting how the melanocyte and the macrophage might have an effective partnership in coping with inflammation in normal skin, however, it is apparent that in vitiligo and in melanom, where melanocytes are arguably abnormal, the melanocytes provoke a deservedly hostile response from the immune system. A study from Van den Wijngaard et al., proposed that immune infiltrates can induce melanocyte apoptosis and that this may occur in hypopigmentation (winner of the Silver Melanocyte

for a poster presentation). Excitingly, nitric oxide, which is produced in large amounts during infection and inflammation, has been proposed to contribute to the detachment of melanocytes during the metastases of melanoma cells and possibly to the loss of melanocytes and hypo-pigmentary disorders (Ivanova et al.). Melanocytes containing pigment were less affected by the addition of nitric oxide releasing compounds than unpigmented cells.

Thus it is possible to see a role for the melanocyte emerging as a cell which is activated by αMSH as part of either a central or a local stress response. There may be several functions for the αMSH produced melanins - to respond to the increased production of free radicals by "mopping up" free radicals - to engage the services of the macrophages in helping mop up unwelcomed materials in the skin? - to terminate the local inflammatory response by blocking the synthesis of further leukotrienes. When the melanocyte, possibly through an intrinsic defect in its ability to respond to such oxidative stress, fails in its function, then it in turn appears to become a target for the immune system.

With respect to melanoma a review of new immunotherapeutic approaches to melanoma was given by Knudh. **Treatment of melanoma** remains very difficult and he made the point that several different approaches should be pursued such as, for example, antibodies to cell surface gangliosides and immunomodulatory therapy. Staying with melanoma tumours, TGFß1 expression in human tumours was found to be associated with tumour progression (Maretti) and a very careful study by Vetterlein et al., showed that human melanoma cells can escape from negative growth control by TGFß1. Normally TGFß1 inhibits proliferation of premature cells only, cells becoming insensitive to growth inhibition by TGFß1, at which point TGFß1 stimulates melanogenesis. The relationship between proliferation, tyrosinase activity and melanin content of a range of human melanoma cells of different melanogenic potential was examined, from which the authors were able to conclude that there are at least two routes by which melanoma cells can escape from negative growth regulation by TGF1.

There was also a small volume of work examining how melanocytes, (normal, naevus and melanoma) interact with their extracellular matrix. Tyrosinase activity in normal adult melanocytes was found to be stimulated by a range of ECM proteins (Hedley et al.), but this was only detectable in the absence of strong mitogenic drives in the culture media, and naevus cells were found to adhere and migrate more strongly than normal melanocytes to ECM proteins (Mengeaud). In a comparison of occular choroidal melanocytes and choroidal melanoma attachment to ECM proteins normal and neoplastic cells were found to differ in their substrate preference but both to show a similar dependency on intracellular calcium and calmodulin for attachment to ECM proteins (Wagner et al., Winner of the Bronze Melanocyte for poster presentation).
There was also a study of cell/cell adhesion in which melanoma cell binding to keratinocytes was found to be less than that of melanocyte/keratinocyte binding. E-Cadherin was found to play a major role in melanocyte/keratinocyte binding as antibodies to E-Cadherin reduced melanocyte binding. However, although melanoma cells expressed E-Cadherin, they bound weakly to keratinocytes suggesting some disturbance of the normal E-Cadherin relationship to the keratinocyte in these transformed cells (Nakazawa).

In conclusion, a very stimulating meeting in which one recurrent theme of the melanocyte playing a major role in coping with oxidative stress and, indeed, possibly being a part of the larger stress response (POMC, ACTH, Corticosteroid etc.) seemed to be emerging.

AWARDS

The meeting organisers offered awards to the three best contributions by young researchers:
(see meeting report for details)

1. **The Golden Melanocyte**: Valverde P. et al. (Dept of Dermatology, University of Newcastle Upon Tyne)
2. **The Silver Melanocyte**: van den Wijngaard RMJGJ et al (Depts of Dermatology and Pathology, Academic Medical Center, University of Amsterdam)
3. **The Bronze Melanocyte**: Wagner M. et al. (University Dept of Medicine, Clinical Science Centre, Northern General Hospital, Sheffield)

Note from the Treasurer

As most of our members will know, the treasurers address is now: Professor Dr. Martin G. Peter, Universität Potsdam, Institut für Organische Chemie und Strukturanalytik, Am Neuen Palais 10, D-14469 Potsdam, FAX (Germany-331) 977 1131. It is possible to pay membership fees by credit card (AMEX, VISA, EUROCARD), Eurocheque, or direct transfer to the Account of ESPCR at Deutsche Bank Bonn, bank sorting code 380 700 59, account no. 0494989.
Unfortunately a few problems have been recognized with some of the payments receivedso far for membership fees 1995. Most of them cause additional expenses and considerable loss of time which should better be spent in science. In order to keep administrative costs at a minimum and to avoid an increase of membership fees in the next future, please read the following instructions carefully:

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Prof. Martin G. Peter

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6079	4. ESPCR Bulletin (c)	11235
4045	5. Contribution to Meetings (d)	nil
37840	**TOTAL**	43695
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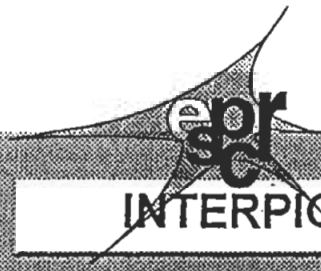

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Animals (35)

Item: C57BL/6J-c2J/c2J B/B
Description: albino black mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-c2J/c2J b/b
Description: albino brown mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-cch/cch B/B
Description: chinchilla black mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-cch/cch b/b
Description: chinchilla brown mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-cp/cp
Description: platinum mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-ca/ca
Description: acromelanic mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-ch/ch
Description: himalayan mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-cem/cem
Description: extreme dilution mottled mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-cm/cm
Description: mottled mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: c6H/cch
Description: albino mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: c14CoS/cch
Description: albino mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J
Description: black mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-pun/pun
Description: pinkeyed unstable mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-slt/slt
Description: slaty mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: fd/fd
Description: faded mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: si/si
Description: silver mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-Miwh/mi
Description: microphthalmia mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-Miwh/misp
Description: microphthalmia mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: mirw/mivit
Description: microphthalmia mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: miws/miws
Description: microphthalmia mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: MiOR/mivit
Description: microphthalmia mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: mice/mivit
Description: microphthalmia mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: mivit/mivit
Description: microphthalmia mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item:
Description: belted mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-WJ2/+
Description: Jay's dominant spotting mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: ls/ls
Description: lethal spotting mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: Ju/FcCtLm-c+c+ Rw/+
Description: Rump white mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-Ay/a
Description: lethal yellow mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-Ay/a b/b
Description: lethal yellow, brown mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-Ay/a mg/mg
Description: lethal yellow, mahogany mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: JU/FcCtLm Ay/a
Description: lethal yellow mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-am/am
Description: nonagouti mottled mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: JU/FcCTLm-am/am
Description: nonagouti mottled mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-e/e
Description: recessive yellow mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Item: C57BL/6J-Eso/Eso
Description: sombre mice
Method: animals
Quantity: upon request
Reference:
Comment: must order in advance - $25 service charge plus shipping costs
Source: Dr. M. Lynn Lamoreux

Biochemicals/Chemicals (17)

Item: catecholamines
Description: labeled compounds, stable isotopes
Method: chemistry
Quantity: upon request
Reference: Liebigs Annalen der chemie, 563-567, 1994
Comment:
Source: Prof. Dr. Martin G. Peter

Item: Quantimel Program
Description: stereological image analysis for quantitation of
Method: melanization
Quantity: electron microscopy
Reference:
Comment:
tool for the estimation of the melanin and
Source: melanosome content, especially for cultured

Item: opiomelanins
Description: soluble melanins from opioid peptides
Method: biochemistry
Quantity:
Reference: Biochim Biophys Acta 1199:123-129, 1994
Comment:
Source: Dr. Maria Anna Rosei

Item: PTCA
Description: standardized solution for HPLC
Method: chemistry
Quantity: 5-10 mg/ml
Reference:
Comment: prepared by degradation of DHICA with alkaline H2O2
Source: Prof. Giuseppe Prota

Item: DOPA melanin
Description: black powder, equilibrated on saturated
Method: CaCl2
Quantity: chemistry
Reference: 10-50 mg
Comment: Gazz Chim Ital 123:241-242, 1993
tyrosinase catalyzed oxidation of DOPA /
Source: pH 7.0, 25 C, 2.5 hr
Prof. Giuseppe Prota

Item: DHICA melanin(s)
Description: black powder
Method: chemistry
Quantity: 5-10 mg
Reference:
Comment: prepared by enzymic oxidation of DHICA
Source: Prof. Giuseppe Prota

Item: DHI melanin(s)
Description: black powder
Method: chemistry
Quantity: 5-10 mg
Reference:
Comment: prepared by enzymic oxidation of DHI
Source: Prof. Giuseppe Prota

Item: 5-S-cysteinylDOPA
Description: white crystalline powder
Method: chemistry
Quantity: 5 mg
Reference: Synth Commun 16:967-971, 1986
Comment: prepared by chemical oxidation of DOPA
Source: Prof. Giuseppe Prota

Item: sepiomelanin
Description: black powder hygroscopic
Method: chemistry
Quantity: 50 mg
Reference:
Comment: prepared by centrifugation of the fresh ink of Sepia, dried
Source: Dr. Anna Palumbo

Item: KUI/1
Description: 4-methoxyphenyl-1alpha(D)-mannopyranosi
Method: de (KUI)
Quantity: biochemistry
Reference: 10 mg
Comment: Melanoma Res 1:273-287, 1991
tyrosinase analogue substrate XXII
Source: Prof. Patrick A. Riley

Item: KUI/2
Description: 4-methoxyphenyl-1b(D)-glucopyranoside
Method: (KUI)
Quantity: biochemistry
Reference: 10 mg
Comment: Melanoma Res 1:273-287, 1991
Source: tyrosinase analogue substrate XXIII
Prof. Patrick A. Riley

Item: 4-propoxyphenol
Description: substituted phenol substrate for tyrosinase
Method: biochemistry
Quantity: 10 mg
Reference: Melanoma Res 1:273-287, 1991
Comment: tyrosinase analogue
Source: Christopher John Cooksey

Item: 4-(2-hydroxyethylthio)phenol
Description: substituted phenol substrate for tyrosinase
Method: biochemistry
Quantity: 10 mg
Reference: Melanoma Res 1:273-287, 1991
Comment: tyrosinase analogue
Source: Christopher John Cooksey

Item: 4-(2-hydroxyethoxy)phenol
Description: substituted phenol substrate for tyrosinase
Method: biochemistry
Quantity: 10 mg
Reference: Melanoma Res 1:273-287, 1991
Comment: tyrosinase analogue
Source: Christopher John Cooksey

Item: 4-isobutoxyphenol
Description: substituted phenol substrate for tyrosinase
Method: biochemistry
Quantity: 10 mg
Reference: Melanoma Res 1:273-287, 1991
Comment: tyrosinase analogue
Source: Christopher John Cooksey

Item: 4(2-bromoethoxy)phenol
Description: substituted phenol substrate for tyrosinase
Method: biochemistry
Quantity: 10 mg
Reference: Melanoma Res 1:273-287, 1991
Comment: tyrosinase analogue
Source: Christopher John Cooksey

Item: 4-(2thioethylthio)phenol
Description: substituted phenol substrate for tyrosinase
Method: biochemistry
Quantity: 10 mg
Reference: Melanoma Res 1:273-287, 1991
Comment: tyrosinase analogue
Source: Christopher John Cooksey

Item: N-acetyl-4-S-cysteaminylphenol
Description: substituted phenol substrate for tyrosinase
Method: biochemistry
Quantity: 5 mg
Reference: Cancer Res 50:3743-3747, 1990
Comment: tyrosinase substrate
Source: Prof. Kowichi Jimbow

Item: melan-a cells
Description: black C57BL/6 murine melanocyte line
Method: cell culture
Quantity: 1 ml
Reference: Int. J. Cancer 39:414-418, 1987
Comment: immortalized from a C57Bl/6 mouse
Source: Dr. Dorothy Bennett

Item: melan-b cells
Description: brown (b/b) murine melanocyte line
Method: cell culture
Quantity: 1 ml
Reference: Development 105:379-385, 1989
Comment: immortalized from a b/b mouse of Falconer's Q-strain
Source: Dr. Dorothy Bennett

Item: melan-c cells
Description: albino (c/c) murine melanocyte line
Method: cell culture
Quantity: 1 ml
Reference: Development 105:379-385, 1989
Comment: immortalized from partially-outbred LAC-MF1 Swiss mice
Source: Dr. Dorothy Bennett

Item: reconstructed epidermis
Description: with melanocytes
Method: cell culture
Quantity:
Reference: Pigment Cell Res (in press), 1995
Comment: allows pharmacological and pathophysiologic studies
Source: Dr. Alain Taieb

Item: melanocyte culture
Description: without pborbol esters and cAMP agonists
Method: cell culture
Quantity:
Reference: Arch Dermatol Res 285:385-392, 1993
Comment: allows physiological assays on melanocytes ex vivo
Source: Dr. Alain Taieb

Item: Irradiated melanoma cells
Description: human cell lines irradiated (240 kV) X-ray
Method: cell culture
Quantity: 108 cells
Reference:
Comment: a system to study increased tyrosine kinase expression
Source: Dr. Ralf U. Peter

Item: Neonatal human melanocytes
Description: black, caucasian or mixed - primary culture
Method: tissue culture
Quantity: 2x106 cells
Reference: J. Invest. Dermatol. 97:395-404, 1991
Comment: will supply only investigators without access to human skin, or who have lost their primary culture lines
Source: Dr. Mary K. Cullen

Dermatology/Clinical (0)

Item: a-PEP1
Description: TRP1 antibody
Method: immunology
Quantity: 1 ml
Reference: J Biol Chem 264:3397-3403, 1989
Comment: recognizes mouse, but not human
Source: Dr. Vincent J Hearing

Item: a-PEP7
Description: tyrosinase antibody
Method: immunology
Quantity: 1 ml
Reference: J Biol Chem 266:1147-1156, 1991
Comment: recognizes mouse and human (weakly)
Source: Dr. Vincent J Hearing

Item: a-PEP8
Description: TRP2 antibody
Method: immunology
Quantity: 1 ml
Reference: EMBO J 11:519-526, 1992
Comment: recognizes mouse and human
Source: Dr. Vincent J Hearing

Item: a-PEP13
Description: silver antibody
Method: immunology
Quantity: 1 ml
Reference: J Biol Chem 269:29198-29205, 1994
Comment: recognizes mouse and human
Source: Dr. Vincent J Hearing

Item: a-PEP5
Description: tyrosinase antibody
Method: immunology
Quantity: 1 ml
Reference: J Biol Chem 266:1147-1156, 1991
Comment: recognizes mouse and human (strongly) if denatured
Source: Dr. Vincent J Hearing

Item: HMSA-1
Description: MoAb to human melanosome specific antigen - 1, mouse
Method: immunology
Quantity: 0.5 ml
Reference: J Invest Dermatol 100:259S-268S, 1993
Comment: these antibodies can also be used for routine paraffin
Source: Prof. Kowichi Jimbow

Item: HMSA-2
Description: MoAb to human melanosome specific antigen - 2, mouse
Method: immunology
Quantity: 0.5 ml
Reference: J Invest Dermatol 100:259S-268S, 1993
Comment: these antibodies can also be used for routine paraffin
Source: Prof. Kowichi Jimbow

Item: HMSA-3
Description: MoAb to human melanosome specific antigen - 3, mouse IgM
Method: immunology
Quantity: 0.5 ml
Reference: J Invest Dermatol 100:259S-268S, 1993
Comment: these antibodies can also be used for routine paraffin
Source: Prof. Kowichi Jimbow

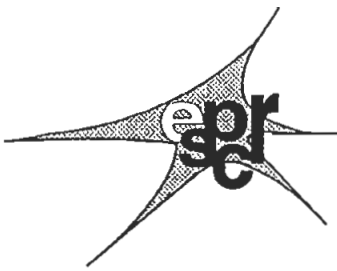
Item: HMSA-4
Description: MoAb to human melanosome specific antigen - 4, mouse IgM
Method: immunology
Quantity: 0.5 ml
Reference: J Invest Dermatol 100:259S-268S, 1993
Comment: these antibodies can also be used for routine paraffin
Source: Prof. Kowichi Jimbow

Item: HMSA-5
Description: MoAb to human melanosome specific antigen - 5, mouse
Method: immunology
Quantity: 0.5 ml
Reference: J Invest Dermatol 100:259S-268S, 1993
Comment: these antibodies can also be used for routine paraffin
Source: Prof. Kowichi Jimbow

Item: HMSA-7
Description: MoAb to human melanosome specific antigen - 7, mouse
Method: immunology
Quantity: 0.5 ml
Reference: Melanoma Res 3:331-335, 1993
Comment: these antibodies can also be used for routine paraffin
Source: Prof. Kowichi Jimbow

Molecular Biology (0)

Other (0)



NEWS FROM THE PASPCR

Kindly provided by Dr V. Hearing

Meeting Report:

by Dr Helene Hill

Annual Meeting - American Society for Photobiology June 17-22, Washington DC

The ASP held its annual meeting in Washington, DC on June 17-22, 1995 at the Hyatt Regency Capitol Hill Hotel. The weather was spectacular and we could sense the nation's heart beat as the days passed. Members of the press, legislators and others with a potential interest were invited to attend a pre-meeting workshop entitled **What is Photobiology?** organized by Frank Gasparro and held on Saturday, June 17. The session was well-attended in spite of weekend lure of the out-of-doors for Washington weekday shut-ins. Even veteran photoscientists had something to gain from this very stimulating session beamed at intelligent and educated laypersons. The workshop's success is reflected in the recent editorial in the ***Journal of the American Medical Association*** (August 9, 1995) entitled **New Light on Skin Cancer Mechanisms** by Charles Marwick. The article is summarized on our Web page which we invite all to visit
(http://www.kumc.edu/ASP/pol_v01.htm).

Nik Kollias, well-known to the pigment cell world, organized a short course on **Photodermatology** along with Rox Anderson. This is a popular annual event which this year provided a critical update on the clinical status of photodynamic therapy in a number of skin conditions.

For us early risers (ugh) there was **Photobiology School** almost every morning at 8:00 AM. Topics covered included Carbenes and Nitrenes as Reagents for Photoaffinity Labeling Experiments by Matthew Platz; Exclusion Studies: a Useful Technique for Assessing the Impact of Solar UV Radiation by Donald Krizek; FDA Approval by David Dolphin and The Possible Biological Effects of Electromagnetic Fields: A Review of Data and Concepts by Jerry Williams.

Division meetings were held on the one morning without a school. The Society has subdivided itself into 5 sub-groups. These are 1.) Photochemistry, Photophysics and Phototechnology; 2.) Photosensory Biology; 3.) Photosynthesis and Photoconversion; 4.) Photomedicine; and 5.) Environmental Photobiology and UVR Effects. Each annual meeting is designed to have symposia, lectures, paper sessions, etc. that will be of interest to each division. Perspectives Lectures focus on each of the 5 divisions and are presented by eminent researchers in each field. Papers in our journal, Photochemistry and Photobiology, are grouped by Division. Pigment cell biologists who would like to join the ASP should have no trouble finding a suitable niche.

One of the most fascinating Symposia, entitled **The Effects of UV-B Light on Natural Ecosystems**, was organized by David Mitchell. The session dealt with such varied topics as photodamage in marine bacterioplankton, DNA damage in plants reared outdoors compared to indoors, the correlation of low photolyase with the decline of amphibian species and the genetic analysis of UVB-induced melanomas in Xiphophorine fish. Two interesting sessions were devoted to the **Biomedical Effects of Ozone Loss** and were organized by Thomas Coohill. Topics varied from measurement of UVB, immune suppression by UVB and assessment of sunscreens to consideration of the effect of increased UVB on phytoplankton. It is clear that there is much still to be learned in this important area.

Of particular interest to pigment cell researchers was the Symposium organized by Nik Kollias

and Arthur Sober on **UV-Induced Cutaneous Malignant Melanoma**. Topics covered included epidemiology by Arthur Sober from whom we learned that about 2/3rds of melanomas worldwide are due to sunlight; hereditary melanoma by Ken Kraemer who demonstrated that lymphoblastoid cell lines from patients with familial malignant melanoma show abnormally high sensitivity to UVB mutagenesis; UV-induced melanomas in marsupials by Ron Ley who showed that the type of dietary fat can influence UV induction of melanoma; wavelength dependence of melanomas in fish by Dick Setlow who warned that conventional sunscreens by decreasing erythema with its action spectrum maximum in the UVB may actually lead to an increase in melanoma due to the disproportionate amount of UVA in sunlight and the enhanced sensitivity of melanomas to longer wave lengths. The final talk was by Meenhard Herlyn who is well-known to the PASPCR and described a model for the study of UV transformation of human melanocytes.

Two ASP members were honored at the meeting. Jim Cleaver received the ASP Award and delivered a lecture on **Mending Human Genes**. Jim, as most already know, discovered the repair defect in xeroderma pigmentosum and has continued to do seminal work in this field ever since. The New Investigator Award went to Thomas Akmar whose award lecture was about the **Photoactive Mechanism of Rhodopsin**.

Of special interest to women and minorities was the Forum which met at noon on Monday, June 19. While all ASP members are invited, the Forum is a gathering where women and minorities can discuss their problems, share experiences and meet and get to know each other. This past year we have produced a register which we hope to circulate to interested parties such as potential employers, organizers of study sections, meetings, review groups, etc. We hope in this manner to get more women and minorities into leadership roles in the Society and in the outside world, as well. At our next annual meeting, we hope to sponsor an eminent female or minority speaker who will not only present good science but will also spend some time talking about the road she/he traveled to arrive where she/he is today. Many young women and minorities feel shy and lonely at national meetings. We hope next year to have a gathering place for people who don t know many others to meet to go to lunch or dinner together. There will, of course, be no restrictions on who participates (i.e. men and majorities are also welcome). This should be especially helpful to students and post-docs.

Next year, the Society will meet in Atlanta, GA on June 15 - 19, 1996. Information about the meeting can be found on our Web page or may be obtained by calling, writing, or faxing to the Secretariat: Dr. Sherwood M. Reichard, 1021 15th Street, Suite 9, Augusta, GA 30901. Tel: 706-722-7511; fax: 706-721-3048. Zalfa Abdel-Malek and I are organizing a Symposium on Melanin Photobiology that will be co-sponsored by the ASP and the PASPCR. It will focus on photoprotection versus photosensitization. If anyone would like to suggest relevant topics and/or speakers (self-nomination is allowed) please let one of us know. On that same subject, I am organizing a Symposium-in-Print to appear in **Photochemistry and Photobiology** some time next year. If anyone would be interested in submitting a manuscript to me, please either do so or let me know of your intent. I would like to have all of the manuscripts in by the end of the year.

Members in the News:

- **Aaron Lerner** was awarded the PASPCR Career Achievement Award for 1996; it was presented to him during the PASPCR Annual Meeting held in Kansas City.
- **Maher Haddad** received a Young Investigator Award at the PASPCR Annual Meeting in Kansas City.
- **William Oetting** received a Young Investigator Award at the PASPCR Annual Meeting in Kansas City.
- **Scott Wildenberg** received a Young Investigator Award at the PASPCR Annual meeting in Kansas City.

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