mediators, including cytokines, prostaglandins and urocanic acid, apparently contribute to immunosuppression [1]. The most important target cells in UVB-induced immunomodulation appear to be epidermal Langerhans cells and keratinocytes. Much of this knowledge has been generated by studying the UVB-induced alterations in the induction of contact hypersensitivity reactions in animal models. However, an increasing number of investigations, both *in vitro* and *in vivo*, are now performed in the human system as well [5, 6]. Recently, several studies have examined the molecular mechanisms underlying photoimmunological processes. These studies indicate that DNA is the major chromophore in UVB-induced immunomodulation, although other molecules such as urocanic acid may also be of some importance [7, 8]. Further studies to define the exact nature of the DNA lesion relevant for immunosuppression and the signal transducing proteins capable of recognising DNA damage are required in order to fill the gap between the known photobiological events and their immunological consequences. A novel and highly important aspect of photoimmunology is the study of immunogenetics of UV-induced immunomodulation [9]. In this regard it was of great interest to learn that individuals which are susceptible to UVB-induced immunosuppression, as was assessed by their capacity to develop contact hypersensitivity to dinitrochlorobenzene, apparently have a higher risk of developing skin cancer than patients who are relatively resistant to UVB-induced immunosuppression [10]. These studies indicate that susceptibility to UVB-induced immunosuppression may represent a risk factor for the development of skin cancer and emphasise the need for future studies to examine which genetic factors determine the UVB-susceptible status in humans.

It should be noted that wavelengths different from UVB light are also capable of exerting immunomodulatory effects. Accordingly, UVA (320–400 nm) irradiation, in combination with the photosensitising compound 8-methoxypsoralen (PUVA), is currently widely used to treat patients with psoriasis and cutaneous T-cell lymphomas. The fact that PUVA, similar to UVB, is capable of suppressing cell-mediated immune responses may be of relevance to the recent observation that long-term PUVA treatment is associated with an increased risk of developing certain types of skin cancer [11, 12]. Irradiation with high doses of UVA1 light (340–400 nm) is a novel phototherapeutic modality, which may be effectively used to treat patients with acute atopic dermatitis [13]. Although it is currently not known whether high dose UVA1 therapy may affect skin carcinogenesis, there is no doubt that high dose UVA1 irradiation has potent immunomodulatory properties, which clearly differ from those associated with UVB irradiation [13, 14].

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IV. Photoprotection

A.R. Young

MOST RESEARCH and discussion of photoprotection of normal skin has focused on sunscreens which are generally formulated and assessed on their ability to prevent 24-h erythema. Modern sunscreens which contain UVB (280–315 nm) as well as UVA (315–400 nm) chemical filters plus physical UVR scattering pigments such as micronised titanium dioxide are highly effective in this respect. More recently there has been interest in the use of particulate melanins as scattering pigments in sunscreens.

Increasingly, the role of sunscreens in preventing the long-term effects of solar exposure is being discussed and promoted. As such, there is generally a (naive) tendency to assume that because sunscreens afford protection from the acute effects of UVR they will *de facto* afford protection against the long-term effects such as skin cancer and photoageing. Animal data are sometimes cited in support of this assumption. However, such data ignore any effects that sunscreen use might have on behaviour; sunscreen and non-sunscreen treated groups of animals are usually exposed for the same period of time. Animal

studies have shown a failure of time–dose reciprocity for skin cancer. Thus a given daily dose is more carcinogenic if obtained over a protracted exposure time [1]. It seems reasonable to assume that many people may use sunscreens to enable them to increase their exposure time. Thus a minimal erythema dose (MED) (or multiple of such) obtained over 5 h with a sunscreen with a sun protection factor (SPF) of 10 may be more carcinogenic than the same dose obtained during 30 min without a sunscreen.

UVR-induced immunosuppression is widely accepted as an important factor in mouse skin photocarcinogenesis. The significance of such immunosuppression in humans is not known but it is suspected that it may play a role. There have been a few recent publications which have reported the failure of high SPF sunscreens to immunoprotect in both mouse and human skin [2, 3]. This is clearly a potentially dangerous situation.

The reality is that we have few data on the role of sunscreens preventing skin cancer; however, there has been a very recent encouraging report that sunscreen use may prevent solar keratoses which are risk factors for skin cancer [4].

As indicated in the opening paragraph, discussion on photoprotection has been largely focused on sunscreen protection of one acute endpoint. It is, however, important to take a much broader view of photoprotection as summarised in Table 1, especially when considering long-term effects.

For example, genetic factors are clearly important. Skin phototypes I and II are most susceptible to skin cancer. Recent data have shown that solar stimulating radiation (SSR)-induced pigment in skin types I and II (but not in skin types III and IV) fail to protect against SSR-induced epidermal DNA damage [5]. It has also been shown that constitutive pigmentation is not immunoprotective [6]. Virtually nothing is known about any differences in DNA repair capacities in different skin types. It may be possible to enhance DNA repair capacity by the topical application of exogenous repair enzymes [7–9] which could be included in sunscreen preparation.

A tan is widely regarded as indicator of UVR-induced skin damage but a recent epidemiological study has suggested that in some cases tanning may protect against malignant melanoma [10].

A recent concept is photochemoprotection. Human studies have shown that a tan induced by a 5-methoxypsoralen (5-MOP) containing sunscreen plus SSR afforded superior photoprotection (against DNA damage by a subsequent challenge dose of SSR) than a comparable tan induced by SSR alone. After treatment with the 5-MOP sunscreen plus SSR, skin types I and II responded more like skin types III and IV after treatment with SSR alone. Thus, 5-MOP appeared to enhance endogenous photoprotection [5]. Although the use of a psoralen for this purpose may be questioned, the benefits of such use may outweigh any risks. However, the principle of persistent enhanced photoprotection has been demonstrated and should trigger research into other methods of inducing improved photoprotection.

Considerable progress has been made on the construction of an action spectrum for non-melanoma skin cancer in the hairless mammalian albino mouse [11] but no such data are available for malignant melanoma. Clearly, such information is vital for the development of photoprotection strategies against malignant melanoma. However, a recent study in fish has shown that UVA is very effective at melanoma induction [12].

Research goals for long-term photoprotection are outlined below.

Table 1. *Aspects of photoprotection*

	Constitutive	Facultative
Genetic	1. Skin colour White Brown, black 2. DNA repair capacity 3. Immunocompetence	Skin phototype (capacity to tan) I, II, III, IV, V, VI
Morphological		Thickening of stratum corneum
Physical		Clothing (hats, shirts, parasols)
Behavioural		Sun avoidance during peak UVB irradiance
Topical Agents		Chemical screens and pigments in various formulations
Photochemoprotection		Psoralen photochemotherapy 1. Topical 5-MOP containing sunscreens 2. Oral PUVA

PUVA, psoralen + UVA radiation.

RESEARCH GOALS

1. Methods of assessing the long-term benefits of sunscreen use.
2. Methods of assessing the effect of sunscreen use on human behaviour.
3. A better understanding of the role of melanin (and types of melanin) and its precursors, and stratum corneum thickening in acute and long-term photoprotection.
4. Improved quantitative and qualitative human action spectra for melanogenesis and knowledge of its protective properties in different wavebands.
5. Knowledge of DNA repair capacity in different epidermal cells and skin types.
6. An understanding of the role of UV-induced immunosuppression in human skin cancer.
7. Development of immunoprotective sunscreens.
8. Development and assessment of agents (topical and systemic) that improve endogenous photoprotection.
9. Development of mammalian models for malignant melanoma so that action spectrum can be determined.

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V. Cutaneous Melanoma: Genetics and Molecular Biology

M. Pierotti

THE PURPOSE of genetic analysis of malignant melanoma is to identify genes involved in the transformation of melanocytes and melanoma tumour cell progression. Three basic approaches have been used to achieve this aim:

(a) Genetic linkage analysis on familial melanoma to identify the chromosomal location of genes which predispose individuals to melanoma.
(b) Cytogenetic analysis of tumour cells to identify frequently rearranged regions of the genome, where genes relevant to onset and/or progression of melanoma cells are located.
(c) Molecular analysis of melanomas to identify mutated oncogenes or tumour suppressor genes playing crucial roles in melanoma development.

A brief summary of the present state of the art will follow for all the three above-reported approaches.

(a) To date, the results of the studies of familial linkage analysis to identify patients who are at increased risk of developing melanoma are controversial. Bales *et al.* [1] reported that the gene for hereditary dysplastic nevus syndrome (HDNS) was on the distal part of the short arm of chromosome 1 (1p36). However, van Haeringen *et al.* [2] performed linkage studies in six large Dutch families with HDNS and did not find evidence of linkage between the putative loci for HDNS and chromosome 1p. The latter conclusion was also supported by a recent analysis of Lynch *et al.* [3].
(b) Although non-random chromosomal rearrangements of chromosomes 1, 6 and 7 have been frequently reported in melanoma, consistent changes have also been detected for chromosomes 2, 3, 4, 10 and 11, and other genetic loci have been found to be affected in this tumour (for review see [4]). Interestingly, Lynch *et al.* [5] have recently completed cytogenetic studies with two kindreds affected by familial melanoma and have found evidence of chromosome instability that is dominantly inherited. Clonal cytogenetic abnormalities were also demonstrated in the skin and naevi of affected patients. The breakage abnormalities tended to involve chromosomes 14, 3, 1, 6, 11 and 22 (in order of decreasing frequency) [5]. Correlation of these cytogenetics results with linkage data may point to possible loci or frequently involved chromosomes containing a gene (or genes) responsible for FAMMM syndrome.
(c) Oncogenes and growth factors. Early analysis by transfection of NIH/3T3 cells indicated the presence of the activated *ras* gene family in approximately 10% of the examined melanomas [6]. In addition, infection of melanocytes with retrovirus containing mutated *ras* genes resulted in a series of transformation-related changes [7], including abnormalities of chromosomes 6 (Albino A, Sozzi G, personal communication). Consequently, although it is now evident that activated *ras* genes are capable of conferring many of the characteristics of tumour progression on virus infected melanocytes, the low frequency of *ras* activation in melanoma *in vivo* suggests that alternative pathways from normal to transformed melanocytes still account for most human melanomas. In this context, a constitutive expression of the basic fibroblast growth factor (bFGF) gene has been reported in metastatic melanoma cell lines that are able to proliferate in the absence of added growth factor [8]. Although bFGF is not produced by normal melanocytes, the relevance of this finding waits to be assessed. Other oncogenes have been implicated in melanoma, mainly by their chromosomal localisation coincindent with recurrent abnormalities such as *c-myb* on chromosome 6q22 or EGF-R on chromosome 7 p12–p13. However, no firm association of these oncogenes with melanoma has ever been made. A gene which predisposes fish to melanoma and shows a high degree of homology to EGF-R has been identified in Xiphophorus [9]. This gene (Tu) represents a novel gene involved in the development of melanoma at least in that animal model.

Finally, recent indirect evidence points at *ret*, a tyrosine kinase receptor gene, as a gene potentially altered in melanoma. In fact, transgenic mice carrying the mouse metallothionein *ret* fusion gene were found to develop a