

**GENETIC MECHANISMS INVOLVING ULTRAVIOLET LIGHT IN THE DEVELOPMENT OF CUTANEOUS
MALIGNANT MELANOMA (MAUVE)**

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Section III: Schematic Description of the Project

Overall objectives of the Project: To be able to anticipate the magnitude of the risk associated with increased human exposure to sunlight, and to produce effective guidelines for preventing the harmful effects of ultraviolet (UV) radiation, a great deal more by way of hard scientific information is needed about the precise nature of the molecular genetic alterations involved in the development of the most aggressive form of skin cancer, cutaneous malignant melanoma (CMM). The primary objective of this project was the identification of key target genes and pathways involved melanoma development and increased understanding of how changes in their function contributes to formation of the cancer. These have provided a basis for molecular epidemiological studies aimed at firmly establishing a link between CMM and specific biological effects of sunlight.

Experimental approach and working method: The project involved a number of powerful, newly established 'in house' techniques/systems to achieve the above goals, eg functional methods for identifying, accurately mapping and isolating novel genes damaged by sunlight in melanoma formation; a new sensitive approach for the detection of UV-specific genetic damage paraffin-embedded melanoma specimens from the clinic; a well-characterized human model for studying skin cancer using cultured cells; and development of a hairless mouse model responsive to the induction of melanocytic lesions (and thus enabling its mechanisms to be studied) enabling the importance of various components of sunlight to be established.

Achievements and results: Major advances were made towards the identification of genetic mechanisms important in human melanoma development. Four novel melanoma suppressor gene candidates were identified using functional monochromosome transfer methods, and two of these loci mapped to specific regions of chromosomes 1 and 9. The role of reactive oxygen species in the spread of melanoma was established by experiment, and model systems for studying these

processes established. Direct evidence was obtained that damage to a single tumour suppressor gene, known as *p16*, plays a key role in melanoma formation. The importance of this change in cell immortalization, together with activation of the 'immortality enzyme' telomerase, was clearly defined. A model system for inducing malignant transformation of human skin cells by UV-A and high temperature, mimicking sunburn, was developed, and results generated that underscored the importance of factors other than UV-B (heat and UV-A) associated with sun exposure in cancer induction. With both UV-A and heat-induced transformation, a specific amplification change to chromosome-11 (11q13) was associated with the acquisition of malignancy. One amplified gene in this region, encoding the cell cycle regulator cyclin D1, was strongly associated with the process of malignant transformation. Substantive advances were made towards the establishment of mouse models for: (i) defining the precise molecular mechanisms leading to the appearance of melanocytic lesions after exposure to ultraviolet light of various wavelengths, (ii) for determining the ways in which our cells' own mechanisms for repairing damage to DNA provide effective protection against this particularly lethal form of malignant skin cancer, and (iii) for testing the efficacy of future new anti-melanoma drugs.