IMIG

International Mesothelioma Interest Group

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MESSAGE FROM THE PRESIDENT

It is a great privilege for me to have been elected President of IMIG for the period 1995-1997. IMIG has remarkably grown since its creation in Paris in September 1991. Credit should be given to my two predecessors as Presidents of IMIG, Marie-Claude Jaurand and Bruce Robinson, as well as to all the members of the Executive Committee. IMIG has truly become an international forum of outstanding scientists of different background and expertise, covering all the basic research and clinical aspects of mesothelioma.

Because of the wide range of scientific issues addressed by IMIG, its scope goes well beyond mesothelioma and extends to many key topics including, to name a few of them, epidemiology, molecular biology, carcinogenesis, pathology, oncology, experimental therapeutics. The summary of the last IMIG meeting in 1995 included in this newsletter by Marjan Versnel, who patiently collected all the data for it, is by itself proof of this remarkable variety of contributions made by many outstanding worldwide investigators.

Our task is now to prepare the next IMIG meeting which will take place in the United States in 1997. After many discussions with members of the Executive Committee, we have decided to hold the next meeting from May 13 to 15, 1997 in Philadelphia, where our colleagues at the University of Pennsylvania are conducting a trial of gene therapy of mesothelioma and have accepted to host the meeting. Also this appears to be an easily accessible location, and the dates do not compete with other major medical conventions.

Looking forward to an exciting meeting and hoping to see you all next year,

A. Philippe Chahinian, M.D.

Report of 3rd International Mesothelioma Interest Group meeting Paris, France, September 1995

Biology of mesothelioma

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The conference was started by Balmain (Glasgow, United Kingdom), who reviewed the studies on carcinogenesis and the role of tumour suppressor genes in a mouse model for skin carcinomas. In a mouse strain extremely resistant to tumour induction, markers to resistance for papilloma development were identified and expression of genes involved in the initiation, promotion and progression of the tumour was analyzed.

Gerwin (Bethesda, USA) addressed the role of tumour suppressor genes in malignant mesothelioma. Several studies on p53 and Rb revealed that these genes are infrequently involved in malignant mesothelioma. The

MDM2 gene, encoding a gene product that stabilizes and inactivates p53, was found to be normally expressed at the mRNA and protein level. The $p16^{INK4}$ gene, encodes a CDK4 inhibitor. Inactivation or deletion of $p16^{INK4}$ will block Rb product mediated pathway of cell cycle control. In the majority of malignant mesothelioma cell lines *p16* was found to be homozygously deleted. Normal mesothelial cell lines and T-antigen immortalized human mesothelial cell lines were found to express $p16^{INK4}$ mRNA and protein. Transfection of p16 into a malignant mesothelioma cell line significantly decreased the colony formation. *In vivo* $p16^{INK4}$ was found to be lost in 70% of the malignant mesotheliomas, while in colon, lung and ovarian tumours no deletions were observed. These observations suggest that loss of function of $p16^{INK4}$ can play a role in the pathogenesis of malignant mesothelioma.

Björkqvist (Helsinki, Finland) showed results of fluorescent Comparative Genomic Hybridization (CGH) applied to malignant mesothelioma specimen and cell lines. Using CGH loss and gain of DNA can be detected. However, no balanced chromosomal aberrations, small mutations or changes in peri-centrometic and heterochromatic regions can be detected. The advantage of CGH is that only DNA is required and compared to cytogenetic techniques and no culturing is needed. In malignant mesothelioma tumour samples the changes detected were gain of chromosome 1q, loss of 9p pand 14q.

Versnel (Rotterdam, the Netherlands) reviewed the studies on PDGF (platelet-derived growth factor) in malignant mesothelioma. Several groups have found elevated PDGF-BB expression in human and mouse malignant mesothelioma cell lines compared to normal mesothelial cells. Malignant mesothelioma cell lines were found to express PDGF-β-receptors, while normal mesothelial cells predominantly express PDGF α-receptors. *In vivo* malignant mesothelioma cells were found to express PDGF and the PDGF β-receptor, whereas the α-receptor was occasionally found.
Studies on the regulation of PDGF chain and receptor expression revealed that differences of the PGDF A- and B-chain and the β-receptor are determined at the transcriptional level. Using various methods two regions (-9.9 kb and bp -64/-61) were identified as relevant for the elevated PDGF B-chain expression in malignant mesothelioma cell lines. Future studies will be directed towards identification of the transcription factor(s) for PDGF B-chain expression and interference in the possible PDGF driven autocrine loop.

Mossman (Burlington, USA) studied rat pleural mesothelial cells (RPM) exposed to asbestos and erionite. In these exposed cultures induction of c-fos and c-jun mRNA was observed. Analysis of the signalling pathways and transcription factors involved in the asbestos induced c-fos and c-jun expression revealed that the Mitogen-Activated Protein Kinase (MAPK) and NF-κB pathways are both activated. Upon asbestos exposure induction of PKCα was observed. Suramin, a polyanionic compound that inhibits the interaction between growth factors and their receptors, was found to downregulate this asbestos induced PKCα. Subsequently, it was demonstrated that asbestos exposure induces phosphorylation of the Epidermal Growth Factor-receptor. These studies indicate that asbestos might interact with the EGF receptor.

Jaurand (Créteil, France) studied the early changes in RPM upon asbestos exposure. Upon asbestos exposure oxygen derivatives, as suggested by experiments with anti-oxidants and by the observed poly (ADP) ribose polymerase activation, lead to DNA damage. DNA-damaged cells can be eliminated by apoptosis. *In vitro* asbestos was found to induce apoptosis in RPMC as detected by DNA fragmentation analysis. However, *in situ* only 5% of the RPMC are apoptotic after asbestos exposure and no evident induction of p53 was detected by immunocytochemistry. These results indicate that asbestos exposed RPMC follow a DNA repair pathway.

Immunology and inflammation in mesothelioma

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McCluskey (Aidelaide, Australia) gave an introductionary lecture on "Immune recognition of cellular antigens - implications for tumour immunity". In summary, tumour cells can evade T cell surveillance by (1) defective antigen presentation, (2) secretion of suppressive factors like TGF-β and (3) secretion of regulatory cytokines e.g. switch from Th1 fenotype to a Th2 phenotype.

Broaddus (San Francisco, USA) postulated that pleural inflammation precedes malignant transformation. Early events observed upon *in vivo* asbestos exposure are influx of neutrophils and macrophages, cytokine production by macrophages and mesothelial cells and mesothelial hyperplasia. The inflammatory potential of mesothelial cells is evident by their possibility to phagocytose and to produce prostaglandins, oxidants and cytokines. Malignant mesothelioma was thought to share many elements with the inflamed mesothelium and may be considered as unregulated inflammation.

Robinson (Perth, Australia) demonstrated that during tumour progression in a mouse model the cytokine production profile by tumour infiltrating lymphocytes deviated from Th1 to Th2. Th1 cytokines have a cytotoxic antitumour effect and Th2 cytokines are considered to be more tumour protective. A switch from Th1 to Th2 production may cause escape by immune recognition. Changing this immunodeviation towards a Th1 response by the potent Th1 stimulator IL-12 could result in tumour destruction.
Malignant mesothelioma cell lines were found to produce the immunosuppressive molecules TGF-β1 and TGF-β2. In malignant mesothelioma TGF-β was considered as an autocrine growth factor. Antisense TGF-β studies showed *in vitro* a decrease in anchorage - independent growth in soft agar and prolonged survival accompanied by increased expression of tumour-infiltrating T cell markers *in vivo*. Blockade of TGF-β seems to reduce tumour growth and inhibit immunosuppression. Immunotherapy by intralesional IFNα application in malignant mesothelioma patients resulted in partial responses. GM-CSF caused in one out of six treated patients local necrosis indicating that a specific anti-malignant mesothelioma response can be generated. Combination therapy with several cytokines like GM-CSF, IL-2 and IL-12 may be more effective.

Garlepp (Perth, Australia) presented data on the effect of introduction of the costimulatory molecule B7-1 in murine malignant mesothelioma cell lines. Malignant mesothelioma cell lines do not express B7-1. The introduction of B7-1 expression on malignant mesothelioma cells would enhance tumour antigen expression and result in an immune response. Murine malignant mesothelioma cell lines transfected with B7-1 had a delayed growth *in vivo*, but eventually all inoculated cell lines formed tumours. Introduction of expression of allogeneic MHC and B7-1 resulted in a strong decrease in tumour development. These data suggest that B7-1 expression enhanced the immunogenicity but tumour antigen in combination with costimulation are required for effective anti-tumour response. Introduction of IL-2 into tumour cells resulted depending on the cell line used in a decrease in growth rate or a decrease in tumour induction, indicating that activation of NK cells is effective. It was concluded that (1) growth of malignant mesothelioma can be slowed down or prevented, (2) tumour specific cytotoxic T lymphocytes can be generated and (3) malignant mesothelioma cells bear antigens recognizable for autologous T cells.

Mesothelioma pathology

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Kane (Rhode Island, USA) studied several biomarkers of response to asbestos exposure in a mouse model of malignant mesothelioma. Intrapleural asbestos injection resulted in an increase in mesothelial proliferation while PMA rather caused an inflammatory response and little mesothelial cell proliferation. DNA damage was increased in mesothelium of asbestos treated cells as detected by