All of them preserved the phenotypic characteristics of the original tumour (morphology, Ig patern) even after several passages. Drugs which are involved in clinical schedules were screened. The transplantable tumours were highly sensitive to cyclophosphamide and methotrexate, reflecting the results obtained in patients' treatment. Other agents including alpha-inteferon produced no or slight response.

2'-5' OLIGO(A) SYNTHETASE LEVELS AND PROTEIN KINASE IN INTERFERON-SENSITIVE OR -RESISTANT BREAST CANCER CELLS

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The levels of 2'-5'oligo(A) synthetase have been studied in three breast cancer cell lines. The activity of 2'-5' oligo(A) synthetase has been measured, both in control and interferon or interferon inducer-treated cells, by two different assays. The activity of this enzyme is increased 20-fold when T47D cells are treated with human interferon or with interferon inducers. In contrast, MCF-7 and BT-20 cells treated or not with interferon, exhibit low activity of 2'-5' oligo(A) synthetase.

The profiles of protein kinase are presently under further investigation.

MARKERS OF HUMAN MAMMARY GLAND DIFFERENTIATION AND THEIR EXPRESSION IN BREAST TUMOURS

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To relate the tumour phenotype to the framework of normal mammary gland differentiation, we compared phenotypic features of the human resting, pregnant, lactating and regressing breast epithelium with those of more thatn 200 benign and malignant breast lesions. Monoclonal antibodies to cytokeratins No. 19, 18, 8 and 7 to epithelial membrane antigens and secreted molecules were produced and employed in immunohistochemistry combined with 1-D and 2-D gel immunoblotting. The results revealed several distinct sub-populations in normal epithelium pertinent to differentiation stage. The phenotypes of benign lesions mainly resembled the resting or pregnant epithelium, whereas some features of late pregnancy and lactation were observed in carcinomas though lacking the co-ordinate expression seen in normal differentiation. The antibodies also proved to be useful in identification of micrometastases and for the differential diagnoses of some human malignancies.

NEOPLASTIC-GROWTH CHANGES IN NON-HISTONE CHROMATIN PROTEINS

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Two fractions of non-histone chromatin proteins (NHCP1 and NHCP2) isolated by a hydroxyapatite procedure were obtained from nuclei of Kirkman-Robbins hepatoma at the 4th, 7th and 9th day of its growth. Electrophoretic (one- and two-dimensional analyses followed by Coomassie Brilliant Blue and silver staining) and immunological (Western blots) techniques revealed some specific non-histone polypeptides (within MW ranges of 16,000-25,000 and 80,000-85,000 in the NHCP1 as well as 17,000-28,000 and 35,000-42,000 in the NHCP2) observed during neoplasia. The growth of neoplastic tissue is accompanied by increase, decrease (or disappearance) of some non-histone components.

POTENTIATION OF ANTITUMOUR EFFECT OF CYCLOPHOSPHAMIDE BY DL-α -DIFLUOROMETHYLORNITHINE (DFMO)

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Potentiating effect of DL-α-difluoromethylornithine (DFMO) in combination with different cytotoxic agents has been reported in experimental and clinical cancer chemotherapy. In order to clarify the mode of action, normal control and P388 leukaemia-bearing mice were treated with DFMO continuously and/or with a single dose of cyclophosphamide. Effects of singular and combined treatments were monitored by determination of metabolite concentrations in blood, urine, liver and tumour cells with respect to the conversion of ornithine into polyamines and urea cycle. Urinary excretion of natural and acetylated polyamines was measured during tumour growth

and drug administrations. It was concluded that (1) metabolic imbalnce of ornithine was markedly changed by polyamine depletion to leukaemia cells and (2) combined therapy enhanced the cytotoxicity of cyclophosphamide and increased the life span of tumour bearing animals by 200 to 300 per cent.

MITOCHONDRIA AS INTRACELLULAR TARGETS FOR ANTICANCER THERAPY

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The presence and expression of DNA within mitochondria is now well established. In a series of studies with various tumour model systems, it has been shown that inhibition of mitochondrial gene expression leads to cell proliferation arrest and in some cases even to tumour eradication. Tetracyclines, which specifically inhibit mitochondrial protein synthesis exert these effects. We consider depleted energy generation capacity to be the most likely explanation. Also MGBG, an inhibitor of polyamine biosynthesis, preferentially impairs mitochondrial biosynthetic processes. The presence of two genetic systems in all tumour cells raises the question whether or not the mitochondrial system is also a target in other treatments primarily designed to interfere with the nucleocytoplasmic system. For doxorubicin and cytosine-arabinoside, effects on mitochondrial biogenesis and function have been observed and the findings are under further investigation.

HERPES VIRUS SPECIFIED EARLY PROTEINS INDUCE CELLULAR DNA SYNTHESIS IN VIRUS INFECTED CERVICAL CANCER CELLS

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The mode of DNA synthesis in virus infected HSV-2 permissive and non-permissive cervical cancer cells was studied. The flow cytometric detection of BrdU in newly synthesized DNA was achieved using a monoclonal antibody. PFA was used to differentiate between cellular and viral DNA synthesis. In the permissive CaSki cells an exponential increase of both DNA-synthesis and amounts of infectious virus was seen. In the non-permissive C-33A cells, a comparable increase of DNA synthesis was seen 6 hr after infection, but not later. The inhibition of viral DNA synthesis by PFA was able to inhibit the virus induced DNA synthesis in the CaSki but not in the C-33A cells. In the CaSki cells the exponentially increasing DNA synthesis corresponded to the virus replication. In the C-33A cells a transient induction of DNA synthesis was noted. This is likely to represent virus induced cellular DNA synthesis. In the CaSki cells, HSV-specified major DNA-binding protein (ICSP 11/12) was seen in the nucleus, whereas in the C-33A cells the protein was located both in the cytoplasm and the nucleus. Early viral proteins are expressed also in the PFA treated cells and show (ICSP 11/12) affinity to DNA. Whether the early viral proteins mediate the virus induced increase in cellular DNA synthesis in the non-permissive cancer cells has been evaluated.

THE E3/19K PROTEIN OF ADENOVIRUS TYPE 2 BLOCKS CELL SURFACE EXPRESSION OF HLA CLASS ANTIGENS AND INTERFERES WITH THE IMMUNE RESPONSE

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The adenovirus type 2 encoded protein E3/19K binds to human HLA class I antigens. The formation of the HLA-E3/19K complex prevents the HLA antigens from being correctly processed by inhibiting their terminal glycosylation and cell surface expression. This reduced level of antigens influence the cytotoxic T cell response. Also the murine H-2 K^d antigen binds to the viral protein whereas the allelic K^k antigen does not. Hybrid genes between the K^d and K^k alleles were constructed and have allowed us to map the 1 and 2 domains of the class I antigen to be the essential structures involved in the complex formation. Interestingly, these domains are also crucial for T cell recognition.

ALKYLATING AGENT-INDUCED MUTAGENESIS AND ACTIVATION OF THE Ha-ras ONCOGENE

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