# Symposium no. 7: Tumour Drug Delivery

7.025

## ANALYSIS OF RESULTS FROM ANTINEOPLASTIC ACTIVITY PREDICTION BY FORMAL STATISTICAL METHODS

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The substructural analysis approach to quantitative structure-activity relationship (QSAR) investigations was applied for predicting the activity of compounds towards *in vivo* tumor models on the basis of the compounds' structures. Analysis of the results obtained is done with respect to the data used and methods applied. A conception for the future development of the substructural analysis approach to antineoplastic activity prediction is outlined.

7.026

Comparative studies on mouse leukemic bone marrow purging ex vivo.

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For model studies on bone marrow ex vivo purging mouse L1210V and monoclonal antibody MoAb-16, specifically reacting with these leukemic cells have been selected. MoAb-16 with complement, immunotoxin composed of MoAb-16 and A-chain of ricin or MoAb-16 together with antiimmunoglobulin coated magnetizable microspheres were applied in comparative studies on their purging efficiency. To achieve complete elimination of leukemic cells single exposure during 60 min to immunotoxin appeared to be sufficient. Treatment with MoAb-16+C' as well as with MoAb-16 and magnetic microspheres had to be repeated at least twice. None of the treatments applied was toxic to the normal bone marrow stem cells.

7.027

ALTERATIONS OF PHOSPHOLIPID METABOLISM INDUCED BY CYTOKINES IN EXPERIMENTAL TUMOURS

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31P and 1H Magnetic Resonance (MR) studies at 9.4 T allowed detection of early biochemical alterations induced by cytokines (rTNF-α, rTNF-β, rIL-1β) on phosphatidylcholine (PC) metabolism in solid tumours implanted in DBA/2 mice by s.c. injection of Friend erythroleukemia cells (FLC). Early alterations induced by these cytokines on tumour blood vessels (prior to the onset of necrosis) were associated with about 3-fold decreases of glycerophorylcholine (GPC), accumulation of glycerophosphate (GP) and choline, more than ten-fold increase of choline/phosphorylcholine ratio and reductions of ATP levels. These results are interpreted on the basis of reduced activity of choline kinase (ATP-dependent cytosolic enzyme) in combination with activation of GPC phosphodiesterase (EC 3.1.4.2), a microsomal enzyme so far detected and studied only in normal tissues, which catalyses hydrolysis of GPC into choline and GP. Moreover, NMR in vitro studies demonstrated that GPC hydrolysis is also markedly enhanced in FLC lysates, following DMSO-induced erythroid differentiation. These results support the conclusion that modulations of enzymes controlling GPC hydrolysis may contribute to regulate alterations of PC turnover in neoplastic vs. normal cell proliferation; suggest a new, possible biochemical model for understanding metabolic effects induced by cytokines on tumour cells in vivo; propose the possible use of in vivo MRS for monitoring early responses of tumours to cytokines or differentiation inducers. (We thank AIRC for financial support and Mr.M.Giannini for technical assistance).

7.028

## The use of HIDA to improve the therapeutic ratio with trimodality therapy.

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The interaction between cisplatin, heat, radiation and HIDA was studied in vivo using a C3H mouse mammary carcinoma grown in the feet of $CDF_1$ mice. Response was assessed by tumour growth time, or local tumour control. Cisplatin (2-8 mg/kg) and heat (43.5°C/60 min) exerted their greatest tumour growth inhibition when given simultaneously. But at the same time there was a substantial increase in mouse toxicity, such that 18% and 83% of mice died when given heat with respective cisplatin doses of 6 mg/kg and 8 mg/kg. When HIDA (100 mg/kg) was given 150 min before cisplatin administration and heat, no mouse toxicity was seen at 6 mg/kg cisplatin, and only 3% with 8 mg/kg. HIDA did not influence the tumour growth time results. In tumour control studies cisplatin (6 mg/kg) and heat (43.5°C/60 min) were given simultaneously 4 hrs after irradiating. Some 45% of mice died from this treatment, but only 5% when HIDA was added to the protocol. Local tumour control was unaffected by addition of HIDA.

7.029

INCREASE OF DOPA-OXYDASE ACTIVITY OF MUSHROOM TYROSINASE BY SPIN-LABELED TRIAZENES.

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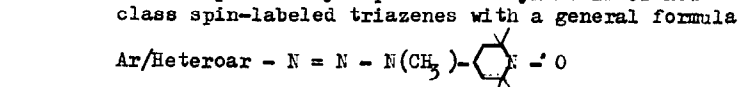
We have previously reported the synthesis of new class spin-labeled triazenes with a general formula



(Z.Raikov, M.Koch, V.Cadgeva, G.Kolar. SEK-Symposium, April 1989, Heidelberg, FRG)
Triazenes with a nitroxyl radical were chosen in this work because of the following reasons; 1)triazenes have been known as an important class of tumorinhibitory agents and some of them are antimelanoma drugs (DTIC); 2)the nitroxyls concentrate mainly in pigment melanomas.It is well-known that the tyrosinase is a key enzyme in the melanin biosyr thesis,which quantity is significant in the pigment melanoma tumors. The results show that all spin-labeled triazenes have increased DOPA-oxydase activity of mushroom tyrosinase what might be due to nitroxyl radical.Increase is dependent on the structure of the compounds.

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7.030

## DEVELOPMENT OF TWO NEW MONOCLONAL ANTIBODIES REACTIVE TO A UNIQUE ANTIGENIC DETERMINANT PRESENT ON HUMAN OVARIAN CANCER CELLS

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Mice were immunized with multiple ovarian cancer cell lines in a sequential manner to amplify the immune response against common antigenic determinants. Spleen cells from the immunized mice were then used to establish hybridomas. After extensive screening, two cell lines were selected on the basis of their selective reactivity to ovarian cancer cells. Monoclonal antibodies OVX1 and OVX2 bound to all 5 ovarian carcinoma cell lines tested and did not bind to normal fibroblast cells. These antibodies recognized a unique antigenic determinant present in ovarian and breast cancer cells. Cross blocking studies showed that the binding of OVX1 and OVX2 is not displaceable by ten other previously described anti-ovarian antibodies including OC125. In immuno-cytochemical studies, OVX1 reacted to a majority of ovarian cancer tissues (17 out of 20) and did not bind to normal ovarian tissues. Preliminary results indicate that OVX1 and OVX2 antibodies are directed to a high molecular weight antigen . These antibodies could be linked to toxin polypeptides to prepare tumor selective cytotoxic conjugates (immunotoxins).