Parallel Symposium No. 7

Tumour Drug Delivery

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PS 7.1

INTRATUMORAL FACTORS INFLUENCING THE ACCESS OF MACROMOLECULES TO TUMOR CELLS. L.M. COBB, MRC Radiobiology Unit, Harwell, Didcot, Oxon., OX11 ORD, UK

While injected macromolecules have fairly unrestricted access to cells in normal tissues this is not so in tumors. A well differentiated carcinoma in the early stages of growth will usually have an adeguate blood supply with free access of antibody to tumor cells (1). With progressive dedifferentiation the tumor cells can form relatively impenetrable "nests". Further dedifferentiation can see the now anaplastic tumor cells only loosely attached one to the other with improved access for injected macromolecules. As the tumor mass expands the intratumoral pressure increases. This can reduce the movement of macromolecules, including antibodies, from the blood vessels into the extravascular space (2). On the other hand, the areas of necrosis that inevitably develop provide "sumps" in which injected antibody, and other macromolecules, can accumulate.

1. Cobb, L.M. Targetting of Drugs, Ed. G. Gregoriadis, Plenum Press, NY, 1990
2. Jain, R.K. J. Natl. Ca. Inst. 81, 570-576, 1989.

PS 7.2

Tumor imaging in human with small radiolabeled hapten dimers and bispecific monoclonal antibodies.

J.M. Le Doussal, M. Delaage and J. Barbet (Immunotech S.A. Marseille, France) and A. Chetanneau and J.F. Chatal (Centre René Gauducheau, Nantes, France).

Bispecific monoclonal antibody fragments (BsfAbs), with binding affinities for a tumor antigen and for a small hapten, are exploited to mediate the binding of small radiolabeled hapten-dimers to tumor cells. Hapten dimers, which exhibit cooperative binding to cell-bound BsfAbs, provide highly specificic and affine vectors with exquisite pharmacokinetic properties (rapid diffusion and clearance).

Imaging, pharmacokinetic and dosimetry results obtained in experimental animal models or in colorectal cancer patients will be presented.

PS 7.3

Tumor targeting with particulate carriers

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Parenterally administered particulate carrier systems have been studied extensively during the past two decades to deliver their contents (drugs) to target sites (drug targeting) or to reduce the delivery to sites where major toxicity occurs (site avoidance delivery). Sustained or controlled release of the drug from the carrier was another reason to utilize particulate systems.
Therapeutically spoken, from these three options the last category has been the most successful up until now.
Many different particulate systems have been developed. They can be categorized as microspheres, microcapsules, nanoparticles, lipoproteins and liposomes. The behaviour of these carrier systems strongly depends on (physico)chemical characteristics as size, surface charge, surface properties ('hydrophilicity') and resistance against degradation.
In this contribution the potential and limitations of particulate carrier systems will be demonstrated by taking liposomes as examples. Their potential to act as a reservoir for sustained drug release, for site avoidance delivery of cytostatics or site specific delivery will be discussed.

PS 7.4

THE c-erbB-2 PROTEIN AS A TARGET FOR DIRECTING CYTOTOXIC AGENTS TO TUMOR CELLS.

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The gp185, c-erbB-2 protein, is a member of the receptor tyrosine kinase family. c-erbB-2 gene amplification and high levels of gp185 have been detected in approximately 30% of primary human breast and ovarian cancer cells. Various reports have shown that patients whose tumors have elevated levels of gp185 have a higher risk of disease recurrence . Its tumor enriched expression and extracellular accessibility make the c-erbB-2 protein a potential target for tumor cell directed therapy. We have prepared monoclonal antibodies (MAb) which specifically recognize the extracellular domain of gp185. These MAbs increase gp185 phosphorylation and inhibit the growth of c-erbB-2 expressing tumor cells, both in tissue culture and in a nude mouse model. The variable domains of several of these MAbs were cloned by reverse transcription of hybridoma cell mRNA and cDNA amplification using the polymerase chain reaction. Fusion genes encoding single chain Fv fragments were made by joining light and heavy chain variable domains with a 15 amino acid linker. The 26kD recombinant single chain Fvs which were expressed and isolated from E.coli, bind to cells expressing gp185 with characteristics similar to those of the original MAbs. The Fv molecule of one of the MAbs, FRP5, was further modified by the addition of enzyme functions to its C-terminal end. A Fv-alkaline phosphatase fusion protein was shown to bind gp185 expressing cells and to retain enzymatic activity. This protein might be useful as a novel diagnostic agent. In addition, we are testing its ability as a prodrug activator. A gene encoding a Fv-exotoxin A fusion protein has also been expressed in E. coli. The Fv-toxin protein has been shown to specifically inhibit the growth of gp185 expressing tumor cells in tissue culture. We are currently testing its effects upon a nude mouse tumor model.