Parallel Symposium No. 11

New Approaches to Cancer Diagnosis and Management

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PS 11.1

MUCINS AS SERUM TUMOR MARKERS IN CARCINOMA PATIENTS
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Polymorphic epithelial mucin is a large glycoprotein on the cell surface of epithelial cells from many epithelia with secretory function, such as the breast. The molecule is highly expressed on virtually all tumors of such epithelia and heavily shed into the circulation of patients with carcinomas. As such it has become an important serum tumor marker and it is now known that levels of the protein in the serum reflects the stage and the progression of the disease.

Scientific synonyms of polymorphic epithelial mucin or PEM include HMFG, NPGP, DCA, MAM-6, Episialin, DU-PAN2 NCRC-11, EMA, SGA, CAM, PAS-0, NCRC-48 and Epitectin. Commercial tests detecting PEM levels are called CA15.3, MCA, BCM, CA549, CAM26, CAM29 and EMCA. The gene is now called PUM-1, as the first in a family of at least 4 genes coding for mucins, all sharing a large number of different tandem repeat structures.

The function of the gene, now under study in transfected cell lines, may be one of protection. It is not inconceivable that expression of PEM on the cell surface interferes with adhesion of carcinoma cells brought about by other surface molecules.

NATURAL IMMUNE RESPONSE TO MUCINS IN CARCINOMA PATIENTS
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We have developed a panel of murine monoclonal antibodies (MAbs) reactive with different epitopes of the tumor-associated mucin TAG12. The glycone-specific MAb 12H12 and the peptide-specific MAb 2E11 were labelled with Europium and used in a sandwich type timeresolved immunoassay to determine TAG12 in sera, effusions and bone marrow aspirations. In parallel the natural immune response to this antigen was analysed. Native TAG12 purified from T47-D mammary carcinoma cells and a 24 amino acid synthetic peptide of the repetitive mucin core peptide were coated in EIA plates and incubated with sera. Human Ig was determined by Delfia with Europium labelled mouse anti-human MAbs. In the group of breast cancer patients with normal TAG12 levels, 35% had significantly elevated IgG titers against this tumor-associated antigen. Presently T-cells from these responders are cultivated and cloned for the analysis of mucin-specific cytotoxic T-cells. Humoral and cellular anti-mucin reactivity offers new possibilities for early tumor detection and therapy.

PS 11.3

Gert Riethmüller: Targeting antibodies to micrometastatic cancer cells

The main emphasis of my presentation will be on the detection of micrometastatic cells from solid tumors. Since antibody therapy directed to solid tumors has thus far been rather disappointing with at best only anectotal reports of therapeutic responses, we reasoned that an appropriate target for monoclonal antibody would be individual cells which have disseminated from their primary tumor but which are not yet protected by a basal membrane. Therefore we have concentrated our effort on the detection of such micrometastatic cells using monoclonal antibodies. As will be demonstrated and also as documented by the accompanying papers the use of monoclonal antibodies against cytokeratin has allowed us to detect with high sensitivity and specificity epithelial cells in the mesenchymal environment of bone marrow. We can demonstrate that these cells are present virtually only in patients with malignant epithelial disorders and that their incidence is correlated to conventional risk factors such as lymph node metastasis and manifest distant metastatsis. The clinical follow-up demonstrates that patients with epithelial micrometastatic cells in the bone marrow have an increased relapse rate of manifest metastases. Additional studies were concerned with the further characterisation of these cells using double staining procedures. It is important to note that a loss of MHC class I antigens was quite frequent on individual disseminated cells. Another point of interest was the expression of the erbB-2 oncogene product.
Longitudinal analyses of cytokeratin positive cells in the bone marrow in individual patients demonstrate that this method is in principle useful for monitoring adjuvant therapies. We have used the method in an randomized adjuvant clinical trial with monoclonal antibodies against the 17-1A epithelial antigen in colorectal cancer. As will be shown, antibodies injected into patients with micrometastases in the bone marrow can label such cells. There will be a short report and an intermediate analysis indicating that there is therapeutic efficacy in an adjuvant trial with the 17-1A antibody. Other antibodies have been developed which are able to destroy individual cells in vivo and in vitro apparently through the activation of human complement.
Overall our opinion is that monoclonal antibodies have a better chance for therapeutic efficacy when applied to minimal residual disease and particularly when the cells are accessable in mesenchymal tissue as individual cells or as microaggregates without an autochtonous vascular system. The exploitation of human complement requires a critical antigen density and the close approximation of Fc regions. Therefore we would propose that selected pairs or triplets of monoclonal antibodies will have potential as therapeutic combinations. Such synergizing antibodies will be demonstrated.

PS 11.4

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RADIOACTIVE LABELED ANTIBODIES FOR IN VIVO DIAGNOSIS OF TUMORDEPOSITS IN OVARIAN CANCER PATIENTS.
Monoclonal-antibody based radioimmunoscintigraphy (RIS) opens prospects for more specific tumor imaging. In 59 patients suspected of having primary or recurrent ovarian cancer the safety and diagnostic accuracy of radioimmunoscintigraphy with OV-TL 3 F(ab')$_2$ labelled with ^{111}Indium has been assessed. Planar images and SPECT were performed between 4 and 96 hours after i.v. injection of 140 MBq of the immunoconjugate, and compared to CT and ultrasonography. Except for a transient rash in two patients, no side effects were noted.
For 42 patients who underwent extensive surgery, a correct diagnosis of tumor presence was made in 86% with RIS, in 67% with CT, and in 63% with ultrasonography. The ratios of tumor to background tissue (as fat, muscle or skin) uptake were in the order of 10. Liver uptake was, however, high. A total of 86 solid tumor localizations was found. The detection sensitivity for these tumor deposits was 60% for RIS, 41% for CT, and 27% for ultrasonography.
Ongoing RIS trials using chimeric antibodies and various other labels will also be discussed.