Localisation and imaging of squamous cell carcinomas with IgG and F(ab)$_2$ monoclonal antibody E48

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Squamous cell carcinoma (SCC) is the most common neoplasm among carcinomas from the head and neck region, lung, cervix and epidermis. Since SCCs are relatively sensitive to radiation therapy, radiolabelled monoclonal antibodies (MAbs) which are able to localise selectively to these tumours show promise for (radio-immuno) therapy. We generated a panel of MAbs to SCC. One of them, designated E48 was demonstrated to exhibit strong reactivity with SCC, while in normal tissues reactivity was only found in bladder and epidermis. The E48 antigen appeared to be a 22 kD antigen associated with desmosomes and the cell surface. E48 IgG and F(ab')$_2$ were used for specific delivery of ^{131}I to SCC xenografts in nude mice. Maximal tumour to blood ratios for IgG and F(ab')$_2$ were 6.4 and 54 respectively, while maximal tumour uptake values were 16.2% and 7.2% id/g respectively. F(ab)$_2$ appeared more suitable than IgG for imaging of xenografts.

Comparative pharmacokinetics and biodistribution of 139H2 Ov-tl3 and OC125 as IgG or F(ab')$_2$ in a human ovarian cancer xenograft model

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Monoclonal antibodies (MAbs) 139H2 and OV-TL3 react with all ovarian cancer subtypes, whereas MAb OC125 reacts with > 80% of the non-mucinous subtypes. The 3 MAbs are of the IgG1 isotype and recognise different antigens. FACs analysis showed strongest, but heterogeneous staining of OVCAR-3 cells by 139H2. Treatment with ^{131}I-139H2 (IgG) of subcutaneous OVCAR-3 xenografts (100–300 mm^3) was very effective in inducing complete tumour regressions. In order to predict the therapeutic efficacy of MAbs OV-TL3 and OC125, we compared the pharmacokinetics and biodistribution of ^{131}I- or ^{125}I-labelled 139H2, OV-TL3 and OC125 [IgG and F(ab')$_2$ fragments] in nude mice bearing subcutaneous OVCAR-3 xenografts. After intravenous injection of a tracer dose of the iodinated MAb, mice were sacrificed at various time intervals and the radioactivity in serum and tissues was determined.

The results we obtained enabled us to make the following conclusions: (1) blood clearance of F(ab')$_2$ was 7 times faster than that of IgG; (2) tumours received 4–6 times less radiation after injection of F(ab')$_2$ fragments as compared to IgG; and (3) highest tumour uptake for IgG as well as F(ab')$_2$ was achieved with MAb OV-TL3.

Pharmacokinetics of internally labelled and iodinated monoclonal antibodies C215 and C242 in the rat and mouse

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C215 and C242 are murine MoAbs (IgG2a and IgG1, respectively) raised against a human colorectal carcinoma cell line CoLo 205. The MoAbs were labelled either internally with ^{75}Se-Met, ^{3}H-amino acids or externally with ^{125}I or ^{131}I and injected intravenously to follow the pharmacokinetics in the rat and mouse. The levels of MoAbs were followed in plasma and in various tissues. The excretion rate in urine and faeces was also studied. The half-lives in mouse were much shorter, 3–4 days with internally labelled MoAbs and 2 days with the iodinated MoAbs, than in rat (15–24 days with internally labelled MoAbs). The activity concentrations of ^{75}Se-MoAbs in tissues were much higher in mouse than in the rat. The two different MoAbs had similar kinetics and biodistribution in plasma and tissues.

The influence of streptavidin on *in vivo* distribution and tumour uptake of ^{99M}TC-biotin

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Radioimmunodetection of tumours with secondary tracers can be performed by use of the biotin–avidin system. We wanted to find out whether streptavidin could influence the biotin distribution *in vivo*. ^{99m}Tc-biotin was injected into healthy Wistar rats or RNU rats with solid HeLa cell tumours. The distribution of ^{99m}Tc-biotin in presence or absence of the streptavidin was investigated. An effect of streptavidin on the kinetics of the biotin clearance was evidenced by dynamic scintigraphic imaging and determined by regions of interest and function curves for the left kidney, the urinary bladder and the tumour. Presence of circulating streptavidin led to a delayed ^{99m}Tc-biotin clearance. Change of the time schedule of streptavidin injection prior to the injection of ^{99m}Tc-biotin greatly influenced the pattern of clearance function curves. The delay of clearance function may be due to the different molecular weights of biotin and biotin-streptavidin aggregates. There was enhanced background radioactivity *in vivo* after interaction of 99mTc-biotin with streptavidin. Therefore the concentration of streptavidin (avidin) in the three-step approach of the biotin–avidin antibody system *in vivo* plays an important part.

Assessment of radiation dose distribution in xenografts

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Following the pioneering work of BW Wessels it became possible to compare radioactivity distribution to dose distribution, the one being assessed by autoradiography, the other by microthermoluminescent dosimeters (TLDs) implanted into nude mouse xenografts. The question can be posed to what extent non-uniformity of radionuclide accumulation will be "levelled out" by the 400 μm range of beta particles. We applied the method to tumours showing qualitatively differing accumulation patterns, i.e. focal (gastric ca., anti-CEA), peripheral (melanoma, anti-gp100) and near-uniform (lymphoma, anti-CD22) accumulation. In parallel, TLD readings were compared to dose estimates obtained by scintigraphy, with a fairly good concordance. When serial 50 μm slices with micro-TLDs *in situ* were followed over distances of 0.5–1 mm, it was observed that fluctuations were dampened down to some extent, but marked variation, often from one slice to the other, was still present, especially in focally accumulation tumours. Our data provides yet another explanation for the limited success of radioimmunotherapy of some tumour types, and emphasises the need for higher energy beta emitters for the therapy of solid tumours.