Biodistribution of radioarsenic labelled vascular targeting anti-PS antibody in small animal prostate and breast cancer tumor models

[1,2]M Jennewein, [3]O Bergner, [2]A Constantinescu , [4]S O'Kelly, [1]S Maus, [5]SM Qaim, [3]PE Thorpe, [2]RP Mason, [1]F Rösch

[1]Institute for Nuclear Chemistry, Johannes Gutenberg-University of Mainz, Fritz Strassmann-Weg 2, 55128 Mainz

[2]Department of Radiology, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

[3]Department of Molecular Genetics, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

[3]Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center, Dallas, TX 75390, USA

[4]Department of Nuclear Engineering, University of Texas at Austin, Pickle Research Campus, Austin, TX 78712, USA

[5]Institute of Nuclear Chemistry, Research Centre Jülich, D-52425 Jülich,

Prostate and breast cancer are the most frequent non-skin cancer among men and women in all developed countries. Antibodies against PS (phosphatidylserine) developed by Thorpe et al. [1,2] have shown a high therapeutic potential as prostate and breast tumor vascular targeting agent. In normal tissue, PS exclusively resides on the cytosolic leaflet of the plasma membrane. Thus, PS normally cannot interact with a vascular antibody. However, in tumors PS becomes externalized and provides a viable target. The agent not only targets various tumors but also induces thromboses and has been shown to induce tumor regression with minimal accompanying toxicity. Therefore, biodistribution studies of this antibodies are of high importance as Vatuximab (ch3G4) is scheduled to enter Phase 1 clinical trials in the near future with application to diverse tumor types.

The biodistribution experiments of [^{74}As]SATA-ch3G4 and [^{77}As]SATA-ch3G4 (synthesis: cf. [3]) were carried out in AT1 Dunning prostate tumor bearing male Copenhagen rats. To obtain tumors, small tumor pieces, excited of a donor animal, were implanted subcutaneously in the right thigh of the rat. Tumors were selected for biodistribution studies when they reached 9-11 mm in diameter. Tumor-bearing rats were injected intravenously via the lateral tail vein with 100 µg of [$^{74 \text{ or } 77}$As]SATA-ch3G4 in 4 ml PBS. At selected times after injection (2,3 and 7 days), the rats were sacrificed by exsanguination and perfusion via cardiac puncture under general anaesthesia. The radioactivity contained in tumor and representative organs was determined in a γ-counter for ^{74}As and a β-scintillation counter for ^{77}As (both Packard) and expressed as a percentage of injected dose per gram of tissue (%IDg^{-1}). [^{77}As]SATA Hu IGg was used as a negative control. All animals had the same weight, the tumors had same age and diameter and the injected dose and mass of AB was equal. As a positive control, the AB was labelled via the standardized IODOGEN-Method with ^{125}I and biodistribution was made after 72 hours.

Results:

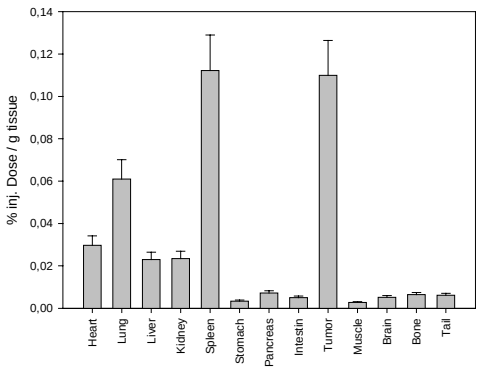

Fig.1: biodistribution of [^{74}As]SATA-ch3G4, 7 days p.i., AT1 prostate cancer in rat.

The biodistribution after the 7th day shows a tumor/liver ratio > 3:1 and a tumor/muscle ratio > 6:1 (cf. Fig. 1). We have also observed an unusually high uptake in the spleen. A possible explanation for this is that AB conglomerates are usually metabolised in the spleen and with the introduction of free sulfhydryl groups in the AB, there is an increased probability for the formation of intermolecular disulphur bonds. In addition, the AsI_3 can work as a linker between two AB molecules.

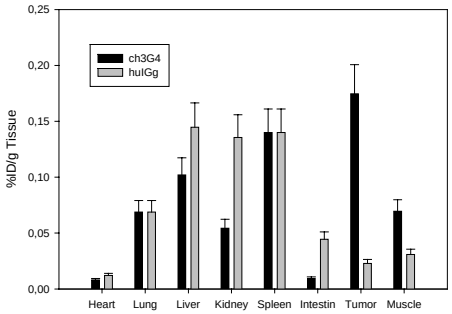

Fig. 2: biodistribution of [^{77}As]SATA-ch3G4 with negative control, 48h p.i., AT1 prostate cancer in rat.

The ratios between %ID/g tumor in rats injected with [^{77}As]SATA Hu IGg and negative control, [^{77}As]SATA-ch3G4 were > 7.5. The negative control also showed a comparable high spleen uptake which indicates, that this is related to the labelling procedure and not a general feature of the ch3G4 AB. The positive control biodistribution gave comparable tumor/ liver ratios of 3:1. The much higher tumor uptake in mouse breast tumor (cf. Fig. 3) can be explained by the dense vasculature in this mushy tumor sort compared to the more encapsulated AT1 prostate tumors.

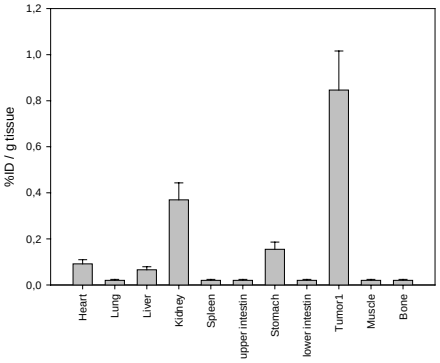

Fig.3 : biodistribution of [^{77}As]SATA-ch3G4, 24h p.i., orthotopic breast cancer in mice.

References:

[1] Ran, S. et al., Cancer Research 62, 6132-6140, 2002

[2] Ran, S. et al., Int. J. Rad. Oncol. **54**, 1479, 2002

[3] Jennewein, M. et al., Annual Report, this issue.

Financial Support of the Boehringer Ingelheim Foundation and the Cancer Imaging Program, an NCI Pre-ICMIC, CA086354, is grateful acknowledged