Contribution ID: **319** Type: **Verbal**

Affibody molecules, a novel class of peptide-based radiopharmaceuticals. Optimising labelling chemistry for the best targeting

Radionuclide molecular imaging is a promising approach to detection of molecular targets for cancer therapy. Small imaging agents provide higher sensitivity and better specificity than antibodies or their fragments. Molecular display techniques (phage, ribosomal, yeast or bacterial display) allow for combinatorial selection of small peptides with high specificity to different proto-oncogene products. The use of scaffolds, robust frameworks, which hold variable amino acid in place, enables to improve both stability and affinity of targeting molecular-display selected peptides. Affibody molecules, small (7 kDa) robust scaffold peptide constitute a new promising class of high-affinity molecular probes for in vivo molecular imaging. Affibody molecules were labelled with ^{99m}Tc, ¹¹¹In for SPECT and ¹⁸F, ⁶⁸Ga, ⁶⁴Cu, ⁷⁶Br and ¹²⁴I for PET, and demonstrated excellent imaging in pre-clinical studies. The first clinical results confirm capacity of anti-HER2 affibody molecules to visualize HER2-expressing breast cancer metastases. Robustness of the affibody scaffold enabled labelling in harsh labelling conditions without loosing specificity of target binding.

It is known, that labelling has profound influence on biodistribution and targeting properties of short peptides, such as somatostatin or bombesin analogues. Biodistribution of monoclonal antibodies or their fragments is rather insensitive to labelling, though label can influence cellular retention of radionuclide in tumours or excretory organs. However, affibody molecules are four-fold larger than typical short peptide and four-fold smaller than the smallest antibody fragment, scFv. This put forward a requirement of systematic studies of influence of labelling chemistry on biodistribution of affibody molecules. This was possible due to the development of site-specific labelling of affibody molecules providing well-characterised uniform conjugates with defined biodistribution. The site-specific labelling was obtained either by an incorporation of chelators during peptides synthesis of affibody molecules or by an introduction of a single cysteine in the originally cysteine-free affibody scaffold and the use of a thiol-directed coupling.

It was shown that labelling chemistry can influence biokinetics of affibody molecules. For example, the use of non-residualizing halogen labels reduced renal retention of radioactivity in comparison with radiometals. ⁶⁸Ga increased clearance rate in comparison with ¹¹¹In, when the same DOTA chelator was used. More hydrophilic chelators enabled to suppress undesirable liver uptake and hepatobiliary excretion, improving contrast in the case of abdominal metastases. It was shown, than not only hydrophilicity of a chelator, but also its position in the peptide influences imaging properties.

Results of our studies show that selection of optimal labelling chemistry is essential for the development of scaffold-based imaging agents.

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Track Classification: Nuclear Methods in Medicine, Radiopharmaceuticals and Radiodiagnostics, Labelled Compounds