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Synthesis and Selection of Radiotherapeutics

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Antibodies against tumor-associated antigens and receptor binding peptide analogues can specifically target tumors in vivo. Labelled with gamma emitting radionuclides or with positron emitters these vehicles can be used to visualize tumours with SPECT and PET, respectively. Labelled with alpha or beta emitting radionuclides these antibodies and peptides can be used for radionuclide therapy, designated as radioimmunotherapy (RIT) or peptide receptor radionuclide therapy (PRRT), respectively.

The first radionuclide that was used in radionuclide therapy is I-131. Antibodies can be labeled with I-131 using an oxidative substitution reaction, resulting in radioiodination of the tyrosine residues. Elegant remote systems have been developed to label antibodies and peptides with high activity doses (>5 GBq) I-131 have been developed. However, when a radioiodinated antibody of peptide is internalized by the target cell it is enzymatically degraded in the lysozymes and the radioiodine is released from the target cell. Therefore, radioiodine is classified as a non-residualizing radionuclide. New radioiodination methods have been developed that cause residualization of I-131 in internalizing tumor cells.

For labeling antibodies and peptides with beta-emitting radiometals such as Y-90 and Lu-177 a series of bifunctional chelating agents have been developed. Initially DTPA analogues were used for this purpose (cDTPA, CHX-A'-DTPA, SCN-Bz-DTPA, a.o.). The in stability of these complexes is varies largely and is highly dependent on the radiometal. Various macrocyclic chelates (DOTA, TETA, NOTA, a.o.) have been developed, and in general these complexes are characterized by a higher in vivo stability. Upon internalization and lysosomal degradation the radiolabelled metabolites of antibody and peptide labelled with these radiometals are retained intracellularily, and thus these radiometals are classified as residualizing radionuclides. Labelling of antibodies and peptides with these radiometals can be performed as a one-pot, one-step procedure, posing less radiation safety issues.

Antibodies and peptides can also be labeled with Re-186 and Re-188 using either sulfhydril groups or MAG3 as a chelator.

The choice of the beta-emitting radionuclide that is used in radionuclide therapy depends on the pharmacokinetics of the targeting vehicle, the fate of the targeting vehicle upon binding the target cell, and the intratumoral distribution of the radiotracer. In general, for antibodies with a relatively slow pharmacokinetics preferably radionuclides with a relatively long half-life (several days) are selected. For internalizing targeting vehicles the use of a residualizing radionuclide is required. And when the intratumoral distribution of the radiotracer is highly heterogeneous one would prefer the use of a beta-emitter with a longer penetration range in tissues.

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