

## A simulation approach to describe Bi-213 radiolabelling on CHX-DTPA-IgG conjugate

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Targeted alpha therapy (TAT) is based on the coupling of alpha particle emitting radioisotopes to target selective carrier molecules. Due to the short range (<100  $\mu\text{m}$ ) and high linear energy transfer ( $\text{LET} \approx 100 \text{ keV}/\mu\text{m}$ ) of alpha particles in human tissue, TAT offers the potential of delivering a highly cytotoxic dose to targeted cells while minimizing damage to surrounding healthy tissue. The efficacy and safety of TAT has been demonstrated in a number of pre-clinical studies and in clinical trials of leukemia, malignant melanoma, lymphoma, glioblastoma and skeletal metastases. Currently, clinical studies using the isotope Bi-213 ( $T_{1/2} = 46 \text{ min}$ ) that can be made available to hospitals via a radionuclide generator loaded with its mother nuclide Ac-225 ( $T_{1/2} = 10 \text{ days}$ ) are the most advanced.

The in vivo stability of the radiolabelled conjugate is optimal when the bifunctional chelator CHX-DTPA is used (1). The radiolabelling protocol has been experimentally optimized and specific activities around 6.5 MBq/ $\mu\text{g}$  can be obtained. Several pre-clinical studies have demonstrated that the specific activity significantly affects the cytotoxicity of Bi-213 radioconjugates, i.e. for a given total activity, the cytotoxicity increases as the specific activity increases (2).

The aim of this study is to assess in which extent the specific activity may be increased using a simulation approach, i.e. Bi chelation is quantitatively described considering the equilibrium reactions occurring in the radiolabelling medium. The parameters describing the interaction of Bi with the inorganic and organic ligands are taken from literature data (3). The parameters characterizing the interaction between Bi and the conjugate CHX-DTPA-IgG (kinetic and equilibrium parameters) were obtained using two displacement methods. In the first case, chelex-100 is used to compete with Bi / conjugate interaction and the speciation is done by solid/liquid separation. In the second case, Cm is used and the speciation is done by Time-Resolved Laser induced Fluorescence Spectroscopy (TRLFS).

Experimental data obtained will be discussed and compared with those already available in the literature. The use of the equilibrium constant Bi / CHX-DTPA to describe Bi / CHX-DTPA-IgG interaction will be discussed based on TRLFS results. Then, simulation results will be presented and the factors affecting the specific activity (thermodynamic parameters? chemical products?...) will be presented. The possible improvement of the labelling protocol will be finally discussed.

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