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Combining Bismuth-213 with Nanobodies: finding the perfect match for Targeted Alpha Therapy

This study investigates a novel targeted therapy which combines the α-emitter Bismuth-213 (213Bi) and HER2-targeting nanobodies (Nbs) to selectively kill HER2+ metastases in breast- and ovarian cancer. The use of nanobodies as vehicles in TAT is promising due to their excellent in vivo properties, high target affinity and specificity, fast diffusion and clearance kinetics. Moreover, Nbs show good tumor penetration due to their small size. The aim of this study is to develop and evaluate the in vitro binding characteristics on HER+ SKOV-3 cells, the in vitro stability using radio-ITLC and HPLC and the in vivo biodistribution of 213Bi-DTPA HER2 targeting Nb.

First, a 213Bi-labeled-Nb was developed using 225Ac obtained from an historical 229Th-source of SCK•CEN. A classical diethylenetriaminepentaacetic acid (DTPA) derivative was used as bifunctional chelator for complexing 213Bi and conjugating the complex to the anti-HER2 Nb. Due to the 46 min half-life, the 213Bi labeling reaction and quality control of the resulting radioconjugate was performed in a very short time frame to limit significant radioactivity losses. Under optimized labeling conditions, the 213Bi-DTPA-Nb remained stable up to 2 h after labeling with a radiochemical purity ≥ 95% in PBS at room temperature and at 37 ℃ and in serum at 37 ℃. In vitro, the 213Bi-DTPA-Nb bound HER2+ SKOV-3 cells in a HER2-specific way and with an affinity of 3.79 +/- 0.96 nM (Figure 1A and 1B).

In a second part, mice were injected with 213Bi-DTPA-Nb using 225Ac obtained from the Institute for Transuranium Elements in Karlsruhe. Extremely low uptake values were observed in normal tissues at all time points (Figure 1C). 213Bi-DTPA-Nb was excreted via the kidney into the urine, leading to a significant kidney retention of the compound of 40% ID/g at 15 min postinjection (p.i.). Coinfusion of 150 mg/kg Gelofusin resulted in a 50% reduction of the kidney retention at 15 min and 30 min p.i.. No significant difference in tumor uptake was observed between the two groups.

Future work will aim at optimizing 213Bi-labeled Nbs regarding optimal in vivo pharmacokinetic properties: high in vivo stability, sufficiently high tumor accumulation, fast clearance of the unbound fraction and limited radiation exposure to healthy risk organs.

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