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Site-Specific Radiolabeling of a Human PD-L1 Nanobody via Maleimide–Cysteine Chemistry

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Introduction Immune checkpoint inhibitors targeting the programmed cell death-1 (PD-1) and its ligand PD-L1 have proven to be efficient for cancer therapy. Being able to distinguish patients that do express PD-1/PD-L1 from patients that do not allows patients to benefit from a more personalized and favorable treatment. To visualize whole-body expression by PET imaging, we developed a nanobody (Nb)-based radioimmunotracer targeting human PD-L1 (hPD-L1) for preclinical trial that was site-specifically labeled with gallium-68 (68Ga).

Methods The cysteine-tagged hPD-L1 Nb was site-specifically conjugated with maleimide-NOTA (A) and the radiolabeling with 68Ga was optimized (B). Affinity and specificity were assayed by surface plasmon resonance (SPR) and on hPD-L1 positive (hPD-L1(C)) or negative (hPD-L1(N)) cells. Xenografted athymic nude mice bearing hPD-L1 positive or negative tumors were injected with 14.13 ± 0.29 MBq of 68Ga(NOTA-68Ga) labeled Nb. The animals were sacrificed 1 h 20 post injection for ex vivo biodistribution studies.

Conclusion The cysteine-maleimide chemistry is a straightforward and reliable strategy for the site-specific coupling of the cysteine-tagged hPD-L1 Nb. An efficient 68Ga-labeling was obtained by increasing the incubation time and temperature. In vivo, 68Ga-NOTA-68Ga-NOTA-68Ga-labeled hPD-L1 Nb kept its functionality and showed a favorable biodistribution profile. Before clinical translation, optimization is needed in order to, on one hand, reduce the kidney retention and, on the other hand, to improve the production yield of the cysteine-tagged nanobody.

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