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Nivolumab radiolabelling with Ga-68: Two different approaches for the formulation of an immunoPET tracer to detect PD-1 expressing tumors

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In recent years, immunotherapy with drugs that inhibit immune checkpoints has shown clinical efficacy in several different types of cancer by blocking PD-L1/PD-1 and CTLA-4 checkpoint pathways. Direct imaging of cell surface targets for immunotherapy using monoclonal antibodies (Mo)Abs labeled with PET and SPECT radioisotopes can visualize drug distribution and tumor characteristics. The aim of this study was to develop an immunoPET probe labeled with the PET radioisotope gallium-68 for imaging PD-1 expressing tumors. For noninvasive detection of PD-1, we chose Nivolumab (Opdivo®; Bristol-Myers Squibb, Princeton, NJ, USA), the first-in-human immunoglobulin G4 (IgG4) PD-1 immune checkpoint inhibitor antibody. We developed direct (free nivolumab) and indirect (functionalized nivolumab with bifunctional cyclic chelators, DOTA/NOTA) labeling approach procedure using the PET isotope Ga-68 obtained from a pharmaceutical grade 68Ge/68Ga generator (Eckert & Ziegler, Berlin, Germany). The 68Ge/68Ga generator was eluted with 0.1 M HCl following the manufacture's protocol. A solution of ultrapure NaOAc 1.25M (Fluka Traceselect, ≥99.99%, metal basis) was added to nivolumab or DOTA/NOTA-nivolumab protein solution and then the eluate 68GaCl3 (ca. 50-100 MBq) bringing the pH to 5–6. The reaction mix was incubated in a heat block at 37°C for 40 minutes and after that the resulting radiopharmaceutical was isolated from free Ga-68 by centrifugation. The radiochemical purity percentage of [68Ga]Ga-nivolumab and [68Ga]Ga-DOTA/NOTA-nivolumab was determined using instant thin layer chromatography (TLC); TLC-SG strips are used as stationary phase and sodium chloride (0.9%) as mobile phase to separate the radiolabelled (Mo)Abs, which remains at the bottom, while the free gallium-68 moved to the top. Our results showed that the indirect approach is a site-specific labeling procedure and these radioimmunoconjugates are more stable than the direct approach. The promising labeling results showed an efficient procedure to label the antibody with Ga-68 providing the model for the future production of immunoPET imaging probe.

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