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Direct radiolabeling of nivolumab with Ga-68: A novel PET tracer to detect PD-1 expressing tumors

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In recent years, the blockade of immune checkpoint molecules with monoclonal antibodies, like those targeting the PD-1/PD-L1 pathway, has enabled the development of breakthrough therapies in oncology, leading to delayed tumor growth and increased survival.

Non-invasive methods permitting whole-body detection of PD-1 and PD-L1 at high sensitivity and resolution could thus be highly useful in-patient selection and monitoring of PD-1/PD-L1 expression during disease progression and treatment, therefore different approaches have been developed in order to label tumor-specific monoclonal antibodies (Mo)Abs with PET and SPECT radioisotopes.

Aim of this study was to develop an immunoPET tracer for imaging PD-1 using Nivolumab (BMS-936558, ONO-4538, or MDX1106, trade name Opdivo®; Bristol-Myers Squibb, Princeton, NJ, USA), the first-in-human immunoglobulin G4 (IgG4) PD-1 immune checkpoint inhibitor antibody, and the PET radioisotope Gallium-68.

Direct labeling approach procedure involves the use of a solution to buffer the acidity of the eluate $^{68}GaCl_3$ of a commercially avaible TiO_2-based $^{68}Ge/^{68}Ga$ generator (Eckert & Ziegler, E&Z, Berlin, Germany) in order to prepare the carboxylic and aminic groups of Nivolumab that can be conveniently used as coordinating sites to bind Gallium-68.

The $^{68}Ge/^{68}Ga$ generator was eluted with 10 ml 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 this 0.1M HCl solution of [^{68}Ga]Ga-Chloride bringing the pH to 4.5-5. The resulting [^{68}Ga]Ga-acetate solution (ca. 50-100 MBq) was added to Nivolumab (10 mg/ml) protein solution.

The [^{68}Ga]Ga-Nivolumab solution was incubated in a heat block at 45°C for 40 minutes. The resulting [^{68}Ga]Ga-Nivolumab was isolated by centrifugation and the radiolabeling yield has been calculated.

The radiochemical purity of [^{68}Ga]Ga-Nivolumab was determined using instant thin layer chromatography (TLC): TLC-SG strips are used as stationary phase and ammonium acetate (sol aq. 10%) : MeOH (1:1) as mobile phase to separate free Gallium-68, which remains at the bottom, while the radiolabelled (Mo)Abs moved to the top.

The promising labeling results show an efficient and rapid direct procedure to label (Mo)Abs with Gallim-68 reducing reaction steps and antibody preparation and allowing the future formulation of freeze-dried kit to obtain a PET imaging of PD-1 expressing tumors.

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