ABSTRACT

Metastatic ovarian cancer currently has a 5-year survival rate of 30% and limited therapeutic options. The FDA-approved targeted therapeutic, rucaparib, is a poly(ADP-ribose) polymerase inhibitor (PARPi) that limits single-strand DNA damage response and can trap the PARP-drug complex nanometers from DNA. Radiolabeled PARPi with Meitner-Auger electron (MAe^-) emitting radionuclides such as ^{77}Br ($t_{1/2}$ = 57 h, 6–7 MAe^- per decay) can exploit this biological mechanism to target the DNA with short-range, high linear energy transfer radiation. Its theranostic pair, ^{76}Br ($t_{1/2}$=16.2 h, 55% β^+), has the potential to be used for diagnostic and patient specific dosimetry with PET imaging. This work investigates the therapeutic and diagnostic potential of $^{77/76}Br$ labeled rucaparib derivative, called [$^{77/76}Br$]RD1.

Radiopharmacological and cytotoxic response of various ovarian cancer cell lines *in vitro* were investigated with [^{77}Br]RD1. The goal of this objective was to characterize the radiopharmaceutical as a therapeutic agent, including its binding properties and cytotoxic effects. Dosimetric calculations were conducted with the goal of converting the cytotoxic response *in vitro* measured as a function of activity concentrations into dose. Further experiments characterizing the ovarian cancer cell characteristics were done to properly inform assumptions to calculate the dose using MIRDcell.

The potential of [^{76}Br]RD1 as a diagnostic PET imager was also investigated through preclinical animal studies measuring the radiopharmaceutical's *in vivo* and *ex vivo* organ and tumor uptake. RAPID and OLINDA dosimetry platforms were used to calculate the dose to organs using [^{76}Br]RD1 organ uptake measured by PET. These calculations were done for both radiobromine MAe^- emitter ^{77}Br and positron emitter ^{76}Br.

This work describes preclinical experiments used to characterize a MAe^- and PET emitting theranostic radiopharmaceutical targeting PARP. It contributes to the understanding of the radiochemistry and radiation biology of MAe^-–emitting radiopharmaceuticals and will inform experimental design for future studies of this and other PARP-targeted agents for the treatment and diagnosis of metastatic cancers.