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Feasibility production of 67/64Cu mixture with SPES cyclotron for the first radiopharmaceutical in-vivo studies

Copper-67 (67Cu, T1/2 61.9 h), as well as Copper-64 (64Cu, T1/2 12.7 h), are under the spotlight of the scientific community as single isotopes for targeted radionuclide therapy, and as a pair for theragnostic applications thanks to the, β- and γ emissions of 67Cu and β- and β+ emission of 64Cu . Their half-lives are suitable for tracking radiopharmaceuticals with slow pharmacokinetics. Although 64Cu is now commercially available from some suppliers and already on clinical evaluation in nuclear medicine for the PET diagnostic procedure, the use of 67Cu is limited by the lack of regular availability in sufficient quantities for preclinical/clinical studies worldwide. This challenge is one of the main goals of the LARAMED (LAboratory of RAdionuclides for MEDicine) project at INFN-LNL. Among the different production routes of 67Cu, there is the possibility of using proton beams and it is of particular importance since at LNL is present a 70 MeV proton cyclotron. In the energy range 35-70 MeV available in the SPES cyclotron, it is possible to produce 67Cu and 64Cu with two different nuclear reactions, 68Zn(p,x)64/67Cu and 70Zn(p,x)64/67Cu. Still, in the entire energy range, both isotopes are always co-produced. The production feasibility of the 64Cu/67Cu pair with thick targets will be performed at LNL when a suitable bunker is completed with a dedicated thick target station installed. However, with this proposal, we would like to start these studies by exploiting the target station already installed in a different bunker and designed specifically for cross section measurements. Despite this limitation, it has been theoretically ascertained that it is possible to use this target station to produce the minimum amount of activity that would allow us to start preclinical studies to evaluate the diagnostic efficacy and the therapeutic effect of the mixture of 67Cu and 64Cu. These studies will be conducted at the LARIM (Laboratory of Radionuclides and Molecular Imaging), situated within the LNL. This facility is equipped with the necessary apparatuses to facilitate the development and characterization of novel specific radiopharmaceuticals both in vitro and in vivo. Moreover, the quantitative analysis of nuclear images will be used to determine the radiopharmaceuticals kinetics and dosimetry. After the bombardment in the SPES building, the irradiated target will be transported to the LARIM where the radiochemical separation procedures will be performed. The obtained 67/64Cu mix will be used to radiolabel novel radiopharmaceuticals for the treatment of prostate cancer (PCa) and ductal pancreatic adenocarcinoma (PDAC). Their effectiveness and safety will then be tested by performing biodistribution studies in both healthy and xenograft mouse models, with the final aim of comparing the obtained data with those of 177Lu-radiopharmaceuticals, currently considered the gold standard for cancer treatment in nuclear medicine.

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