PhD Thesis Title: Titanium-45: development and optimization of the production process in low energy cyclotrons

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ABSTRACT:

Introduction: Modern practice of Medicine includes the use of technological innovations such as in Medical Imaging. In vivo imaging techniques can be used to evaluate biological structures and functions non-invasively in almost all living subjects.

This thesis was highlighted in Nuclear Medicine. As a simple definition, Nuclear Medicine is a medical imaging modality based on the measurement of an internal source from an internal tracer using radiolabeled compounds to study in vivo physiologic processes. So, Nuclear Medicine relies on the supply of radionuclides.

In the specific context of Positron Emission Tomography (PET) imaging, positron emitters are used to label several different compounds, allowing the study of almost all the major biological systems. Although there are several radionuclides to be potentially applied in PET imaging, routine clinical applications are still based on a small group constituted by ^{18}F, ^{11}C, ^{13}N and, more recently, ^{68}Ga. However, recent literature indicates that this trend is changing. Among others, ^{45}Ti is being proposed as a potential candidate for PET imaging, since it presents some interesting properties: abundant positron emission, reduced positron energy, physical half-life of 3.09 h, and relevant chemical properties (that enable radiolabeling with bifunctional chelates), ligands or even to radiolabel titanium dioxide nanoparticles. Given this, several issues should be solved before the real possibility of implementing ^{45}Ti clinical applications.

Aim: Radionuclide production is the first crucial technical step involved in PET. However, production of ^{45}Ti is yet very poorly explored in literature. This project was designed and implemented with the aim to study the viability of the production of ^{45}Ti in low energy cyclotrons, expecting the characterization of the excitation functions of the appropriate nuclear reaction, yield determination and development of a critical analysis to select the best methodology.

Materials and Methods: To evaluate nuclear reaction excitation functions one should implement nuclear activation studies. Nevertheless, the execution of nuclear activation studies deserves special attention and a careful integration of all the available information already collected. In this sense, the first step of this activation experiment was the adequate planning using Monte Carlo simulation codes in a way to obtain several results that were totally integrated in the design of experimental studies.

Before the experimental activation study, some preliminary experimental studies with gamma-spectroscopy were performed with calibrated radionuclide sources as demonstration of the ability of the technique to illustrate physical phenomena, such as, radioactive decay and radiation interaction with matter, and in a way to refine the analysis of the main experiment. Then, the stacked foil technique was implemented in a 18 MeV cyclotron to study

the $^{45}Sc(p,n)^{45}Ti$ nuclear reaction and its feasibility to effectively produce ^{45}Ti. Activation was measured using HPGe gamma-spectroscopy. Theoretical insights about the potential applications of ^{45}Ti for PET imaging were also reviewed, analyzed, proposed and discussed.

Results: According to TALYS code, and also due to other practical considerations, $^{45}Sc(p,n)^{45}Ti$ nuclear reaction was selected as the one with much more potential for industrial implementation in the way to obtain significant quantities of ^{45}Ti. SRIM code simulations were used to understand the beam energy degradation along the stacked foil designed for the activation study, while SSSM sub-routine was used to study the implantation of the beam in the successive targets.

Results of the main excitation function were collected under this study, with the addition of information regarding concurrent reactions leading to ^{44m}Sc, ^{44}Sc and ^{44}Ti. Experimental results showed that $^{45}Sc(p,n)^{45}Ti$ nuclear reaction seems to be feasible in low energy cyclotrons, with cross-section values presenting a peak for proton beam energies in the range between 14 and 10 MeV, while energies higher than 17 MeV should be avoided due to the increased production of contaminants, such as ^{44}Ti, ^{44}Sc and ^{44m}Sc. Thick target yield for a saturation condition was experimentally determined as 433.64 MBq.μA^{-1}sat.

Theoretical evidence collected demonstrate that ^{45}Ti could provide good PET image quality, with some preclinical applications already tested in studies related to a new class of anticancer drugs based on titanium complexes. Other possible applications already cited include ^{45}Ti-ligands for theranostics and personalized medicine. An innovative proposal on the use of ^{45}Ti to radiolabel of titanium dioxide nanoparticles will also be presented and discussed.

Conclusion: There is the possibility to effectively obtain significant quantities of ^{45}Ti allowing its possible commercial and industrial production, distribution and use. Given this, ^{45}Ti could then provide good PET images and be used for labeling different compounds already tested or to be incorporated in the development of nanoparticle-based radiopharmaceuticals.

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