Production, labeling and in vivo studies with the theranostic positron-emitting radiometals ^{44}Sc, $^{55/58m/58g}$Co, $^{61/64}$Cu, ^{86}Y and ^{69}Ge

Hector F Valdovinos

Under the supervision of Robert J Nickles

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As a result of the recent advances in targeted radionuclide therapy (TRT), the demand for the cyclotron-produced positron-emitting radiometals ^{64}Cu, ^{61}Cu, ^{86}Y and ^{44}Sc has been gradually increasing in the last two decades, partly due to the diagnostic complement for treatment planning that they provide to their therapeutic analogues ^{67}Cu, ^{90}Y and ^{47}Sc. The positron emitters labeled to a targeting vector directed to a molecular signature of disease not just allow for noninvasive diagnosis via positron emission tomography (PET), but also for the prediction, via internal dosimetry calculations, of how effective the targeted agent labeled with the therapeutic analogue would be in a treatment scenario. Another explanation for the increase in demand for these PET radiometals is their gradual transition beyond the small animal preclinical environment into clinical applications, where more strict requirements in the quality of the radiolabel may be delaying their full incorporation into this setting. Hence, novel production methods that are more amenable to automation, more reproducible in terms of radiochemical separation yields and effective specific activities are necessary to satisfy this growing market.

In this dissertation, novel radiochemical separation methods for these radiometals that satisfy such requirements are presented, including a detailed characterization of the separated radionuclide in terms of radionuclidic purity, radionuclidic identity, reactivity to conventional chelators, trace metal purity and spatial resolution in a small animal PET scanner.

This dissertation also presents novel targetry and radiochemical separation methods for the production of other less conventional radiometals that constitute "theranostic" (therapeutic and diagnostic) pairs, namely the Auger electron emitters ^{58m}Co and ^{71}Ge and their positron emitting complements ^{55}Co and ^{69}Ge. These separated radiometals, except ^{71}Ge, are also fully characterized upon radiochemical separation.

The theranostic potential of each one of the radiometals that is covered in this thesis is demonstrated first by collecting biodistribution and pharmacokinetic data from PET imaging of tumor-bearing mice intravenously injected with radiolabeled agents, followed by internal dosimetry calculations using the Medical Internal Radiation Dose (MIRD) formalism, focusing on the therapeutic and radiotoxic implications caused by the radiolabeled agent when the radiometal is substituted with a therapeutic analogue. Special attention is given to the radionuclides with intrinsic theranostic properties in themselves: ^{64}Cu and the parent-daughter pair $^{58m/58g}$Co.

The radiolabeled agents that are employed include the radiometal by itself, that is, weakly bound to a simple ligand in solution (all radiometals in this thesis), strongly bound to a chelator-conjugated tumor-targeting antibody called TRC105 (^{55}Co, ^{58m}Co, ^{58g}Co, ^{64}Cu and ^{86}Y) or incorporated into the structure of a super paramagnetic iron oxide nanoparticle (^{69}Ge).