University of Victoria | Graduate Studies

Notice of the Final Oral Examination
for the Degree of Doctor of Philosophy

of

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MSc (University of Victoria, 2010)
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"New Technologies for ^{211}At Targeted Alpha-Therapy Research Using ^{211}Rn and ^{209}At"

Department of Physics and Astronomy

Thursday, June 16, 2016
9:30 A.M.
David Turpin Building
Room A144

Supervisory Committee:
Dr. Andrew Jirasek, Department of Physics and Astronomy, University of Victoria (Co-Supervisor)
Dr. Wayne Beckham, Department of Physics and Astronomy, University of Victoria (Co-Supervisor)
Dr. Thomas Ruth, Department of Physics and Astronomy, UVic (Member)
Dr. Dean Karlen, Department of Physics and Astronomy, UVic (Member)
Dr. Julian Lum, Department of Biochemistry and Microbiology, UVic (Outside Member)

External Examiner:
Dr. Stephen Larson, Nuclear Medicine, Memorial Sloan Kettering Cancer Center

Chair of Oral Examination:
Dr. Wanda Boyer, Department of Education Psychology & Leadership Studies, UVic

Dr. David Capson, Dean, Faculty of Graduate Studies

Abstract

The most promising applications for targeted *α*-therapy with astatine-211 (^{211}At) include treatments of disseminated microscopic disease, the major medical problem for cancer treatment. The primary advantages of targeted *α*-therapy with ^{211}At are that the *α*-particle radiation is densely ionizing, translating to high relative biological effectiveness (RBE), and short-range, minimizing damage to surrounding healthy tissues. In addition, theranostic imaging with ^{123}I surrogates has shown promise for developing new therapies with ^{211}At and translating them to the clinic. Currently, Canada does not have a way of producing ^{211}At by conventional methods because it lacks *α*-particle accelerators with appropriate beam characteristics. The work presented here was aimed at studying the ^{211}Rn/^{211}At generator system as an alternative production strategy by leveraging TRIUMFS ability to produce rare isotopes. Recognizing that TRIUMF provided production opportunities for a variety of astatine isotopes, this work also originally hypothesized and evaluated the use of ^{209}At as a novel isotope for preclinical Single Photon Emission Computed Tomography (SPECT) with applications to ^{211}At therapy research.

At TRIUMF's Isotope Separator and Accelerator (ISAC) facility, mass separated ion beams of short-lived francium isotopes were implanted into NaCl targets where ^{211}Rn or ^{209}At were produced by radioactive decay, *in situ*. This effort required methodological developments for safely relocating the implanted activity to the radiochemistry laboratory for recovery in solution. For multiple production runs, ^{211}Rn was quantitatively transferred from solid NaCl to solution (dodecane) from which ^{211}At was efficiently extracted and evaluated for clinical applicability. This validated the use of dodecane for capturing ^{211}Rn as an elegant approach to storing and shipping ^{211}Rn/^{211}At in the future. ^{207}Po contamination (also produced by ^{211}Rn decay) that is intrinsic to this generator system war (also produced by ^{211}Rn decay) was evaluated. ^{207}Po impurities were shown to compromise antibody labelling procedures, demonstrating the necessity of purifying ^{211}At (from ^{207}Po) before proceeding with biomolecule labelling, which was accomplished using a tellurium column. Although the produced quantities were small, the pure ^{211}At samples demonstrated these efforts to have a clear path of translation to animal studies.

For the first time in history, SPECT/CT was evaluated for measuring ^{209}At activity distributions using high energy collimation, in mice and phantoms. The spectrum detected for ^{209}At by the

SPECT camera presented several photopeaks (energy windows) for reconstruction. The 77-90 Po X-ray photopeak reconstructions were found to provide the best images overall, in terms of resolution/contrast and uniformity. Collectively, these experiments helped establish guidelines for determining the optimal injected activity, depending on scan parameters. Moreover, ^{209}At-based SPECT demonstrated potential for pursuing image-based dosimetry in mouse tumour models, in the future. Simultaneous SPECT imaging with ^{209}At and ^{123}I was demonstrated to be feasible, supporting the future evaluation of ^{209}At for studying/validating ^{123}I surrogates for clinical image-based ^{211}At dosimetry. This work also pursued a novel strategy for labelling cancer targeting peptides with ^{211}At, using octreotate (TATE, a somatostatin analogue for targeting tumour cells, mostly neuroendocrine tumours) prepared with or without N-terminus PEGylation (PEG_2), followed by conjugation with a *closo*-decaborate linking moiety (B10) for attaching ^{211}At. Binding affinity and *in vivo* biodistributions for the modified peptides were determined using iodine surrogates. The results indicated that B10-PEG2-TATE retained target binding affinity but that the labelling reaction with iodine degraded this binding affinity significantly, and although having high *in vivo* stability, no ^{123}I-B10- PEG2-TATE tumour uptake was observed by SPECT in a mouse tumour model positive for the somatostatin receptor (sstr2a). This suggested that further improvements are required for the labelling reaction.

A new method for producing ^{211}At at TRIUMF is established, and ^{209}At -based SPECT imaging is now demonstrated as a new preclinical technology to measure astatine biodistributions in vivo for developing new radiopharmaceuticals with ^{211}At. Combined with the theranostic peptide labelling efforts with iodine, these efforts provide a foundation for future endeavours with ^{211}At -based α -therapy at TRIUMF. All procedures were performed safely and rapidly, suitable for preclinical evaluations.