Monitoring the treatment of AR42J tumor-bearing mice with ^{225}Ac-crown-TATE

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Introduction

Alpha (α) emitting radionuclides can be used to kill cancer cells.

^{225}Ac ($t_{1/2}$ = 9.9 d) is a desirable α-emitter, releasing four α particles before reaching stable ^{209}Bi. When these α particles traverse a cancer cell's nucleus, they are able to break double-stranded DNA, thereby inducing cell apoptosis (Figure 1).[1]

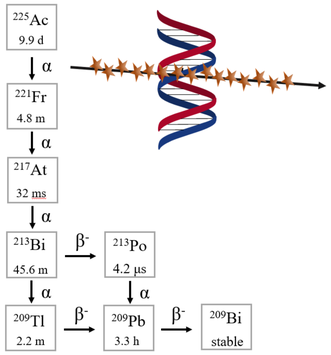


Figure 1. The decay scheme of ^{225}Ac shows this radionuclide is a potent alpha-emitter, releasing four α particles (and two β^- particles) before decaying to stable ^{209}Bi.

Given tumors have different molecular expressions to healthy cells, if their unique features can be targeted, it is possible to employ radionuclides in cancer treatments via the administration of radiopharmaceuticals (Figure 2).[2]

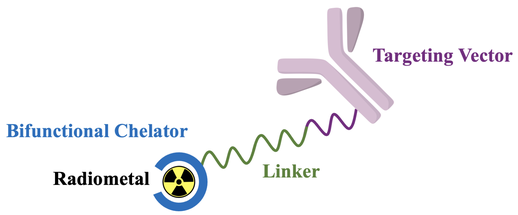
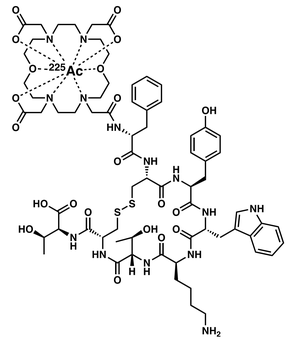


Figure 2. A schematic diagram of a radiopharmaceutical able to target cancer cells with minimal off-target radiation. The targeting vector is a biomolecule that binds to cancer cells, and the linker bridges the biomolecule to a chelator-radiometal complex.

Based on this principle, a new radiopharmaceutical known as ^{225}Ac-Crown-TATE (Scheme 1) was designed to target inoperable, progressive neuroendocrine tumors (NETs) positive for somatostain receptor (SSTR) expression.



Scheme 1. The chemical structure of ^{225}Ac-Crown-TATE; a somatostain peptide analogue 'tagged' with ^{225}Ac.[3]

Aim of the study

The main aim of the study was to perform a therapy study that establishes the treatment efficacy of 225Ac-Crown-TATE in AR42J tumor-bearing mice. To support this aim, biodistribution and histopathology studies will be included to check whether there are toxicity issues for organs.

Results

Before conducting the therapy study, the development of 225Ac-Crown-TATE was established:[3]

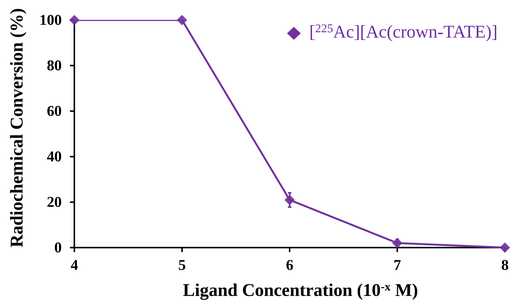


Figure 3. As a radiopharmaceutical precursor, Crown-TATE is able to coordinate (or 'wrap up') 40 kBq of $[^{225}Ac]Ac^{3+}$ ions at ligand concentrations as low as 10^{-5} M, total reaction volume 100 µL, within 30 minutes at room temperature.

In addition, a biodistribution study involving ^{225}Ac-Crown-TATE and four healthy mice was conducted to test how well the drug cleared from the body, and how stable it was while in the body:

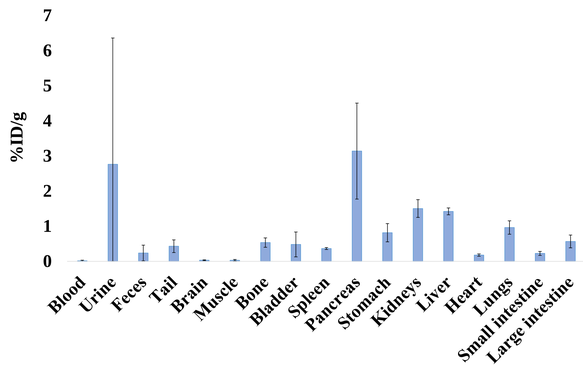


Figure 4. The ^{225}Ac distribution in the organs of mice two weeks post ^{225}Ac-Crown-TATE injection shows the pancreas, kidneys and liver should be examined for toxicity in histopathology studies (n = 4).

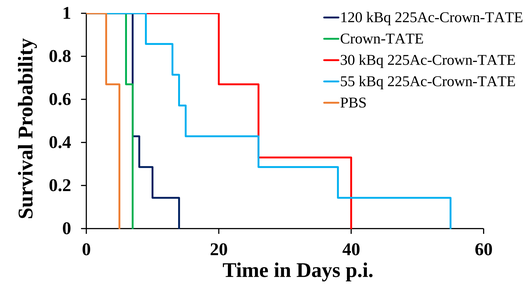


Figure 5. The Kaplan-Meier plot shows AR42J tumor-bearing mice (starting tumor volume 50-550 mm^3) injected with 30 kBq or 55 kBq had the highest chance of survival over one-two months. The end-point was determined by -20% weight loss, tumor sizes reaching ~1000 mm^3, or poor health observations. Currently, the sample sizes consist of: 120 kBq n = 7, Crown-TATE n = 3, 30 kBq n = 3, 55 kBq n = 7 and PBS n = 3.

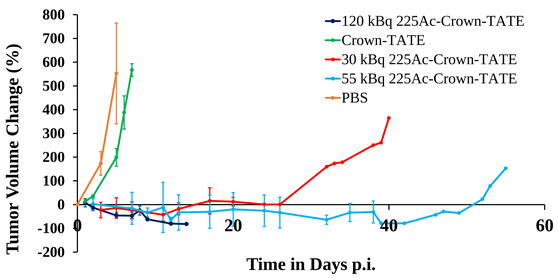
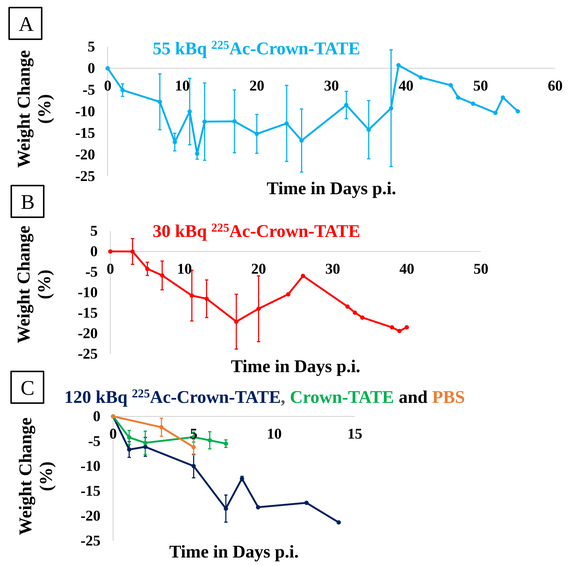


Figure 6. Tumor growth was generally found to be delayed in mice injected with ^{225}Ac-Crown-TATE (30, 55 and 120 kBq). The intermediate dose performed the best in terms of growth suppression. The PBS and Crown-TATE control groups had rapid tumor growth, meaning the mice were euthanized ~within one week.



Figures 7A, 7B and 7C. Weight loss was found to be the main reason for euthanasia in the treatment groups, indicating drug toxicity. Conversely, the control groups did not experience significant weight loss and were euthanized due to tumor growth.

Conclusion and further work

^{225}Ac-Crown-TATE shows promise in that it delays tumor growth in AR42J tumor-bearing mice (involving starting tumor volumes around 50-550 mm^3) and improves their survival probability compared to non-treatment groups.

That said, the doses need to be optimized in future studies since the mice experienced significant weight loss during treatments involving 30 kBq, 55 kBq or 120 kBq doses of drug. Furthermore, tumor growth was found to reoccur in those mice that survived the initial weight loss phase.

Optimized treatments may be achieved by administering multiple small doses of ^{225}Ac-Crown-TATE, for example, 3 x 10 kBq over a six-week time period.

In the short-term, further work entails finishing the therapy study, with each group being 7-9 mice in sample size. Also, biodistribution studies will be conducted and analyzed in tumor-bearing mice to analyze the distribution of ^{225}Ac at five different time points (1 h, 4 h, 24 h, 48 h and 120 h). Finally, the pancreas, tumor, liver and kidneys of randomly chosen mice in each group of the therapy study will be selected for histopathology studies to check the extent of toxicity.

References

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Acknowledgements

TRIUMF
THE UNIVERSITY OF BRITISH COLUMBIA
BC Cancer Agency
CARE + RESEARCH
NET NEUROENDOCRINE TUMOR RESEARCH FOUNDATION