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:

![Image](image_url)

**Scheme 1.** The chemical structure of 225Ac-Crown-TATE; a somatostatin analogue 'tagged' with 225Ac.

In addition, a biodistribution study involving 225Ac-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:

![Image](image_url)

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

Concentration (%)

- 120 kBq 225Ac-Crown-TATE
- Crown-TATE
- 30 kBq 225Ac-Crown-TATE
- 55 kBq 225Ac-Crown-TATE
- PBS

**Figure 5.** The Kaplan-Meier plot shows AR42J tumor-bearing mice (starting tumor volume 50-550 mm³) 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 mm³, or poor health observations. Currently, the sample sizes consist of 120 kBq n = 7, Crown-TATE n = 3, 30 kBq n = 5, 55 kBq n = 7 and PBS n = 3.

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

![Image](image_url)

**Figure 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.

**References**


Acknowledgements

225Ac-Crown-TATE shows promise in that it delays tumor growth in AR42J tumor-bearing mice (involving starting tumor volumes around 50-550 mm³) 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 225Ac-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 225Ac 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.

**Conclusion and further work**