User project report

Druglike FAPIs with extended tumor residence time

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1. Authors

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2. Context of the project (800 characters max. including spaces)

Despite progress, new therapies are needed to improve cancer outcomes. Targeted radiotheranostics, combining diagnostic and therapeutic radionuclides, hold great promise with higher efficacy and lower toxicity. Fibroblast activation protein (FAP), highly expressed in cancer-associated fibroblasts that drive tumor growth and metastasis, is a prime target. While FAP ligands for imaging advanced, radionuclide therapies remain limited due to short tumor residence times. We propose novel FAP-targeted ligands (Mw<1000) with covalently bound ^{18}F for imaging, or ^{211}At for therapy, optimized via quaternary ammonium linkers and an electrophilic warhead to enhance tumor retention and minimize background. To realise this project, access to scarce ^{211}At, (unavailable in Belgium) is requested through PRISMAP. The primary aim is to optimize radiolabelling conditions with ^{211}At, followed by preclinical evaluation.

3. Results and discussion (1000 characters max. including spaces)

Starting from an organotin precursor, **UAMC-5612**, **[^{211}At]CREANT-305** was synthesized via electrophilic radioastatodestannylation with n.c.a. **^{211}At** using *N*-chlorosuccinimide (NCS) in acetic acid. After 30 min reaction at room temperature, the crude product was purified by semi-preparative RP-HPLC to obtain the final product with radiochemical yield (RCY) of 68 ± 12%, radiochemical purity (RCP) of >99%, and molar activity (A_m) of 85 ± 20 GBq/µmol (n=4). The identity of the radiolabeled product was confirmed with co-injection of respective iodinated analog (radio-LCMS). *In vivo* evaluation of **[^{211}At]CREANT-305** in U87MG xenografts showed specific tumor uptake of ~8% ID/g, which was reduced upon blocking with **UAMC-1110** (Figure 1). However, **[^{211}At]CREANT-305** showed low metabolic stability (only 8% intact at 2 h post injection) mainly due to deastatination (Table 1). Single doses of **[^{211}At]CREANT-305** resulted in a dose-dependent delay in tumor growth without causing normal organ toxicities.

4. Conclusions (800 characters max. including spaces)

The electrophilic astatodestannylation of organotin precursor yielded **[^{211}At]CREANT-305** with excellent yields and optimal molar activities. The *in vivo* investigation of **[^{211}At]CREANT-305** in xenograft mice showed specific uptake in tumor, hepatobiliary excretion and low metabolic stability. Currently, the therapy efficacy studies are ongoing. Nevertheless, further structural improvements of the compounds are required to enhance the stability of ^{211}At-labeled compounds towards the radiodeastatination.

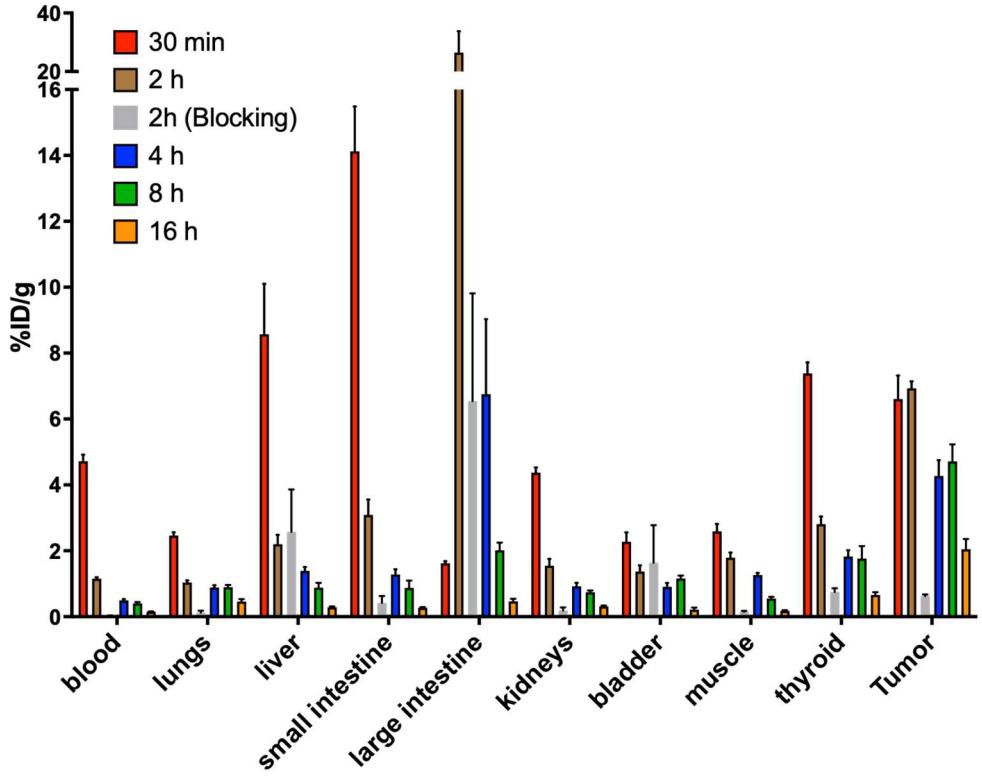

Figure 1. Biodistribution of [^{211}At]CREANT-305.

caption

Table 1 is an example for a table (if necessary).

Table 1. Intact amount (%) of [^{211}At]CREANT-305 at different post-injection time in U87MG xenograft mice.

Post injection time	30 min	2 h	4 h	8 h
Intact **[^{211}At]CREANT-305 (%)**	62.6	8.2	4.6	2.7

5. Involvement of the PRISMAP services (600 characters max. including spaces)

PRISMAP services allowed us to practically execute our research proposal, which would otherwise be impossible since there is no access widespread access to ^{211}At, including in Belgium. The ^{211}At delivery from Arronax allowed us to optimize the radiolabeling conditions, leading to the development of **[^{211}At]CREANT-305** as a potential therapeutic candidate. Furthermore, we were able to investigate **[^{211}At]CREANT-305** preclinically to investigate its metabolic stability, biodistribution and therapeutic efficacy.

6. Feedback to PRISMAP (600 characters max. including spaces)

PRISMAP has provided us full support for the project application. Additionally, the timely deliveries of ^{211}At were ensured so that our experiments could be carried out. Very pleased with the collaboration with Arronax. Professionalism, good communication and timely deliveries.

7. Publications and other dissemination activities (conferences etc.)

An abstract describing the in vitro characterization and biodistribution was presented in May 2025 in the International Symposium for Radiopharmaceutical Sciences 2025 (Gold Coast, Australia). Currently, a manuscript is “in preparation” phase.

Appendix 1. Dissemination guidelines for user projects as agreed in the signed User Agreement

Dissemination rules

Only user groups that are allowed to disseminate the results which they have generated under the project may benefit from the access, unless they are working for SMEs.

For each user group project, a publishable project summary and a publishable summary of the results will be published on the European Union Horizon 2020 PRISMAP project website www.prismap.eu. The publication of results in journals or at conferences is strongly encouraged.

To ensure the long-term sustainability of the PRISMAP initiative, proper recognition of the contributing facilities, their services and the involved persons is necessary. All participating PRISMAP facilities shall be acknowledged in the publication. Acknowledgement and co-authorship of PRISMAP staff members who participated in the experiment shall be considered according to the research field best practices and verified with the PRISMAP Technical Manager before any publication.

The user group shall contact the PRISMAP Technical Manager 30 days prior to submission of publications or other communications of results that were obtained by making use of services provided by PRISMAP (radionuclides delivered or medical services provided). The Technical Manager will communicate to the user group the list of PRISMAP facilities and persons that have contributed to each specific project and the way this contribution must be acknowledged in the publication/communication or where co-authorship is required to reflect specific scientific contributions.

Users must comply with Horizon 2020 dissemination rules (i.e. acknowledge that their work was financially supported by the European Union's Horizon 2020 Research and Innovation Programme by including the following acknowledgement: "This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008571 (PRISMAP)"), and grant open access to resulting publications and related data.

Dissemination shall take place only once legitimate interests regarding intellectual property have been safeguarded. A maximum publication delay of 90 days may be granted for this purpose.

Acknowledgements

The list of name(s) to be mentioned in the acknowledgment section is sent to the technical manager by the main contact of the involved facilities.

A general sentence will be added by the corresponding author of the article (user side):

"The authors would like to thank the members of the PRISMAP consortium and of the PRISMAP user selection panel, coordination and management team for their advice and support."

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