Targeted alpha-radioimmunotherapy with Ac-225 for Neuroblastoma using Dinutuximab beta

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This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101008571 (PRISMAP). This document reflects only the view of the author(s). The Agency is not responsible for any use that may be made of the information it contains.

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

Neuroblastoma (NB) is the most common extracranial solid tumour of childhood. ~50% of NB patients are categorised as high-risk, with the 3 year event free survival currently just over 50%. In high-risk NB, molecular radiotherapy – using ^{131}I-mIBG – has an established place in the management of refractory and relapsed disease. An additional therapeutic target in NB is GD2 with the EMA-approved antibody targeting GD2, Dinutuximab Beta (DB) improving survival in high-risk NB. We have validated ^{177}Lu-labelled DB (^{177}Lu-DB) as a beta-emitting molecular radiotherapeutic against GD2-positive NB. However, due to the potential benefits of alpha-particles for treating tumours and micrometastases, we wished to radiolabel DB with ^{225}Ac to create GD2-targeted alpha radioimmunotherapy for high-risk NB.

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

Two radiolabelling attempts were made with specific activity of 0.4 kBq/ug of DB at a 120 ug scale reaction. The radiochemical yields were 45.7 % and 21.4 % by iTLC. The antibody was purified via size exclusion chromatography using a PD-10 column with fractions combined and formulated in PBS + 5 mM DTPA + 50 mM sodium ascorbate. The radiochemical purity, post-purification was 99.9 % and 99.6 % by iTLC. After 24h the RCP was measured again by iTLC which were 99.8 and 99.6 %. HPLC chromatograms (Figure 1) at each timepoint showed a peak at 17 min matching the native DB antibody, confirming radiolabelling.

4. Conclusions (800 characters max. including spaces)

Dinutuximab beta has been successfully radiolabelled with ^{225}Ac, however due to isotope access issues (outlined in section 6) further validation has not been possible.

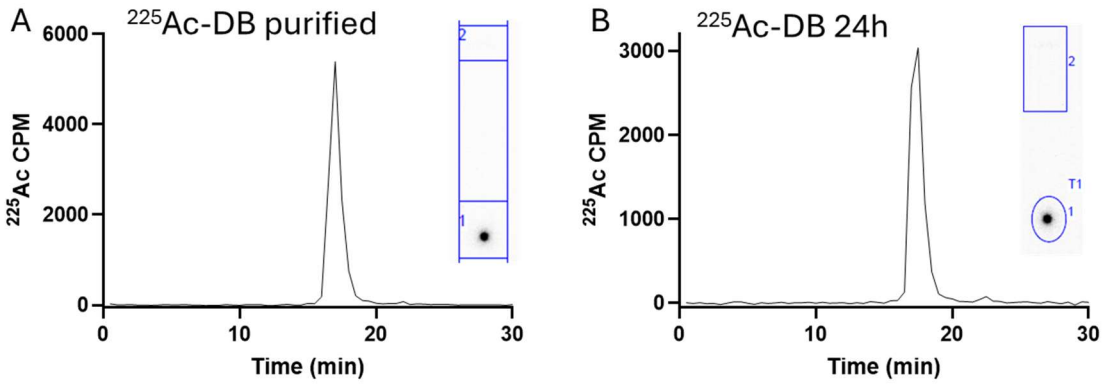

Figure 1. Representative HPLC chromatograms of A) ^{225}Ac-DB post-purification and B) ^{225}Ac-DB at 24h in formulation buffer. In each case 30 s fractions were collected off the HPLC and placed in the gamma counter to measure the daughter emissions 24 h after collection. Note: the corresponding iTLC for each timepoint is in the top right of each chromatogram.

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

^{225}Ac is not produced in the UK, where this work took place, and we do not have access to this radionuclide. Hence, receiving ^{225}Ac from PRISMAP was essential for us to expand our goals for this project towards alpha-based radioimmunotherapy of high-risk Neuroblastoma.

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

As part of the initial agreement with PRISMAP we requested three batches/deliveries of ^{225}Ac of approximately 5 MBq to be delivered at appropriate times across 2024 to allow maximum usage of the isotope. The initial agreement was signed with JRC at around December 2023. However, after multiple failed attempts over months to get in touch with the JRC, it was brought to our attention by other members of PRISMAP that this supplier was unable to supply this isotope to us. An alternative supply was found via CERN-MEDICIS who was supplying NPL with Ra-225, who would then in turn extract Ac-225 from that source to be delivered to us at QMUL. Another user agreement was signed in Nov 2024 in time for a delivery in December 2024. However, due to last minute nature of this delivery and prior experimental obligations at the time, only limited radiochemical experiments could be carried out. Additionally, we only received one delivery, so were limited in how much of our initial experimental plans we could carry out. Despite this, we appreciate the help and support from other PRISMAP users/suppliers to get us the requested Ac-225 at short notice.

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

N/A

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."

Funding acknowledgement

"This work was supported by the European Union's Horizon 2020 research and innovation programme as a user project of PRISMAP – The European medical radionuclides programme (GA 101008571)".