User project report

In vitro and *in vivo* validation of new chelators for Ac-225 targeted α-therapy

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2. Context of the project

Ac-225 decays into a sequence of short-lived daughter isotopes, including Fr-221, At-217, and Bi-213, each emitting α-particles before reaching a stable state at Bi-209. The emission of these isotopes results in a total of four potent α emissions per atom, creating a high cumulative dose at the tumour site and ensuring effective cell destruction. The objective of the project was to synthetise, characterise and test for Ac-225 labelling new flexible ligands able to chelate firmly Ac-225 and its daughter isotopes and thus attempting to reduce the recoil effect. Once the optimal chelator for Ac-225 labelling is found, the synthesis of a bifunctional chelator and its conjugation to a specific vector for PSMA targeting was attempted in order to allow in vivo testing of the therapeutic probe.

3. Results and discussion

Mesocyclic structures like 6-amino-6-methyl-1,4-perhydrodiazepine (AMPED) and 2-aminomethylpiperidie (AMP) functionalized with picolinic arms were considered a suitable compromise between the rigidity needed to enhance the thermodynamic stability of the complex and the flexibility to adapt their geometry to the different dimension of the radioisotopes. In this case, the cage could be able to expand to label Ac-225 but also to encapsulate the smaller daughter isotope Bi-213 (Figure 1). Three ligands were synthesized and characterized via spectroscopic techniques. The AMP-3PIC ligand was successfully labelled with Ac-225 and it seemed promising for stably complexing both actinium and bismuth as evidenced in stability tests carried out for 48 hours. Based on that, we proceeded with the synthesis of the corresponding bifunctional AMP ligand to be conjugated with the PSMA617 ligand. Unfortunately, attempts to synthesize the bifunctional ligand using two different methods have so far been unsuccessful.

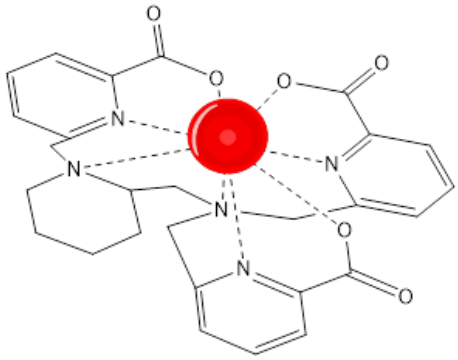

Figure 1. The ligand AMP-3PIC with the possible coordination geometry.

4. Conclusions

The first part of the project went smoothly with the synthesis of the chelators and the preliminary testing at TUM by the PhD student that spent one and half month in the Host institution. These measurements were also repeated at TUM and the results confirmed that the ligand AMP-3PIC has shown promise for

the labelling of 225-Ac and 213-Bi. However, the synthesis of the AMP-3PIC-PSMA probe resulted complicated, and despite two different synthetic approaches were tested, both were unsuccessful. The completion of the project will still be attempted after the end of the PRISMAP project which will be acknowledged by the authors.

5. Involvement of the PRISMAP services

To test Ac-225 labelling of our new ligands, the support provided by PRISMAP through the JRC centre in Karlsruhe was fundamental. For our project, we have combined a 1 and ½ month research stay of the PhD student Sara Camorali to the delivery of 225Ac to the Department of Nuclear Medicine of TUM MRI, allowing us to carry out the experimental work in the best possible way. Further experiments were conducted by the PhD student Adriano Bolognani from Prof. Calogero D'Alessandria's team. The TUM MRI team will continue to support the completion of the project beyond the completion of PRISMAP.

6. Feedback to PRISMAP

The process of grant application and assignment was smooth and clear. The only had some problem in reimbursing the PhD student as PRISMAP had not yet provided for reimbursement of expenses for PhD students who went to carry out research activities at the chosen location. However, thanks to the commitment of the host in TUM we were able to obtain a partial reimbursement for the PhD student. Regarding the delivery of 225-Ac, the host at TUM has maintained contact for deliveries which, as far as I know, occurred regularly.

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

We are committed to acknowledge PRISMAP in future publications that will originate upon completion of the project.

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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