User project report

New chelators for complexation of medically useful lanthanide and actinide radioisotopes

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1. Authors

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

Chelator chemistry for stably incorporating the radiotherapeutic isotope, $^{161}Tb^{3+}$, into targeting biomolecules is underdeveloped. Whilst radiolabelled complexes of the widely used chelator, DOTA, are stable *in vivo*, and deliver $^{161}Tb^{3+}$ to target tissue, DOTA has limitations. Radiolabelling requires high temperatures, which is incompatible with proteins and antiboies, which often denature when heated above 40 °C.

We have prepared novel chelators that are designed to be radiolabelled with $^{161}Tb^{3+}$ under mild conditions. We aimed to assess radiolabelling of these chelators, including:

(1) A series of novel hybrid macrocyclic chelators with pendant hydroxypyridinone motifs;

(2) A aza-crown macrocycle with pendant hydroxyquinoline groups;

(3) A well-established "macropa" chelator.

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

(1) 3C-TRIHOPO, consisting of a triaza crown ether with three hydroxypyridinone groups, was radiolabelled in 95% radiochemical yield at room temperature and near-neutral pH, albeit under carrier-added conditions, as measured by radio-HPLC. ^{161}Tb-3C-TRIHOPO, was administered i.v. to healthy mice, and its biodistribution at 1 h post-administration compared to that of ^{161}Tb-chloride. ^{161}Tb-3C-TRIHOPO cleared the bloodstream faster than that of ^{161}Tb-chloride, as measured by lower ^{161}Tb concentration in the blood pool and heart, and higher ^{161}Tb concentrations in the kidneys for mice administered ^{161}Tb-3C-TRIHOPO. However, there was also significant amounts of ^{161}Tb radioactivity in the bone, suggesting that ^{161}Tb-3C-TRIHOPO dissociates *in vivo*. (*Figure 1*)

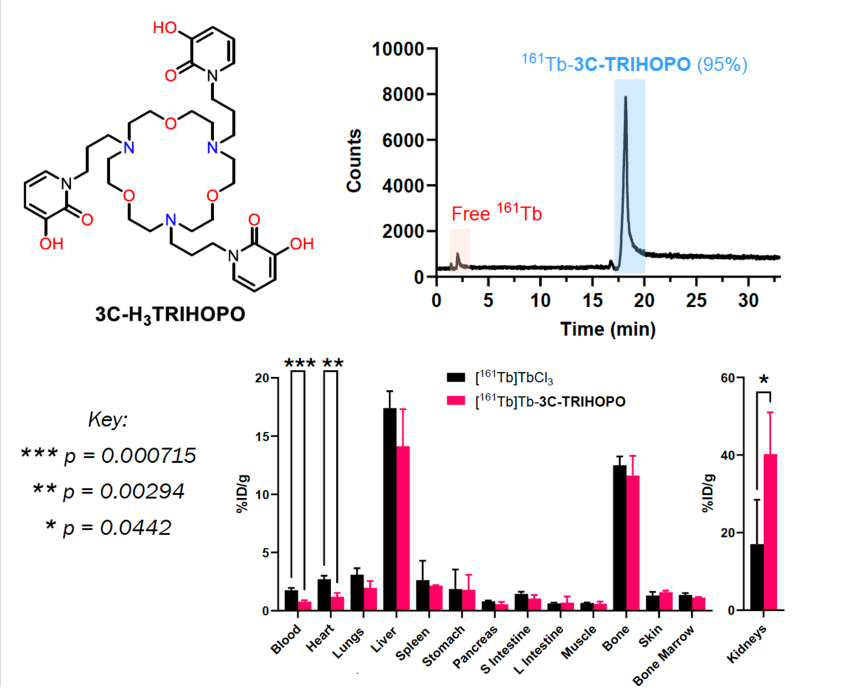

Figure 1. ^{161}Tb-3C-TRIHOPO can be radiolabelled in high yield, as evidenced by radio-HPLC. The biodistribution of ^{161}Tb-3C-TRIHOPO 1 h post-administration shows it is excreted via a renal route, but also that it is unstable, releasing ^{161}Tb that accumulates in bone.

(2) Using radio-HPLC, we have shown that the macropa chelator binds β$^-$-emitting ^{161}Tb in >80% radiochemical yield under mild conditions (25 °C, pH 6.5, 30 min) at a desirably low chelator concentration (20 µM). (*Figure 2*)

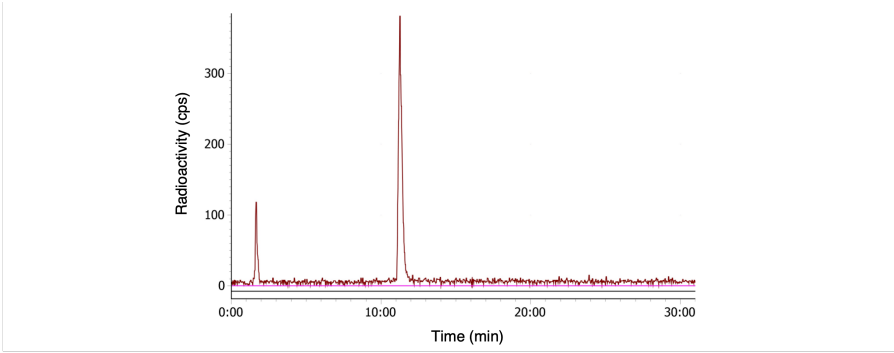

Figure 2. The macropa chelator binds β$^-$-emitting ^{161}Tb in >80% radiochemical yield, as evidenced by radio-HPLC.

4. Conclusions (800 characters max. including spaces)

The new 3C-TRIHOPO chelator is unlikely to be suitable for preparation of stable ^{161}Tb-labelled radiotracers, even though it can be radiolabelled at room temperature. However, macropa chelator, previously developed for radiolabelling with $^{225}Ac^{3+}$, could be highly suitable for $^{161}Tb^{3+}$ radiolabelling under mild conditions.

5. Involvement of the PRISMAP services

We would not have had access to ^{161}Tb without PRISMAP services. Furthermore, $^{161}Tb^{3+}$ radiolabelling studies with macropa were included in a portfolio of preliminary data for an application to Cancer Research UK. This funding was awarded, and it will allow us to develop a macropa-based bifunctional chelator for site-specific radiolabelling of antibodies.

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

PRISMAP is not only well-organised as a service, but the symposia it runs seeds valuable scientific discussion, promotes collaboration and brings the nuclear medicine community together. I have really enjoyed working with PRISMAP collaborators and I hope to be involved in future initiatives.

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

PRSIMAP activites

I presented our ^{161}Tb work at the **PRISMAP Radiolanthanides Workshop**, September 2024: *Hybrid hydroxypyridinone-macrocyclic chelators for coordination of lanthanide and actinide radionuclides*

PhD dissemination activities

My PhD student, Rory Kenrick, has presented the following presentations and posters on project 1. We will draft a paper on this work in 2026:

Oral presentations

- *New hybrid hydroxypyridinone-aza-crown-macrocyclic chelators for molecular imaging and radiotherapy*, 45th **International Conference on Coordination Chemistry** (ICCC), 28th July – 3rd August 2024, Colorado, United States, 28th July – 3rd August 2024
- *New hybrid hydroxypyridinone-aza-crown-macrocyclic chelators for molecular imaging and radiotherapy*, Royal Society of Chemistry **Dalton 2025**, 1st April – 3rd April 2025, Warwick, United Kingdom

Poster presentations

- *New hybrid hydroxypyridinone-aza-crown-macrocyclic chelators for molecular imaging and radiotherapy,* Fifth Symposium on Preclinical Nuclear Imaging (PNI), 28th October 2024, London, United Kingdom

Submitted papers

In collaboration with co-author, Nicholas Long, and with PRISMAP collaborators at PSI, we have submitted a manuscript on an adjacent project that has used ^{161}Tb from PRISMAP:

Christina Siakalli, Bradley E. Osborne, Ryan K. Brown, Claudia Rocco, Dominik Weiss, Enrique V. García-España, Pascal V. Grundler, Anzhelika N. Moiseeva, Zeynep Talip, Nicholas P. van der Meulen, Michelle T. Ma, and Nicholas J. Long, *Hydroxyquinoline-functionalised aza-crown macrocycles for stable lanthanide coordination*, submitted to Dalton Transactions

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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