User project report

Terbium radiolabelling of new multimodal SPECT/MRI cyclodextrin inclusion complexes

Dr Deborah Sneddon

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1. Authors

Isabelle Herbert[a], Dr David Viertel[b], Chris Dadswell[a] and Dr Deborah Sneddon[a]

[a]Department of Chemistry, University of Sussex, Brighton, UK

[b]Laboratoire Translationnel des Sciences Radiopharmaceutiques, Service de Médecine Nucléaire et Imagerie Moléculaire, Rue du Bugnon 46, CH-1011 Lausanne

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

Despite the recognition that multimodality imaging has several benefits, there have been limited advances in the development of suitable imaging tools in clinical use. New multimodal imaging agents based on cyclodextrin scaffolds were proposed, that combine Tb for either optical or radionuclide imaging with Gd for magnetic resonance imaging (MRI). The goal of this proof-of-concept pilot study was to validate the radiolabelling conditions of two 161-Tb complexes that differ in their side chain and their Tb coordination sphere, and assess their stability against small molecule chelators and biological macromolecules. From these results, we will be able to further optimise these imaging agents for the next generation of multimodality probe.

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

The radiolabelling conditions of two small molecule ligands was optimised (buffer, pH, ligand concentration, activity) and were successfully labelled in 15 min in NaOAc buffer (0.5 M), pH 4, 0.1 mM ligand, 95 °C with 0.25-10 MBq of $^{161}TbCl_3$ (iTLC). The robustness of the labelling method was examined, and it was found that <0.1 mM ligand concentration, no radiolabelling occurred. Radio-HPLC determined the presence of multiple species in complex **2** directly after labelling, where complex **1** gave a singular species. After 3d in solution, no free ^{161}Tb was observed (iTLC). In challenge experiments with ETDA, both complexes were unstable, determined by the presence of free ^{161}Tb-EDTA (24 h). However, when challenged with DTPA or Zn, no free ^{161}Tb was observed in either complex (24 h). In human serum experiments, no free ^{161}Tb was observed after 3 d for **1** or **2**, but a new, secondary species was observed in complex **2** (iTLC). This data points to complex **1** being the more stable chelator.

4. Conclusions (800 characters max. including spaces)

The radiolabelling conditions for two complexes was successfully optimised and the stability of the complexes in solution and against human serum albumin and small molecule chelators was determined. Although complex **1** was unstable against EDTA, resulting in free ^{161}Tb observation, it was overall the most stable ^{161}Tb ligand as multiple species were determined in complex **2** after labelling and in competition experiments. Clearly, further work is necessary to find the best chelator for ^{161}Tb to allow ease of labelling and optimum stability with a focus on speciation. With this information in hand, we will be able to further optimise these imaging agents for the next generation of multimodality probes.

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

This project could not have been undertaken without the use of PRISMAP services. We do not have a radiochemistry laboratory at our university and therefore have no access to isotopes or the necessary equipment. The PRISMAP consortium connected us to Dr. David Viertel, who has been instrumental to the results obtained in this project, whose experience and expertise working with this isotope was necessary. Through PRISMAP, my PhD student was not only able to visit an experienced laboratory, but the results obtained will shape our next generation of compounds.

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

Prior to project application submission, I contacted the PRISMAP helpdesk who connected me to Dr Viertel. The opportunity to discuss the project prior to application and consider the experiments we could undertake contributed to a successful project award. The delivery schedule was planned taking into account all parties and we were able to update the delivery which was greatly appreciated. For future consortiums like PRISMAP, if it were possible to build in more opportunities for hands on student training, that could be beneficial.

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

Working title: "*Preliminary radiolabelling and relaxivity studies on multimodal SPECT/MRI inclusion complexes*". In preparation but further results are required prior to publication. Please be aware that the author list may be updated when new results are obtained. Conference dissemination has not yet been secured.

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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