User project report

"Terbium-161 radiolabelling of an engineered PARP1 inhibitor bearing AAZTA chelator"

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2. **Context of the project:** PARP-1, a key DNA repair enzyme, maintains genome integrity but is often disrupted in tumors. Cancer cells then rely on alternative repair pathways, which can be blocked by inhibitors to trigger cell death—a concept known as synthetic lethality. PARP inhibitors show promise in BRCA-mutated cancers, though not all patients benefit, highlighting the need for biomarkers and imaging tools. Radiolabelled PARP inhibitors enable tumor visualization and therapy, delivering radiation directly to DNA. Terbium-161, with superior short-range emissions, offers enhanced efficacy over lutetium-177. Building on recent advances, we aim to develop the first Terbium-161-labeled PARP-1 inhibitor with an AAZTA chelator for targeted radionuclide therapy.

3. **Results and discussion:** The synthesis of the precursor was successfully completed. However, trace amounts of zinc were found to interfere with the subsequent radiolabelling process, necessitating multiple purification cycles delaying the following steps. Dr. JA. Bolcaen performed radiolabelling trials with lutetium-177 yielded the desired tracer with an encouraging yet suboptimal radiochemical yield of 47%. Following Dr. G. Destro's relocation to Edinburgh, substantial progress was achieved using gallium-68, a radionuclide with comparable coordination chemistry to lutetium-177, resulting in a markedly improved radiochemical yield of 93% at room temperature. Upon transfer of the purified compound to PSI, the optimized labelling protocol successfully reproduced these results. Furthermore, Dr. R. Rizzo confirmed the efficient cellular internalization of the fluorescent probe through confocal microscopy, thereby validating its biological activity and supporting its potential for subsequent in vitro radiolabelling and imaging investigations.

4. **Conclusions:** Although time constraints prevented the full completion of the planned experiments, the promising outcomes in both chemistry and radiochemistry provide a strong foundation for continuing the project and advancing toward full in vitro and in vivo evaluation.

5. **Involvement of the PRISMAP services:** none

6. **Feedback to PRISMAP:** none

7. **Publications and other dissemination activities:** Oral presentation of preliminary results at "Network di Ricerca in Radiochimica" September, 2025, Italy by Dr. Gianluca Destro.

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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