User project report

ScandAL
Scandium-43 Antibody-fragment Labelling

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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

Immunotheranostic strategy is a game-changer in patient-care in oncology. It combines the targeting potency of antibodies and the properties of radioisotopes, either for diagnosis or for vectorised internal radiotherapy. To match the slow pharmacokinetics of full antibodies, Zr-89 (half-life: 78 h) is usually used for ImmunoPET but leads to high radiation exposure and requires imaging 3 to 5 days post injection to obtain interpretable images. To unlock these limitations, ScandAL proposes to use the emerging Sc-43 β^+ emitter (half-life: 4 h) conjugated to a minibody or to octreotide (faster pharmacokinetics) targeting the PD-L1 immuno-check point or the somatostatin receptor, respectively. This proof of concept in imaging could then be extended to therapy with the Sc-47 β^- emitting isotope.

3. Results and discussion

The first step for labelling of biomolecules with Sc-43 was their conjugation to a chelating group. Following published results,[1] we choose DOTA and used two methods for its incorporation, a rebridging strategy of native disulfide bridge for octreotide (Fig 1, A) and a random labelling strategy on lysine residues for minibody (Fig 1, B). Incorporation of the chelate was confirmed by LC-MS or MALDI prior to labelling experiments. Octreotide labelling was performed at 25°C in 0.1 M NaOAc pH 4-5. After 15 min, HPLC analyses showed nearly complete conversion of the free Sc-43 to ^{43}Sc-octreotide (82 %, n = 3). After purification, ^{43}Sc-octreotide was injected on ARJ42 animal model (10 µg/6.5 MBq per animal). Labelling of minibody was performed at 40°C and proved more challenging due to minibody instability. After purification, the pure ^{43}Sc-minibody was obtained with an 18 % yield (ndc) and injected to B16F10 animal model (10 µg/3 MBq per animal, Fig 1, C).

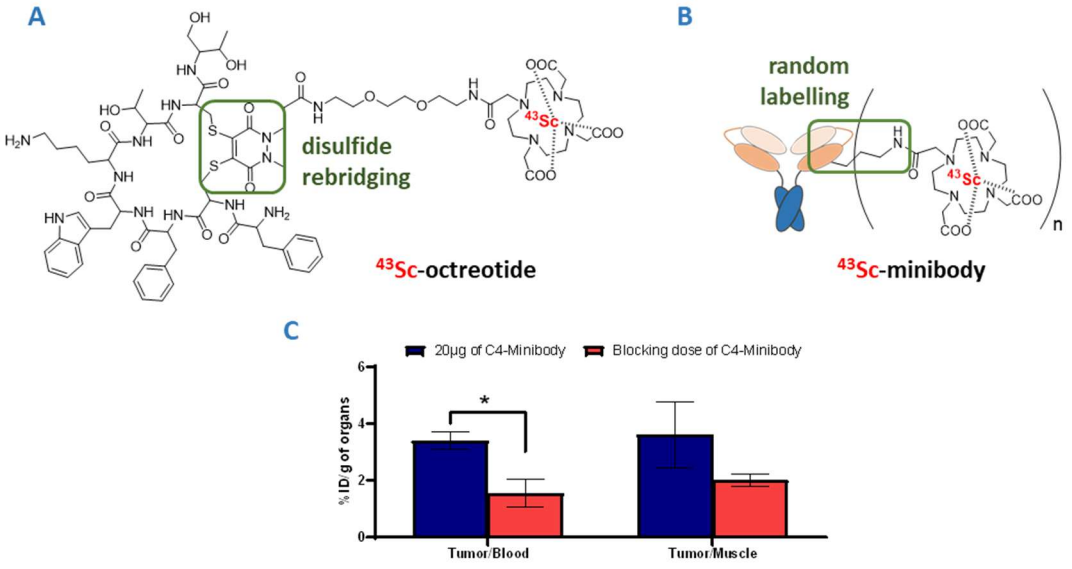

Figure 1. Structures of ^{43}Sc-biomolecules (A & B) and biodistribution (tumor/blood ratio) of ^{43}Sc-minibody in B16F10 animal model (C)

4. Conclusions

The labelling of two biomolecules (octreotide peptide & PDL-1 targeting minibody) with scandium-43 was successfully carried out. These ^{43}Sc-labelled molecules were then injected to relevant animal models (ARJ42- and B16F10-tumor bearing mice, respectively). Regarding ^{43}Sc-octreotide, labelling was fast and efficient. Unfortunately, biodistribution studies and PET imaging did not show any specific uptake in the tumor. Labelling of minibody was more challenging due to its fragility and complexity. However, we could obtain the pure ^{43}Sc-minibody in sufficient yields for biodistribution and PET studies. Biodistribution showed a specific uptake in the tumors and blocking experiments led to a decrease of signal in the tumor, confirming the specificity of ^{43}Sc-minibody for B16F10 tumors.

5. Involvement of the PRISMAP services

This project required the production of three doses of Sc-43 (800 MBq on 19/07/23, 808 MBq on 16/11/23 and 973 MBq on 12/06/24) at PSI in Zurich and delivery of those doses to CHUV in Lausanne where we had access to the microPET/CT imaging facility managed by Dr David Viertl. We performed radiolabelling of the biomolecules, injection to small animals and imaging and biodistribution studies in the nuclear medicine department at CHUV. The small animal models were also implemented at CHUV, according to procedures developed at SHFJ.

6. Feedback to PRISMAP

In the context of the ScandAL project, 3 doses of Sc-43 were delivered in the nuclear medicine department at CHUV in Lausanne. The delivery of the doses from PSI in Zurich, coordinated by Dr Charlotte Duchemin, was reliable and efficient. We got detailed information on the produced doses (purity, activity, volume …) for each batch as soon as it was available from the production team at PSI. We would like to thank Dr David Viertl for granting us access to the microPET/CT imaging facility and his help with small animal model preparation, dose injections and images interpretation.

7. Publications and other dissemination activities

We are in the process of writing and submitting these results for publication in *Bioconjugate Chemistry*.

This work will also be presented in national (GDR AIM, 10/2024) and international (2025) conferences.

References

(1) Huclier-Markai, S.; Sabatie, A.; Ribet, S.; Kubícek, V.; Paris, M.; Vidaud, C.; Hermann, P.; Cutler, C. S. Chemical and Biological Evaluation of Scandium(III)-Polyaminopolycarboxylate Complexes as Potential PET Agents and Radiopharmaceuticals. **2011**, *99* (10), 653–662.

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)".