User project report

UTOPY: Unleashing the Theranostic Potentiality of Silver-111

Applicant: Mattia Asti

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1. Authors

Mattia Asti: Radiopharmaceutical Chemistry Section, Nuclear Medicine Unit, Oncologic and High Technologies Department - AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

Marianna Tosato: Department of Chemistry - Simon Fraser University Burnaby, Canada; Life Sciences, TRIUMF, Canada

Lars Hemmingsen: Department of Chemistry, University of Copenhagen, Copenhagen, Denmark

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

Targeted radionuclide therapy is a potent approach, especially for cancer patients that have exhausted all other therapeutic options. Silver-111 (^{111}Ag, $t_{1/2}$ = 7.47 d) has suitable theranostic features possessing a medium-energy β^- ($E_{\beta-}$, max = 1.04 MeV) and a low-energy γ ($E_{\gamma1}$ = 245.4 keV, $I_{\gamma1}$ = 1.24 %; $E_{\gamma2}$ = 342.1 keV, $I_{\gamma2}$ = 6.7 %) emissions that could be exploited for theranostic application. From a chemical point of view, silver belongs to the transition metals of the 11th group and shares some chemical similarities with copper. Unfortunately, its coordination (radio)chemistry is poorly characterized. The overarching aim of this application has been the development of innovative chelators able to form stable and inert complexes with Ag^+ in order to establish the possible use of ^{111}Ag for clinical applications.

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

A series of sulfur-containing ligands (Figure 1) has been devised. Characterization and ability to form complexes with Ag^+ have been pursued through fundamental coordination chemistry techniques (NMR spectroscopy, potentiometry, mass spectrometry, DFT calculations). The outcomes obtained have been verified by radiolabelling tests using $^{111}Ag^+$ and stability assays were conducted for chelators showing promising labelling properties. For some chelators, the estimation of the stability in human serum was performed using PAC-spectroscopy as alternative to standard techniques usually applied (i.e. radio-TLC). CB-TE2S and DO2SPy showed the best performance providing quantitative labelling of 1 MBq of ^{111}Ag up to 10^{-7} ligand concentration and stability in human serum > 80% up to 24 hours. Biodistribution and SPECT-imaging of ^{111}Ag-CB-TE2S have been evaluated in murine models and compared to the physiological biodistribution of free$^{111}Ag^+$. PAC was also used to attest stability of the complexes in biological fluids.

4. Conclusions (800 characters max. including spaces)

Analysis of biodistribution is still ongoing but the first SPECT-imaging showed both ^{111}Ag-CB-TE2S and free$^{111}Ag^+$ mainly accumulating in the mice liver. PAC-spectroscopy analysis could settle if this accumulation is due to a physiological metabolization of the complex or a leakage of ^{111}Ag from the ligand but elaboration of the data are still running. The outcomes of this project have expanded the knowledge of Ag^+ coordination chemistry and found potential chelators that will move the application of a new radionuclide toward the clinical setting. The possible use of PAC spectroscopy as useful techniques for the evaluation of ^{111}Ag-complexes stability *in serum* and in mice organs has been proved.

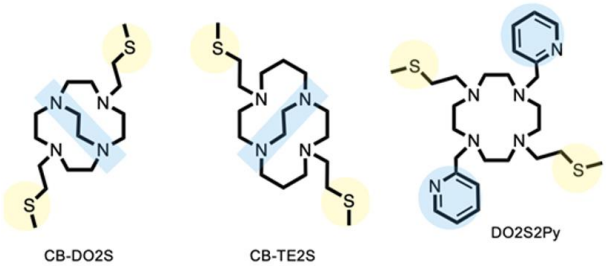

Figure 1. Chemical Structures of the chelators developed in the frame of the project

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

PRISMAP have guaranteed the provision of ^{111}Ag for all the duration of the project.
In particular, three ^{111}Ag-productions have been delivered to the Hevesy Lab Facilities (Roskilde, Denmark) at different stages of the project, with the aim to i) perform and optimize labelling and stability studies ii) unfold *in vitro* PAC-spectroscopic applications and calibration of the micro-SPECT instrumentation iii) perform *in vivo* studies + PAC-measurement of the stability in biological fluid and main accumulating organs. Travel, subsistence, and local accommodation costs for two of the applicants (Mattia Asti and Marianna Tosato) was also partially sustained by the consortium.

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

The applicants acknowledge all the components of the advisory board of the PRISMAP consortium for the assistance and availability to solve any problem occurred during the project. They also thanks the personnel of the Hevesy Lab for hosting and assisting them in the compliance of the project in Roskilde.

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

Publications:

A Hybrid Pyridine-Thioether Octadentate Macrocycle to Chelate Group 11 Theranostic Radiometals, *manuscript in preparation*

Oral and Poster presentations:

iSRS Gold Coast, Australia (poster presentation): “Silver Gate”: Chelation of Theranostic Silver Radioisotopes Using a Cross-Bridged Sulfur-Containing Macrocycle

“V Convengo Italiano sulle Terapie Avanzate e Radiofarmaci Innovativi”, Rimini, Italy (oral presentation): Nuovi radionuclidi per applicazioni diagnostiche e terapeutiche

“3° Network di Ricerca in Radiochimica” Reggio Emilia, Italy (oral presentation): Tuning Coinage Radiometals Coordination for Cancer Theranostics

NFRF Symposium, Sheerbrooke, Canada: Enhancing the Biological Stability of Coinage Radiometal Complexes with Cross-Bridged Sulfur-Containing Macrocycles for Theranostic Radiopharmaceuticals

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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