User project report

Bisphosphonate – diamine mixed complexes of ^{103}Pd for Auger electron therapy of bone cancer metastasis

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1. Authors

Aleksander Bilewicz, Geeva Prasanth Annamalaisamy, Monika Łyczko, Magda Piątkowska

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

The presented project concerns the synthesis and chemical and biological studies of 103Pd bisphosphonate – diamine mixed complexes and their application in the treatment of bone metastases. The aim of our project was to implement a relatively new concept for treating bone cancer metastases using Auger electron emitters. In our approach, synthesized mixed complexes of ^{103}Pd with bisphosphonates and aromatic diamine will accumulate in bone cancer cells, pass through the cell and nuclear membranes and intercalate into DNA, just as non-radioactive analog complexes which have been previously studied. Subsequently, as a result of nuclear decay $^{103}Pd \xrightarrow{EC} {}^{103m}Rh$, the Auger electron emitter 103mRh will be partially released from the ^{103}Pd complex. In the chemical form of $^{103}Rh_{aq}^{3+}$ it will bind to the DNA, inducing cytotoxic effects by Auger electron emission.

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

In our studies, we synthesized mixed complexes of ^{103}Pd with bisphosphonate and an aromatic diamine. These complexes accumulate on bone cancer cells, penetrate cell and nuclear membranes, and intercalate with DNA, similar to their non-radioactive analogues. We found that the complex exhibited very high cytotoxicity, significantly greater than that observed for other ^{103}Pd complexes and for bisphosphonates of other radionuclides, such as ^{177}Lu, ^{166}Ho, or ^{161}Tb.

In the second approach, we used ^{103}Pd to synthesize the ^{103}Pd-cyclam-PSMA radiopharmaceutical. For this purpose, the PSMA molecule was conjugated to a bifunctional cyclam ligand synthesized by Professor Herman from Charles University in Prague. After synthesis, the conjugate was successfully labeled with ^{103}Pd and tested for stability, cellular affinity, and cytotoxicity on DU145 prostate cancer cells. The results demonstrated that the conjugate exhibited high stability and significant cytotoxicity. The radiopharmaceuticals developed in this project are the first to utilize the ^{103}Pd radionuclide for targeted Auger electron therapy.

4. Conclusions (800 characters max. including spaces)

The synthesised $^{103}Pd_2$(bpy)$_2$ale complexes show high affinity to the surface of hydroxyapatite grains, which is the main mineral component of bone. Nonradioactive and radioactive complexes exhibit high cytotoxicity against the human prostate (DU 145) and ovarian Her2+ (SKOV-3) cancer cell lines, higher than trastuzumab labeled with Auger electron emitter ^{125}I and also cisplatin. The radioactive $^{103}Pd_2$(bpy)$_2$ale conjugate exhibits multimodal toxicity, emitting Auger electrons, and demonstrate chemotoxicity comparable to the commonly used chemotherapeutic cisplatin. However, the radiotoxic effects of Auger electrons become dominant due to the relatively high internalization of the radiobioconjugate into the cell nucleus and its expected intercalation with DNA. In studies using ITLC, we also found complete retention of the daughter isotope ^{103m}Rh in the $^{103}Pd_2$(bpy)$_2$ale complex after decay of ^{103}Pd.

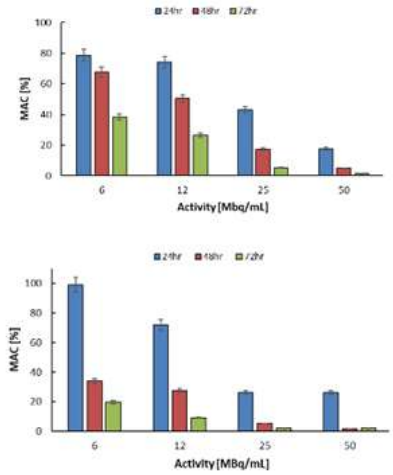

Fig. 1 Metabolic viability of SKOV-3 (top) and Du-145 (below) cells after treatment with different activity of $^{103}Pd_2(bpy)_2ale$

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

Between 2023 and 2025, the Institute of Nuclear Chemistry and Technology received three shipments of ^{103}Pd radionuclide from Institut Laue–Langevin (ILL) Grenoble with a total activity of approximately 10 GBq. The targets were dissolved in NCBJ-Polatom.

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

Both the activity and purity of the radionuclide were very high. Also the application process and delivery of the radionuclide were very well-organized.

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

Publications:

1. G. Prasanth Annamalaisamy, M. Łyczko, A.Bilewicz, The radioactive 103Pd and 109Pd palladium bipyridyl–bisphosphonate complexes for radionuclide therapy of bone metastatic tumor cells. RSC Adv., 2025, 15, 18501. https://pubs.rsc.org/en/content/articlepdf/2025/ra/d5ra02172c
2. G. Prasanth Annamalaisamy, M. Wierzbicki, M. Łyczko, A. Bilewicz, The ^{103}Pd-DOTMP complexes for conversion and Auger electron therapy of bone metastatic tumor cells. In preparation
3. M. Piątkowska, M. Wierzbicki, M. Łyczko, A. Bilewicz, ^{103}Pd labeled PSMA for targeted Auger electron therapy. In preparation

Conferences:

1. G. Prasanth Annamalaisamy, M. Łyczko, A. Bilewicz, Preparation and Characterization of Palladium-103/109 bisphosphonate2,2'-bipyridyl complexes for the treatment of bone cancer metastasis – Preliminary studies, International Symposium on Trends in Radiopharmaceuticals (ISTR2023) Vienna, Austria.
2. G. Prasanth Annamalaisamy, M. Łyczko, , A. Bilewicz, Synthesis of $^{103/109}$Pd- bipyridyl-bisphosphonate complexes for the treatment of bone cancer metastasis. International Conference on development and applications of nuclear technologies at Cracov, Poland.
3. G. Prasanth Annamalaisamy, M. Łyczko, , A. Bilewicz, $^{103/109}$Palladium-2,2'-bipyridyl-bisphosphonate complexes for the treatment of bone cancer metastases. Tumor Targeting, Imaging and Radiotherapies. Canceropole workshop Erquy- France 2024.

4. M. Piątkowska, G. Prasanth Annamalaisamy, M. Łyczko, , A. Bilewicz, P. Herman, 103/109Pd-cyclam bis(phosphonate)complexes for the bone cancer metastasis therapy. Canceropole workshop Erquy- France 2025.

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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