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Preparation of 212Pb-labeled monoclonal antibody using a novel 224Ra-based generator solution

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Summary: Introduction: Alpha-emitting radionuclides have gained considerable attention as payloads for cancer targeting molecules due to their high cytotoxicity. One attractive radionuclide for this purpose is 212Pb, which by itself is a β -emitter, but acts as an **in vivo** generator for its short-lived α -emitting daughters. The standard method of preparing 212Pb-labeled antibodies requires handling and evaporation of strong acids containing high radioactivity levels by the end user. An operationally easier and more rapid process could be useful since the 10.6 h half-life of 212Pb puts time constraints on the preparation protocol. In this study, an **in situ** procedure for antibody labeling with 212Pb, using a solution of the generator nuclide 224Ra, is proposed as an alternative protocol for preparing 212Pb-radioimmunoconjugates.

Methods: Radium-224, the generator radionuclide of 212Pb, was extracted from its parent nuclide, 228Th. Lead-212-labeling of the TCMC-chelator conjugated monoclonal antibody trastuzumab was carried out in a solution containing 224Ra in equilibrium with progeny. Subsequently, the efficiency of separating the 212Pb-radioimmunoconjugate from 224Ra and other unconjugated daughter nuclides in the solution using either centrifugal separation or a PD-10 desalting size exclusion column was evaluated and compared.

Results: Radiolabeling with 212Pb in 224Ra-solutions was more than 90% efficient after only 30 min reaction time at TCMC-trastuzumab concentrations from 0.15 mg/mL and higher. Separation of 212Pb-labeled trastuzumab from 224Ra using a PD-10 column was clearly superior to centrifugal separation. This method allowed recovery of approximately 75% of the 212Pb-antibody-conjugate in the eluate, and the remaining amount of 224Ra was only $0.9 \pm 0.8\%$ ($n = 7$).

Conclusions: The current work demonstrates a novel method of producing 212Pb-based radioimmunoconjugates from a 224Ra-solution, which may be simpler and less time-consuming for the end user compared with the method established for use in clinical trials of 212Pb-TCMC-trastuzumab

 **Article**, 2017

Edition: [View all formats and editions](#)

Publication:

Nuclear Medicine and Biology, 51, 201708, 1

ISSN:

0969-8051

DOI:

[10.1016/j.nucmedbio.2017.04.005](https://doi.org/10.1016/j.nucmedbio.2017.04.005)

OCLC Number / Unique Identifier:

7072654339

Subjects:

[Lead-212](#)

[Radioimmunoconjugate](#)

[Radium-224](#)

[TCMC-trastuzumab](#)

[Targeted alpha therapy](#)

Notes:

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This is a free access article and can also be viewed on the journal's Web site (www.nucmedbio.com). Complimentary access to this article is available until the next issue publishes online

Language Notes:

English

More Information:

dx.doi.org

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