High-yield cyclotron production of ^{203}Pb using a sealed ^{205}Tl solid target

Bryce Nelson, Ph.D. Candidate in Oncology, University of Alberta

John Wilson, Ph.D., Faculty Service Officer, University of Alberta

Jonathan Doupe, Ph.D., Cyclotron Radiation Safety Officer, Medical Isotope and Cyclotron Facility, Alberta Health Services

Michael Schultz, Ph.D., Associate Professor of Radiology, University of Iowa

Co-Founder and Chief Scientific Officer, Viewpoint Molecular Targeting

Jan Andersson, Ph.D., Director, Edmonton Radiopharmaceutical Centre, Alberta Health Services; Assistant Adjunct Professor, University of Alberta

Frank Wuest, Ph.D., Professor and Chair, Department of Oncology, University of Alberta

Introduction

Nuclear medicine theranostics involves labeling a biological targeting vector first with a radionuclide for diagnostic imaging, followed by a particle-emitting radionuclide for targeted radionuclide therapy. Lead-212 (^{212}Pb, $t_{1/2}$ = 10.6 h) is a particularly attractive therapeutic radionuclide due to its payload of one α and two β^- particles in its decay chain, and the rapid decay of its progeny to stable ^{208}Pb. A recent clinical trial (*J Nucl Med*. 2022;63(9):1326-1333) using [^{212}Pb]Pb-DOTAMTATE to treat metastatic neuroendocrine tumors resulted in an 80% overall patient response rate, significantly exceeding standard-of-care treatments. However, diagnostic scans to track ^{212}Pb therapy were performed with conventional fluorine-18 and gallium-68 radiotracers. This is suboptimal, as dissimilar chemistries between the diagnostic and therapeutic radionuclides could result in different radiopharmaceutical biodistribution, potentially leading to unintended α-irradiation of healthy tissues.

^{212}Pb is ideally paired with the chemically identical lead-203 (^{203}Pb, $t_{1/2}$ = 51.9 h) to provide diagnostic SPECT imaging using the 279 keV (81%) gamma-photons emitted during ^{203}Pb decay. However, worldwide supply of ^{203}Pb is extremely limited since cyclotron ^{203}Pb production requires irradiating highly toxic thallium (Tl) material.

Our objectives were to develop a high-yield ^{203}Pb cyclotron production route using isotopically enriched ^{205}Tl target material and the ^{205}Tl(p,3n)^{203}Pb reaction as an alternative to lower energy production via the ^{203}Tl(p,n)^{203}Pb reaction. A robust cyclotron target and efficient chemical purification process must be designed to maximize ^{203}Pb yield and purity for research and clinical applications, while maintaining stringent radiation and chemical safety given the significant hazards presented to the operators and cyclotron facility.

Methods

Our entire process was designed around preserving radiation and chemical safety. To reduce Tl contamination risk, we employed our patent-pending sealed cyclotron target design that is used to produce other radionuclides. ^{205}Tl metal (99.9% isotopic enrichment) was pressed using a hardened stainless-steel die. High purity aluminum (Al) target discs (99.999%) were machined with a central depression and annulus groove. A ^{205}Tl pellet was placed into the central depression

of the Al disc, and indium wire was laid in the annulus. An aluminum foil cover was then pressed on, cold welding the cover to the disc via the indium with an airtight bond. Targets were irradiated at 23.3 MeV for up to 516 min on a TR-24 cyclotron at proton currents up to 60 μA to produce ^{203}Pb via the ^{205}Tl(p,3n)^{203}Pb nuclear reaction. Following a period of >12 h to allow decay of ^{204m}Pb ($t_{1/2}$ = 67 min, 899 keV (99%)), the target was removed and ^{205}Tl was dissolved in HNO_3. A NEPTIS Mosaic-LC synthesis unit performed automated separation using Eichrom Pb resin, and ^{203}Pb was eluted with HCl or NH_4OAc. The waste solution was diverted to a vial for subsequent ^{205}Tl recovery in an electrolytic cell. ^{203}Pb product radionuclidic and elemental purity were assessed by high-purity germanium (HPGe) gamma spectroscopy and inductively coupled plasma optical emission spectroscopy (ICP-OES), respectively. Radiolabeling and stability studies were performed with PSC, TCMC, and DOTA chelators, and ^{203}Pb incorporation was verified by radio-TLC analysis.

Results

Cyclotron irradiations were performed at a 60 μA proton beam current and 23.3 MeV energy without any target degradation. Automated purification took <4 h, yielding >85% decay-corrected ^{203}Pb with a radionuclidic purity of >99.9%. Purified ^{203}Pb yields up to 12 GBq were attained, and ^{203}Pb was successfully chelated and exhibited >99% incorporation after 120 h in human serum.

Radiation safety implications: In over 100 production runs, there were no cyclotron target station or processing equipment contamination incidents. Targets were irradiated during the afternoon and removed the following morning to permit decay of short-lived impurities. By allowing >12 hours (>10 ^{204m}Pb half-lives) prior to target removal, operator dose was minimized. Utilizing high purity Al target components nearly eliminated long-lived activation products, minimizing operator extremity dose when performing target recycling. When combined with a target retrieval shielding cart, a custom-designed lead-shielded processing castle, and an efficient automated process, the operator radiation dose per full production run is <10 μSv (measured by electronic personal dosimeter).

Conclusion

Our recently published high-yield ^{203}Pb production process significantly enhances ^{203}Pb production capabilities to meet the rapidly growing worldwide preclinical and clinical demand for ^{203}Pb radiopharmaceuticals alongside ^{212}Pb alpha particle therapy.

Since January 2022, we have successfully shipped over 60 batches of ^{203}Pb to customers and collaborators in 11 locations across 5 countries for research and diagnostic SPECT imaging clinical trials of metastatic melanoma and neuroendocrine tumors. Although we anticipate continually increasing demand, we are confident that our robust process design will maintain operator radiation dose at a small fraction of the permitted annual limit.