Toward Auger radiotherapy with Rhodium-103m: Bifunctional 16aneS4 chelator synthesis and development of a Rhodium-103m generator

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Objective: Auger electron emitters represent an attractive modality for internally targeted radiotherapy. Auger electrons have short ranges of less than a cell diameter and high-energy deposition. Small tumors lesions, such as micro metastases, can therefore be targeted while sparing surrounding healthy tissue. Rhodium-103m (¹⁰³mRh, T½ = 56.1 min) has been identified as a very promising therapeutic Auger electron emitter due to its high electron-to-photon yield. ¹⁰³mRh can be obtained as the decay daughter of Palladium-103 (¹⁰³Pd, T½ = 17 days). Macro cyclic thioethers have previously been found to form strong chelates with Rhodium. Here, we present our efforts to synthesize a bifunctional macrocyclic chelator for ¹⁰³mRh, based on the 16aneS4 ring. Further, we hypothesized that the decay of chelated ¹⁰³Pd would result in the expulsion of radiochemically pure ¹⁰³mRh. We utilized this principle in the development of a radionuclide generator for ¹⁰³mRh.

Methods: The macrocyclic thioether 16aneS4-ol (5) was synthesized in five consecutive steps (fig. 1). The linear diol (1) was prepared in quantitative yield. By tosylation and conversion of (2), compound (3) was obtained in 97% yield. Finally, deprotection of (4) with subsequent ring-closing, gave the macrocyclic thioether-alcohol (5) as the final product in excellent purity and 50% yield. Compound (5) offered functionality for further modification. The oxo-butanoic acid derivate (6) was formed in one-step in 74% yield. Compound (7) was formed from octanol mesylate and compound (5) in excellent purity and 40% yield. Compound (6) was conjugated to human epidermal growth factor (hEGF) using EDC and NHS. [¹⁰³Pd]Pd was then chelated by compound (7) in excess. The chelate was applied to a C18 solid support, which was eluted with hydrochloric acid. Eluates were analyzed by liquid scintillation and X-ray spectrometry.

Results: We synthesized 16aneS4-ol, and this was further functionalized into compound (6). Preliminary studies show that (6) has been conjugated to hEGF. hEGF is an internalizing and nucleus-localizing small protein that was recently used in phase I clinical studies. To achieve efficient therapy, Auger decays must occur near the DNA, making internalization paramount. [¹⁰³Pd]Pd was successfully chelated by compound (7) and captured on a C18 solid support. By eluting with aqueous hydrochloric acid (1.0 M), radiochemically pure (RCP: >99%) could be obtained. Maximum effective molar activities were 23 MBq/nmol, decay-corrected to dissolution of the target. Elution yields, as percentage of theoretical maximum, were generally modest at about 5%. It has been previously calculated that recoil energy alone would not be sufficient for Szillard-Chalmers based expulsion. We suggest that transient ionization of the daughter may play a role in the observed expulsion, but that this may not be sufficient to achieve near quantitative elution yields.

Conclusion: We successfully synthesized bifunctional derivatives of the 16aneS4-ol chelator and conjugated these to a nucleus-localizing vector (hEGF). In addition, we developed a practical generator capable of furnishing ¹⁰³mRh in high radiochemical purity, although in modest yields. We will continue this work through optimization of both technologies, as well as combining the two into therapeutically effective ¹⁰³mRh based Auger radiotherapeutics.
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