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Optimized anion exchange column isolation of zirconium-89 (^{89}Zr) from yttrium cyclotron target: Method development and implementation on an automated fluidic platform

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ABSTRACT

Zirconium-89 (^{89}Zr), produced by the (*p, n*) reaction from naturally monoisotopic yttrium (^{nat}Y), is a promising positron emitting isotope for immunoPET imaging. Its long half-life of 78.4 h is sufficient for evaluating slow physiological processes. A prototype automated fluidic system, coupled to on-line and in-line detectors, has been constructed to facilitate development of new ^{89}Zr purification methodologies. The highly reproducible reagent delivery platform and near-real time monitoring of column effluents allows for efficient method optimization. The separation of Zr from dissolved Y metal targets was evaluated using several anion exchange resins. Each resin was evaluated against its ability to quantitatively capture Zr from a load solution high in dissolved Y. The most appropriate anion exchange resin for this application was identified, and the separation method was optimized. The method is capable of a high Y decontamination factor (>10^5) and has been shown to remove Fe, an abundant contaminant in Y foils, from the ^{89}Zr elution fraction. Finally, the method was evaluated using cyclotron bombarded Y foil targets; the method was shown to achieve >95% recovery of the ^{89}Zr present in the foils. The anion exchange column method described here is intended to be the first ^{89}Zr isolation stage in a dual-column purification process.

1. Introduction

Access to long-lived positron-emitting radionuclides for use in positron emission tomography (PET) and PET/Computed Tomography (CT) can benefit the medical imaging community. Slow physiological processes within the body can be monitored over many days versus only a few hours, as is the case with most short-lived PET isotopes in use today [1,2]. The availability of longer-lived positron emitters have made possible PET-based imaging of tumors by radiolabeling monoclonal antibodies (mAbs) [2–5], mAb fragments [6,7], and aptamers [8,9], a process referred to as immunoPET [10–14]. ImmunoPET combines the high sensitivity and spatial resolution of PET imaging with the antigen specificity of mAbs. Some long-lived positron emitters being evaluated for immunoPET applications include copper-64 (^{64}Cu, $t_{1/2} \approx 13$ h), bromine-76 (^{76}Br, $t_{1/2} \approx 16$ h), yttrium-86 (^{86}Y, $t_{1/2} \approx 15$ h), zirconium-89 (^{89}Zr, $t_{1/2} \approx 78$ h), and iodine-124 (^{124}I, $t_{1/2} \approx 100$ h) [15–18].

Employing ^{89}Zr as a long-lived positron emitter for PET imaging was originally suggested and demonstrated by Link et al. [19]. The use of this isotope in immunoPET applications has since been the subject of several reviews [13,14,20–24]. In addition to opportunities for new and emerging medical modalities, the long half-life of ^{89}Zr enables the potential for off-site isotope production and distribution.

Zirconium-89 half-life is reported as 78.41(12) h [25] and 78.42(13) h [26], although a new value of 78.333(38) has been recently reported [27]. The isotope can be produced by the ^{89}Y (*p, n*) ^{89}Zr reaction from the naturally mono-isotopic Y as a foil [28–33], oxide [34–36], or sputtered surface [37–39]. While ^{89}Zr is predominantly produced on cyclotrons with (degraded) ≥15 MeV proton beams [39,40], Link et al. recently reported an optimized target design that facilitated good ^{89}Zr production yields using an 11 MeV cyclotron [33]. The proton capture from an Y target occurs with high cross sections over a proton range of ~5 to >18 MeV [35,36,41]; however, the undesirable isotopes ^{88}Zr and ^{88}Y are produced at proton energies ≥14 MeV.

Effective chemical purification of ^{89}Zr from dissolved Y foil, and the suite of metal impurities that contaminate the Y foil, is of utmost

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importance. Zirconium-89 labeling is primarily accomplished via chelation of the isotope into the deferoxamine siderophore that is first conjugated onto the mAb [42]. Although Zr(IV) has a high affinity for deferoxamine, other transition and basic metals such as Ti(IV), Fe(III), Ga(III) and Al(III) are likewise strongly bound [43–46]. Hence, ^{89}Zr immunoPET applications do not tolerate the presence of these competing metal ions, as inadequate labeling (and ineffective diagnostic imaging) can result.

Column-based separation schemes for Zr in hydrochloric acid media have typically utilized cation [34,47,48] and anion [34,49–52] exchange resins, and hydroxamate ligand-based resin. At present, hydroxamate resin columns are the predominant means of purification of ^{89}Zr from Y targets dissolved in strong HCl. The use of this ligand for ^{89}Zr purification is originally attributed to Mejis et al. [37]. Since then, many researchers have employed a single hydroxamate resin column for ^{89}Zr purification from dissolved Y targets in strong HCl [29,32,38,40,53]. The method has recently been reevaluated and automated by this research team [54].

The use of automated fluidics to routinely and consistently produce high purity medical isotopes is emerging in this field [55]. Automation allows for isotopes to be purified remotely in shielded locations, which results in reduced radiological dose to personnel, improved laboratory efficiency, and improved run-to-run consistency. Some recent applications of automation in medical isotope production (including those for ^{89}Zr) have been recently presented by this research team [54], and will not be included here.

Herein, we describe the development of an optimized ^{89}Zr separation method using an anion exchange resin column. Three strongly basic anion exchange resins were evaluated. Each had quaternary amine functional groups with different polymer supports. The supports ranged from macroporous and 10% cross-linked styrene-divinylbenzene copolymers to a hydroxylated methacrylic polymer. The resins were evaluated for their ability to load and elute Zr in neat solutions and in solutions containing high concentrations of dissolved Y. Additionally, the method had to ensure removal of Fe from the ^{89}Zr product, as Fe is a contaminant in Y foils that competes with ^{89}Zr for deferoxamine-conjugated mAb labeling sites. For anion exchange-based separations in HCl media, it is known that Fe(III) will follow a similar sorption/desorption pattern as Zr(IV) [37,56]. However, this method demonstrates that Fe separation from the ^{89}Zr eluent solution is possible.

The ^{89}Zr purification method involves dissolution of cyclotron bombarded Y foil, loading of ^{89}Zr from the dissolved target onto an anion exchange column, column wash, and ^{89}Zr elution. This sequence of steps was accomplished with a prototype automated fluidic platform configured with an on-line gamma detector and in-line UV–vis absorbance detector to monitor column effluents in near-real time; effluents could be subsequently directed to a fraction collector for off-line measurements.

The primary objective of this work was to develop new methodologies that will improve the purity and concentration of ^{89}Zr in an effort to increase the efficacy of this isotope for the medical imaging community. The ^{89}Zr eluent purified by this method is likely not in a chemical matrix that is immediately amenable to follow-on radiolabeling, but it is directly amenable to follow-on purification. A subsequent article will describe another level of purification of ^{89}Zr using a secondary separation column that can be fluidically coupled to the primary anion exchange column. Tandem column-based radioisotope isolation processes have been previously employed to achieve the high degrees of purity commonly required in nuclear medicine applications [57,58]. In a similar vein, the next stage in this method and system development will be to demonstrate a tandem column separation process capable of producing concentrated and highly pure ^{89}Zr products that are suitable for mAb labeling.

2. Experimental

2.1. Reagents, standards, and materials

TraceMetal™ and Optima™ grade hydrochloric acid (34–37% HCl, Fisher Scientific, Waltham, Massachusetts, USA) working stock solutions were prepared as-is or as dilutions into deionized water (18.3 MΩ cm) using a Barnstead E-Pure water purification system (Dubuque, Iowa, USA). Method development work and Y foil processing used TraceMetal™ and Optima™ grade acids, respectively. Sodium fluoride (99.99+ %) and hydrogen peroxide (30%) were purchased from Sigma-Aldrich (St. Louis, Missouri, USA). Yttrium metal pieces (99.9% (REO) w/w), dissolved and used for column optimization studies, were obtained from Alfa Aesar (Ward Hill, Massachusetts, USA). Cyclotron targets were prepared from 0.25 mm thick Y foil (99.9% (REO) w/w, Alfa Aesar).

Three ion exchange resins were evaluated: AG MP-1M (Cl^- form, 200–400 mesh) and AG 1-X10 (Cl^- form, 100–200 mesh) strongly basic anion exchangers, each on styrene-divinylbenzene co-polymer (Bio-Rad Life Science, Hercules, California, USA), and Toyopearl QAE-550C strongly basic anion exchanger (Cl^- form, 50–150 μm) on hydroxylated methacrylic polymer (TOSOH Bioscience, King of Prussia, Pennsylvania, USA). The AG MP-1M resin is macroporous, with an effective surface area of ~23 m^2 per dry gram, with 20% porosity. The AG 1-X10 resin is a gel-type resin with 10% cross-linkage. Both resins exhibit quaternary amine functional groups. The Toyopearl QAE-550C resin is functionalized with quaternary amino ethyl functional groups.

Zirconium-88 (^{88}Zr, $t_{1/2}$ = 83.4 d) and yttrium-88 (^{88}Y, $t_{1/2}$ = 106.6 d) radiotracers were purchased from the U.S. Department of Energy Office of Science National Isotope Development Center (NIDC). The ^{88}Zr was periodically purified of in-grown ^{88}Y using a method similar to that described herein. Zirconium-89 was obtained from the University of Washington Department of Radiology (Seattle, Washington, USA) as a cyclotron (CTI Eclipse/111) bombarded Y foil (Alfa Aesar), using a target design and method described by Link et al. [33]. Following an initial decay period of ~2 h, the ^{89}Zr target activity was determined by a dose calibrator and corrected to activity at end of bombardment (EOB). Upon delivery to PNNL, this activity was verified using a 20% relative efficiency high purity germanium (HPGe) detector (Ortec, Oak Ridge, Tennessee, USA) that was energy and efficiency calibrated with National Institute of Standards and Technology (NIST)-traceable standards.

2.2. Distribution coefficient measurements

Distribution coefficients (K_d) for each radiotracer (^{88}Zr, ^{88}Y) were measured on an assortment of anion exchange media across a range of HCl concentrations, and conc. HCl containing a range of Y concentrations. Solution contact volumes were typically 5 mL in 2-dram borosilicate glass vials, and "as-received" (wet) masses of the resins were dispensed at ~20 and ~100 mg. The duration of the solid/liquid phase contact was ~4 h; this time interval was found to be more than adequate for the tracers to be fully equilibrated between the phases. Evidence of this is shown in the electronic supplement to Section 2.2, Fig. SI 1.

A detailed description of the batch contact experimental protocol was recently published in detail [54], so it will not be repeated here. Briefly, known masses of resins were contacted with known volumes of ^{88}Zr or ^{88}Y spiked solutions. Samples were agitated by orbital shaker for ~4 h, then they were filtered to remove the resin. The resulting filtrates were analyzed by a Wizard 1470 (PerkinElmer, Meriden, Connecticut, USA) automatic gamma counter containing a well-type NaI(Tl) scintillation detector to determine the activity of spike remaining in the resin-contacted

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