Final Technical Report

10/31/2011

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Novel Cyclotron-Based Radiometal Production

Accomplishments:

1) Construction of prototype solution target for radiometal production.
2) Testing of prototype target for production of following isotopes:
    a. Zr-89. Investigation of Zr-89 production from Y-89 nitrate solution.
        i. Defined problems of gas evolution and salt precipitation.
        ii. Solved problem of precipitation by addition of nitric acid.
        iii. Solved gas evolution problem with addition of backpressure regulator and constant degassing of target during irradiations.
        iv. Investigated effects of Y-89 nitrate concentration and beam current.
        v. Published abstracts at SNM and ISRS meetings.
3) Design of 2nd generation radiometal solution target.
    a. Included reflux chamber and smaller target volume to conserve precious target materials.
    b. Included aluminum for prototype and tantalum for working model.
    c. Included greater varicosities for improved heat transfer.
4) Construction of 2nd generation radiometal solution target started.

Publications

(see appended abstract and poster)

Abstract: Society of Nuclear Medicine Annual Meeting, 2011

Feasibility of production of ^{89}Zr using an aqueous cyclotron target

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The physical decay characteristics of the positron emitter ^{89}Zr ($T_{1/2}$=78.4 h, E_{ave}(β+)=396.9 keV) make it a well suited radiolabel for PET imaging studies of radiolabeled monoclonal antibodies (mAbs). To date, the production of ^{89}Zr has commonly employed proton bombardment of Yttrium foils with subsequent acid dissolution and isotope separation. This technique requires transport of the activated foil to the processing hot cell. The current work explored the feasibility of production of ^{89}Zr by bombardment of an aqueous target matrix of yttrium nitrate (100% isotopic abundance of ^{89}Y), thereby avoiding the foil transportation and dissolution processes. Such a method would be compatible with self-shielded PET cyclotrons that typically lack sophisticated foil handling capability. A commercial ^{18}F-fluoride target (Bruce Technologies, LLC, niobium body, 0.127mm titanium window) was loaded with 3.2 mL aqueous solution of 259 mg/mL yttrium nitrate tetrahydrate. The target was bombarded for 30 min with 16.5 MeV protons (25 μA) in a GE PETTrace cyclotron. After a 20 h delay period to allow decay of the short-lived isotopes (^{13}N, ^{11}C, and ^{18}F), the target matrix was delivery to a processing hot cell for isotope separation on hydroxamate resin column (50 mg).

Poster:

ISRS 2011; Amsterdam

A solution target approach for cyclotron production of ^{89}Zr: Understanding and coping with in-target electrolysis

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Introduction

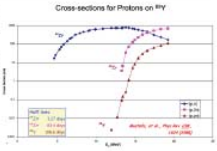
Longer-lived positron-emitting radiometals (e.g., ^{64}Cu, ^{86}Y and ^{89}Zr) are playing an increasing role in radiolabeling of immunological targeting probes for PET. However, the majority of PET cyclotrons are self-shielded and not easily adapted to accommodate commonly employed solid target systems. Therefore, we sought to establish a solution target method for production of radiometals. This approach has been recently introduced for production of ^{86}Y [1] and ^{68}Ga [2]. Although production yields are lower than achelvable with solid targets, the solution target approach is readily implemented on commercial PET cyclotrons.

Objectives

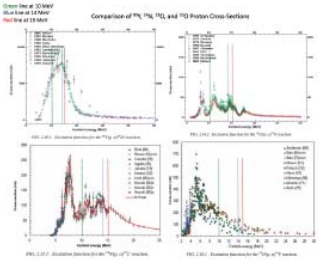
The objective of the research program was to develop a solution target system that would be capable to produce ^{89}Zr, ^{64}Cu, and ^{86}Y in purity and quantity suitable to support preclinical studies. Since ^{89}Zr ($T_{1/2}$ = 78.4h) is produced from proton bombardment of natural ^{89}Y (100% isotopic abundance) in the form of yttrium nitrate, this isotope was selected for the pilot studies and target prototyping.

Methods

The cross-sections for protons on natural ^{89}Y are shown at right (Mustafa et al). Cross-section for the ^{89}Y(p,n)^{89}Zr reaction has broad maximum from 10-15 MeV, whereas the undesirable longer lived ^{88}Zr ($T_{1/2}$ = 83.4d) produced via (p,2n) reaction has proton energy threshold of ~13 MeV. It was determined that the ideal incident proton energy for production of ^{89}Zr is between 13 and 14 MeV.



Since the target material includes water and nitrate ions in addition to yttrium ions, the protons have competing nuclear cross-sections with ^{18}O, ^{16}O, and ^{14}N, to produce ^{13}N, ^{18}F and ^{11}C, respectively. These radionuclides are short-lived relative to ^{89}Zr, and were therefore allowed to decay away before processing of the target contents by overnight decay. The competing cross-sections are shown below.

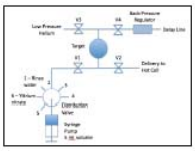


Methods

The target used in this study was the Bruce Technologies TS-1650. This target has a replaceable target body insert of volume ~3 mL. Three different insert body compositions were studied: Nb, Al and anodized Al. Window foils of Ti, Ta, Al or anodized Al were tested. The target was bombarded by 16.5 MeV protons in a GE PETTrace cyclotron. An aqueous solution of yttrium nitrate with 200-400 mg equivalent of ^{89}Y filled the target at the beginning of each run. Beam current was varied from 15-25 μA.

Incident proton energy was estimated by the SRIM program (version 2008-4).

The design of the target loading system included a syringe pump connected to a 6-port distribution valve for selection of different solutions to load the target. Valves V1-V4 were constructed to allow filling of the target (V1), delivery to the hot cell (V2), nitrogen for delivery pressure (V3) and venting of the target (V4) to a delay line that allowed decay of short-lived volatiles released from the target. A backpressure regulator (Alltech) allowed control of backpressure to 100 psi, while venting target gases.

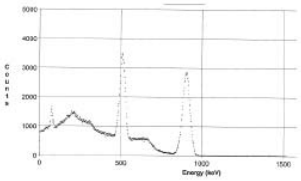


Effective Specific Activity (SA) was determined by the method of Holland et al. [3].

Results

Initial irradiations were stopped prematurely due to a rise in target pressure. Since irradiations without yttrium salt showed no rise in pressure, it was postulated that yttrium nitrate was catalyzing in-target electrolysis of water with subsequent evolution of hydrogen and oxygen. Indeed, yttrium salts are known to catalyze electrolysis [4]. A backpressure regulator (100 or 150 psi, Grace Davison, Deerfield, IL) was installed at a tee on the top target outlet to allow release of evolved gas and maintain target pressure (above). The short-lived radioactive gases ($^{11}CO_2$ and [^{13}N]NOx) that are concomitantly released are held for decay in a delay line within the cyclotron vault. A hydrogen detector (SRI Instruments, Torrence CA) confirmed hydrogen as a component of the evolved gas. The rate of gas evolution from the target (>2 mL/min) suggested that multiple electrolysis events were generated per incident proton.

The gamma emission energy spectrum is shown below for a run in which a 0.5 mm Al foil window degraded proton energy to ~13 MeV. The characteristic 909 keV photon of ^{89}Zr was seen but there were no characteristic photons from ^{89}Zr (393 keV) observed.



Results

Run	Beam energy (MeV)	Yttrium (mg)	Yield mCi/(μA h)	Specific Activity (mCi/μg)	Comments
1	15.5	200	0.054	0.560	Nb target; Ti window
2	15.5	200	0.059		"
3	13.0	200	0.015		Al target; Al window; precipitates
4	13.0	200	0.024		"
5	12.8	200	0.011		Al target; Ta window; precipitates
6	12.8	200	0.020		"
7	12.8	400	0.057	2.420	Nb target; Ta window
8	12.8	400	0.026	0.110	Al target; precipitates
9	13.0	400	0.053	0.030	Nb target; Al window
10	13.0	400	0.043	0.390	Anodized Al target & window
11	13.0	400	0.042		"
12	13.0	400	0.039	1.190	"
13	13.0	400	0.042	1.800	"

Production yields varied from 0.011-0.059 mCi/(μA h), depending on incident proton energy, and target/window foil combination. Precipitates were observed in multiple runs, possibly due to electrolysis products, particularly heavily seen for Al target body.

Highest effective specific activities (~2mCi/μg) were seen in Nb, Ta and anodized Al target bodies and/or window foils. However, anodized Al was not stable against electrolysis, particularly at the beam strike of the foil.

Evaporative loss of water was identified as a challenging problem for increasing the bombardment duration beyond 1 h. Two approaches are currently under development to solve this problem: 1) Supplementation of water to the target during beam by automated control of the syringe pump, and 2) redesign of the target to include a chilled condensor functionality to retain the water within target.

Conclusions

Production of radiometals, such as ^{89}Zr, using solution targets is feasible, albeit with moderate isotope production rates. In-target electrolysis of water can be catalyzed by salts of rare earths, but the evolved gas is practically handled by use of a backpressure regulator and delay line. Ongoing development efforts are aimed at solving the problem of evaporative water loss from the target and increasing beam durations.

References

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Acknowledgements

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