DESC0008657

Production of Positron Emitting Radiometals: Cu-64, Y-86, Zr-89

Washington University School of Medicine

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Final Report
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Project Overview:

This proposal seeks support to increase our production of the radionuclides yttrium-86 and zirconium-89 while continuing to produce copper-64. We have the advantage that we already ship out copper-64 to some 20-25 institutions per week (over 60 different institutions total including 4 Canadian sites) and thus our group already has significant experience with producing, purifying and shipping radioactive materials. A significant portion of the funds requested supported the purchase of a new hotcell for the production of zirconium-89 and yttrium-86.

This proposal aimed to produce quantities of copper-64, yttrium-86 and zirconium-89 in quantities and schedules suitable for distribution and in support of current and upcoming clinical trials. This involved the design, construction and commissioning of two new automated purification modules for the purification of zirconium-89 from irradiated yttrium target material and the purification of yttrium-86 from irradiated strontium oxide target material.

All isotopes undergo quality control procedures including effective specific activity and radioisotopic purity. With the support of this project we are producing copper-64, yttrium-86 and zirconium-89 on a regular (weekly or biweekly) basis.

Our facility currently has a DOT/Type A certified shipping system available in which to ship the radionuclides. However, there are limitations as per the IATA/ICAO regulations to the amount of radionuclides that can be shipped in this 19 lb. shipping configuration. Currently the limits per nuclide are 1Ci for copper-64, 18 mCi for yttrium-86 and 20 mCi for zirconium-89. The cost of the container (non returnable), packing and personnel per package is $70 per shipment. The price of the actual shipment varies depending on the destination. Washington University has a standard MTA which is signed by all users to cover the liability of shipping radioisotopes to outside users.

We have met all the milestones proposed in the initial application packet as detailed below. The project progressed smoothly and on budget. We are pleased to report that we are now shipping copper-64, yttrium-86 and zirconium-89 to sites across the United States and in Canada.

Project Control Milestones and Accomplishments

Milestone #1: Design and construction of Zr-89 automated purification system
This milestone was completed as December 2012.

The objective for this work was to automate the process for previously published separation chemistry for purification of ^{89}Zr from proton irradiated Y targets.

A stock of hydroxamate resin was made by functionalizing the weak cation exchange resin with hydroxamate groups. Using a custom software program made in LabView running on a laptop outside the hot cell 10 mL 2 M HCl is added to the dissolution vessel to dissolve the ^{nat}Y target. After waiting ~1 h for complete dissolution, the dissolved target is transferred to the column through tubing using compressed air. Then, the Y is eluted from the column in 10 mL 2 M HCl and collected in a waste vial, leaving the ^{89}Zr bound on the column. The column is rinsed with 10 mL water, which is collected in the same waste vial, and then the ^{89}Zr is eluted in 1 mL 1 M oxalic acid and collected in a product vial as ^{89}Zr chelated by the oxalate ions (^{89}Zr-oxalate). The product is eluted in a small volume. After collection of ^{89}Zr in the product vial, the product is retrieved from the hot cell manually and then dispensed in 2 mL skirted microcentifuge tubes for distribution within our institution and/or shipping to extramural researchers.

A photograph of the completed system is shown in Figure 1.

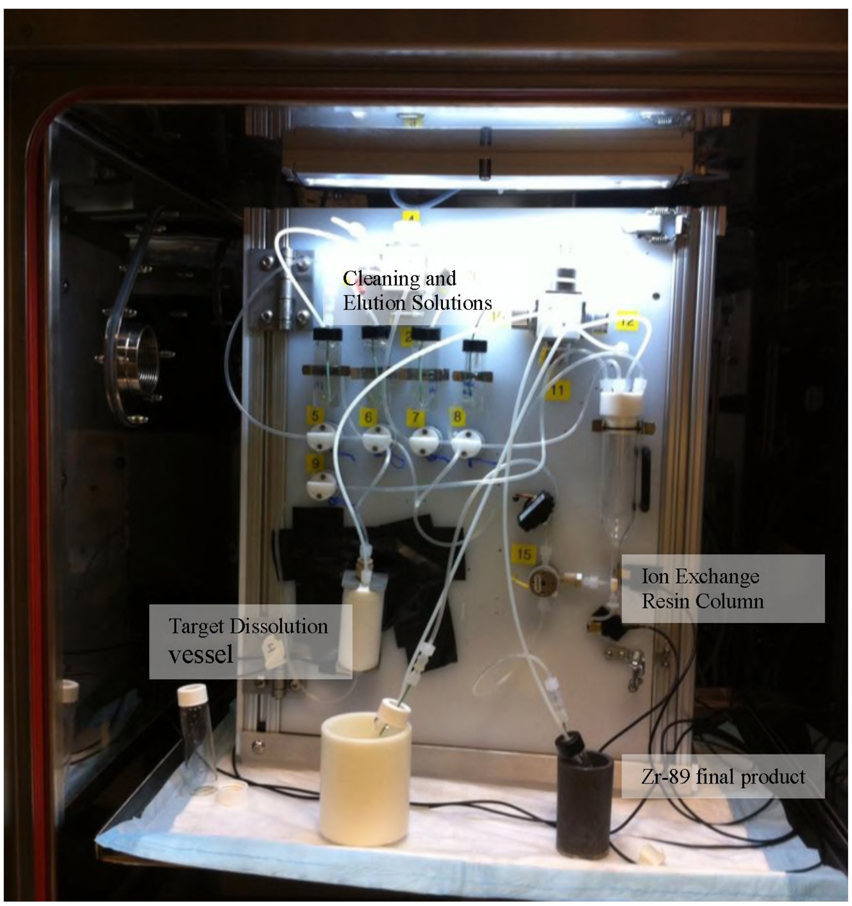

Figure 1. Washington University Zr-89 purification system

Milestone #2: Commissioning and testing of Zr-89 automated purification system
This milestone was completed as April 2013

The automated system was tested and the produced radioisotope tested for radionuclidic purity and chemical purity. Radionuclidic purity as analyzed by gamma spectroscopy is routinely >99% as shown below in Figure 2. Yields of up to 100 mCi have been processed with this system which is more than our demand at this time.

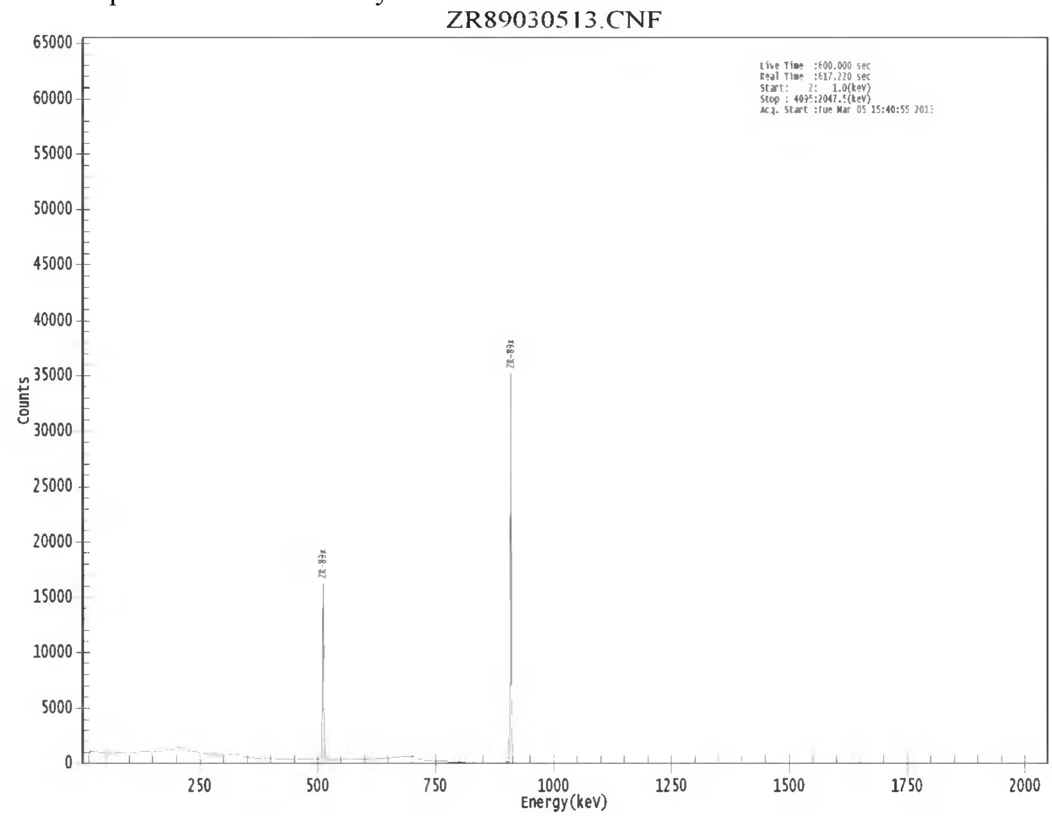

Figure 2. Gamma Ray spectrum of ^{89}Zr produced on March 5th, 2013. Note peaks at 511 keV (positron annihilation peaks) and 909 keV (signature gamma ray from ^{89}Zr)

We have been analyzing the specific activity of this isotope using a chelator (desferrioxamine) titration technique. The average specific activity of the product is 50-100 mCi/μmol. As we proceed to longer runs, yielding higher radioactivity batches, we are confident that this will increase. We are currently producing ^{89}Zr for in-house chemistry, small animal imaging and clinical trials as well as shipping to several external sites using this automated system.

We are producing ^{89}Zr on a weekly or biweekly basis and have scaled up for additional external sites coming on line.

Preclinical results with radiolabeled antibodies in our lab have yielded high radiolabeling efficiencies and high quality small animal PET/CT images as shown in Figure 3.

Figure 3. Small animal PET/CT of tumor bearing mouse injected with ^{89}Zr-anti-LAT1 antibody showing high and specific tumor uptake. Image was acquired in a 30 minute static scan 7 days post injection of the radiopharmaceutical. T-tumor, L-liver, K-kidney.

Milestone #4: Design and construction of Y-86 automated system

This milestone was completed as April 2013.

We have the same chemistry which we have used previously to separate ^{86}Y from enriched ^{86}Sr oxides using a manual method. ^{86}SrCO3 is baked for one hour at 1100° C, under Ar, to produce SrO. The target material is pressed into a Pt target and bombarded using a (p,n) reaction to produce ^{86}Y. The target material is introduced into the hot cell, dissolved in 3 ml of 6 M HCl. Once dissolution is observed, 8ml of 3 M NH_3OH is slowly added. The pH is checked to ensure that it is above 10, ensuring the formation of $Y(OH)_3$ and $Sr(OH)_3$ and the solution is pushed remotely onto filter paper. A slow vacuum filtration and wash with pH 10 adjusted MilliQ water and collection with 1M HCl ensures high recovery (>90%) and specific activity. Collected fractions are evaporated to dryness.

The ^{86}Y purification system was designed and the automated module was constructed. A schematic of the system is illustrated in Figure 4.

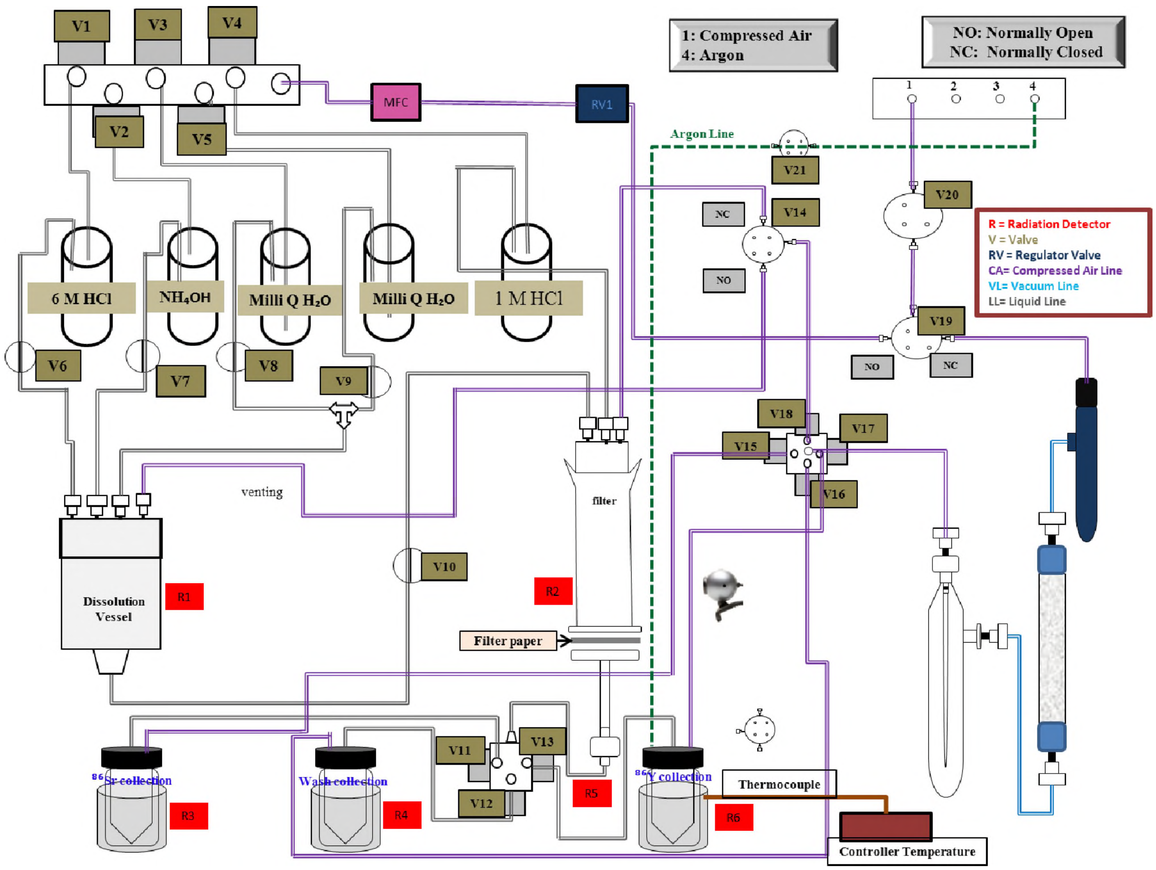

Figure 4. Schematic of the ^{86}Y automated purification system. Irradiated ^{86}SrO targets are dissolved in the dissolution vessel. The liquid is pH adjusted and then transferred over the filter paper. By manipulating the pH of the solutions, the Sr target material can be separated from the ^{86}Y product.

Milestone #3: Routine use of Zr-89 automated system and production scale up

This milestone was completed as July 2013

This involved radiation safety assessment of the maximum amount of ^{89}Zr allowable while maintaining ALARA dose levels. Additional local shielding was required. Quality control will be assessed for each production and feedback from users was sought to allow us to improve our product.

The automated system was completed and described in previous progress reports is now in routine use. Feedback from both internal and external users has been positive, pertaining both to our reliability and quality of the product

We have one internal NIH sponsored clinical trial with a compound using this isotope (Investigation New Drug application submitted March 7, 2013, PI Farrokh Dehdashti, MD) and one industry sponsored trial. The information pertaining to these are listed in the table below

Table 1. Clinical Trials with ^{89}Zr-antibodies at Washington University.

Title	Identifier	PI	Study Start Date	Estimated Primary Completion Date
^{89}Zr-Trastuzumab Breast Imaging With Positron Emission Tomography	NCT02065609	Farrokh Dehdashti	February 2014	February 2019
A Phase I Study of Positron Emission Tomography (PET) Imaging with ^{89}Zr-Df-IAB27FA in Patients with classical Hodgkin Lymphoma (cHL), systemic Anaplastic Large Cell Lymphoma (sALCL), and Diffuse Large B-Cell Lymphoma (DLBCL)	N/A	Nancy Bartlett	July 2014	July 2015

Milestone #5: Commissioning and testing of Y-86 automated system

This milestone was completed as October 2013

The ^{86}Y purification system described in Milestone #4 was commissioned and tested. A photograph of the system is illustrated in Figure 5.

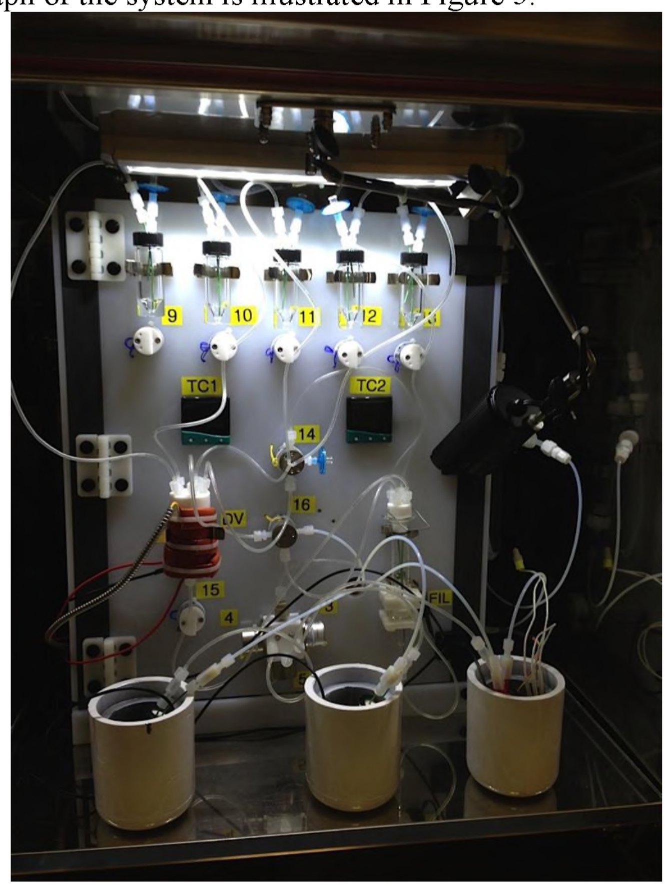

Figure 5. Photograph of the ^{86}Y automated purification system. Irradiated ^{86}SrO targets are dissolved in the heated dissolution vessel (above valve 15). The liquid is pH adjusted and then transferred over the filter paper (FIL). By manipulating the pH of the solutions, the Sr target material can be separated from the ^{86}Y product.

The Y/Sr separation process can be monitored visually by looking through a lead glass window on the front of the hot cell or by the built-in single camera in the hot cell. This module also includes microcameras that are mounted on the system to monitor various components from a very close perspective. In addition to visual monitoring, the movement of radioactivity can be tracked through the system using Si PIN-type photodiode detectors that are strategically mounted throughout a system. All of the electronic components in each system are controlled and monitored by a graphical user interface (GUI) running on a laptop outside of the hot cell. The GUI designed for the ^{86}Y module features an interactive (clickable) process flow diagram, step-by-step pre-programmed procedure, stopwatch (for wait steps), pressure transducer output, heating element control panels (with thermocouple outputs), and valve "bump" controls to slowly move fluids in the system by only opening isolation valves for brief pulses (~ms) at an interval (~s). A second screen in the GUI shows outputs for two microcameras (and the camera included in the laptop itself), as well as live graph displays for the radiation detectors at various locations in the system. The communication between the laptop and the module inside the hot cell is modulated by electronic components in a separate box installed in a side compartment of the hot cell. These electronic components include a DC power supply, data acquisition module, multichannel digital input/output rack with digital DC output modules installed to control various components, and RS232 serial-to-usb converters to digitize the analog signal from the photodiode radiation detectors.

Milestone #6: Routine use of Y-86 automated system and production scale up

This milestone was completed as January 2014

This involved radiation safety assessment of the maximum amount of Y-86 allowable while maintaining ALARA dose levels. The automated system completed and described in previous progress reports is now in routine use.

Milestone #7: Routine Zr-89 and Y-86 supply to external users

This milestone was completed as June 2014

We have implemented the two new automated systems into routine (biweekly) production and are shipping isotopes to external users in the US and Canada.

We continue to produce ^{89}Zr biweekly or weekly if we have a scheduled dose for a clinical trial. Figure 6 shows the total produced ^{89}Zr as well as the amount shipped to external users as of July 1st, 2014. We are supplying researchers engaged in basic radiochemistry as well as preclinical and clinical studies. Feedback from our users has been very positive pertaining both to our reliability and quality of the product.

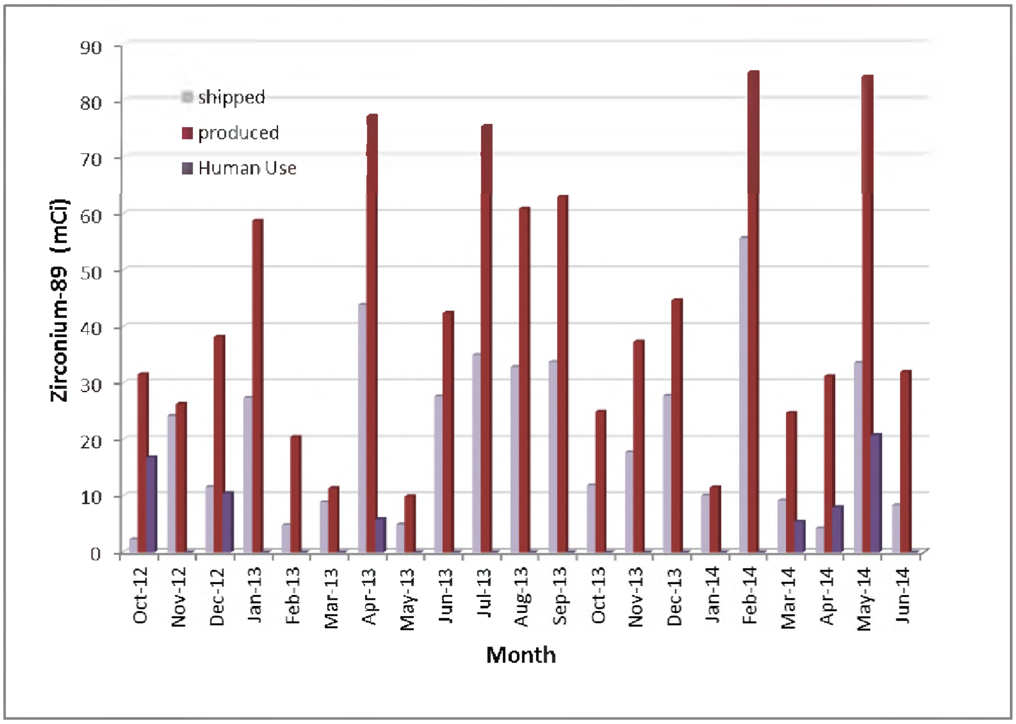

Figure 6. ^{89}Zr production at Washington University

We are also supplying two clinical trials (internal) with this isotope as previously mentioned.

We have begun supplying ^{86}Y to external sites. As demand for this isotope is somewhat lower than that for ^{89}Zr we have had fewer requests. Figure 7 shows the total produced ^{86}Y as well as the amount shipped to external users as of July 1st, 2014. We are supplying researchers engaged in basic radiochemistry as well as preclinical studies. Feedback from our users has been very positive pertaining both to our reliability and quality of the product.

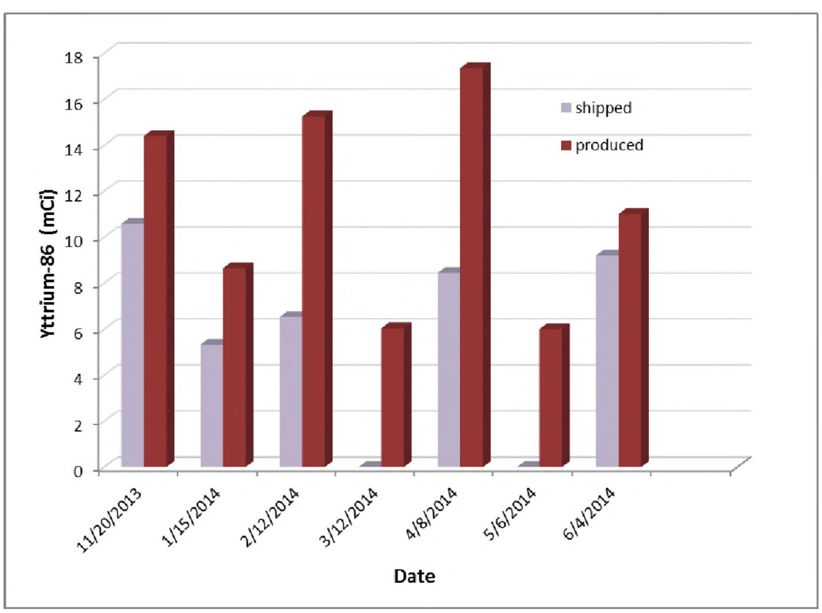

Figure 7.
^{86}Y production at Washington University

Additional Accomplishments

A manuscript detailing the construction and operation of the ^{89}Zr purification module has been published and the funding from DOE NP has been acknowledged.

A. Lake Wooten, Evelyn Madrid, Gordon D. Schweitzer, Luke A. Lawrence, Efrem Mebrahtu, Benjamin C. Lewis and Suzanne E. Lapi Routine Production of ^{89}Zr Using an Automated Module Appl. Sci. 2013, 3(3), 593-613

Several invited lectures have included material resulting from this funding and the DOE NP isotope program has been acknowledged:

Lapi, S.E. (2014) Accelerator production of isotopes for medical use: A tale of two energies, Presented at American Physics Society Annual Meeting, Savannah, GA

Lapi, S.E. (2014) Radiometals for PET and SPECT: Data from the present and thoughts on the future. Presented at Turku PET Symposium, Turku, Finland

Lapi, S.E. (2014) Cyclotron Production and Separation of Positron Emitting Radiometals Presented at Canadian Society of Chemistry annual meeting, Vancouver, Canada

Project Expenditures

- **Major hardware procurements**.

Item	Critical Path (Y/N)	Estimated Cost	Procurement Date
Hotcell	N	$145,000	June 2013

- **Budget breakdown**

WBS or ID #	Item/Activity	Baseline Total Cost (AY$)	Costed & Committed (AY$)	Estimate To Complete (AY$)	Estimated Total Cost (AY$)
1	Start-up costs for Zr-89 production	$122,050	$122,050	$0	$122,050
2	Start-up costs for Y-86 production	$122,050	$122,050	$0	$122,050
3	Hotcell purchase	$145,000	$145,000	$0	$145,000
Totals:		$389,100	$389,100	$0	$389,100

Summary of expenditures by FY:

	FY 2013	FY2014
a) Funds allocated	$ 389,100	$42, 002
b) Costs accrued	$ 218,843	$42,003
c) Uncosted commitments	$ 128,255	$0
d) Uncommitted funds (d=a-b-c)	$ 42,002 (to FY14)	$0

Project Schedule

Start and completion dates were on schedule as originally forecasted with the exception of a delay in routine operation due to a delay in obtaining parts for the ^{86}Y purification system

- **Project Schedule**

Milestones/Tasks	Q1	Q2	Q3	Q4	Status
1. Design and construction of Zr-89 automated purification system	■				Complete
2. Commissioning and testing of Zr-89 automated system	■	■			Complete
4. Design and construction of Y-86 automated system	■	■			Complete
3. Routine use of Zr-89 automated system and production scale up		■	■		Complete
5. Commissioning and testing of Y-86 automated system		■	■		Complete
6. Routine use of Y-86 automated system and production scale up				■	Complete
7. Routine Zr-89 and Y-86 supply to external users				■	Complete
Prepare final report for DOE Isotope Program				■	Complete

- **Summary of Schedule.**

	Baseline Start Date mo/year	Baseline Completion Date mo/year*	Percent Complete
Design	09/2012	03/2013	100
Procurement	09/2012	06/2013	100
Fabrication	11/2012	09/2013	100
Operation	01/2013	06/2014	100

* These include the time period over which both the Zr-89 and Y-86 systems will be designed, constructed, commissioned and placed into routine operation.