DOE Grant Final Report

(unlimited distribution authorized)

DE-SC0008384

University of Wisconsin – Madison

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Executive Summary:

This project proposed to improve the infrastructure at the University of Wisconsin Medical Physics cyclotron facility, enabling it to double the production capability to provide Cu-64 and a list of other 3-d and 4-d subshell metals to a wider community of users on the national scale. A series of improvements and target developments were accomplished that have been shared with others through publications and conference presentations. At every step, the economic consequences were weighed:

- shielded mini-cells were chosen by competitive bid, yielding the greatest value
- separation chemistry was automated with a consistent approach of *building* remote modules, controlled by LabView, tailored to the above mini-cells, rather than purchasing extravagant "black boxes" from commercial vendors.
- other major improvements needed, such as the five-port external beam line for our PETtrace cyclotron, or the Agilent 4200 micro-wave plasma atomic emission spectrometer, were acquired from internal funds that were freed up by this generous DOE award.

All together, the symbiosis of these acquisitions has transformed our small-scale distribution efforts to a significant national presence in the PET radio metal community with a broadening network of users. This user base, in 30 labs across the country, promises to bring molecular imaging, with targeted peptides, antibodies and nanostructures labeled with our Cu-64, Zr-89 and other synthons to bear on a variety of diseases.

Goals / Actual accomplishments.

The various projects of this grant (Award #MSN149063) were originally aligned along a three-year timeline below.

Work

A. Develop high current targets for PETtrace beamline with BPM and IR/Vis CCTV monitoring
B. Install and fit out dual minicell for Cu-64 + Zr-89
C. Install and perfect trace metal analysis w/ GFAAS
D. Develop RF induction / H_2 reduction of SrO-> Sr
E. Install and fit out I-124 minicell, develop -30° beam for high current irradiation of Te-124 target.

Milestone

A. Double prod of Cu-64, Zr-89
B. Bring Ga-66 to routine prod
C. Provide trace metal CoA's.
D. Bring up Y-86 prod
E. Push I-124 to 10's mCi.

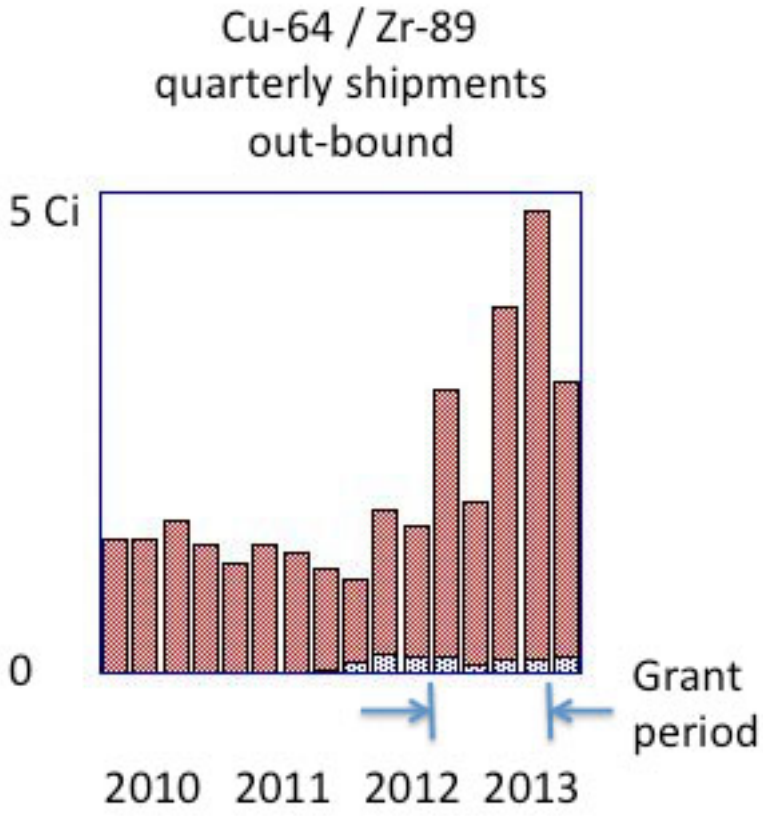
With the compressed time-line of a single year awarded, the goals remained the same, but with an accelerated attack tailored to our budget, with efforts focused more on the scale-up of Cu-64, Zr-89 and gallium isotopes.

Milestone A: Doubling the Cu-64 activity outbound.

Previously about 10% of our westbound deliveries were stalled for 24 hours at the Memphis FedEx hub. This seems to have been resolved by our new shipping containers, DOT 7A boxes, shown below better suited to the automated handling facilities.

The Cu-64 and Zr-89 shipment log for the past 4 years is shown below, with the erratic behavior, even with quarterly binning, evident as our users feel the oscillations of funding and conference abstract submission deadlines. What is evident, however, is that this DOE grant has **tripled** our Cu-64

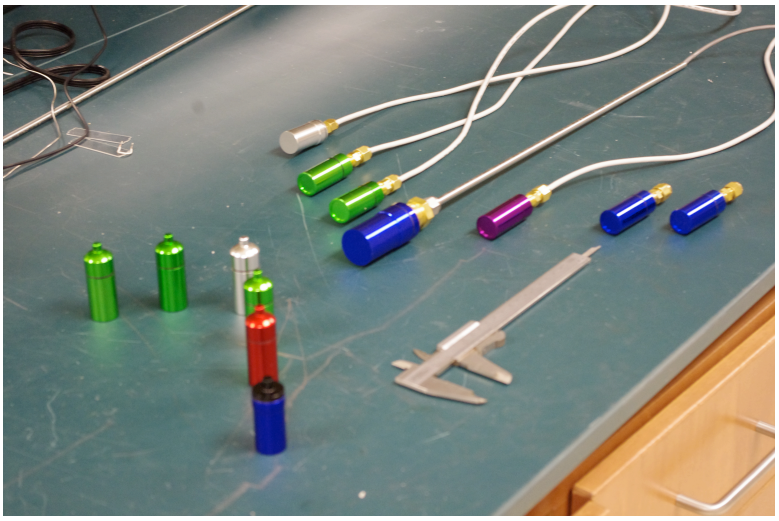
activity shipped out, from 4 Ci/year to 13 Ci/year over the 2012-13 grant period. This plot shows just the activity that was requested and billed. The actual out-shipments are about 2 times higher than this, but we only charge our users for the amount that they request, though they all are pleased to receive the two-fold extra activity.



Furthermore, the separation of the Zr-89 from the irradiated yttrium target foil has been automated by Hector Valdovinos (supported on this grant) and our visiting scholar Jonathan Siikanen from Lund, shown below.

The automated chemistry modules are installed in the first of the Radiation Sciences dual mini-cells shown below on the left, while, while the second dual mini-cell is populated with a more generic unit that should handle the future Br-76 separations.

These two mini-cells represent the major expenditure of this DOE grant award. The Zr-separator is installed in the left hand side of the mini-cell, is a LabView driven system patterned after a system developed earlier by Jonathan Siikanen and reported at the 14th Targetry Workshop, with improvements presented both at the SNM Conference in Vancouver and Radiometals 2013 (Sonoma) in June. The improvements include the incorporation of a number of point-like radiation detectors, shown below, to monitor the activity through the dissolution, ion-exchange chromatography and chelation steps.



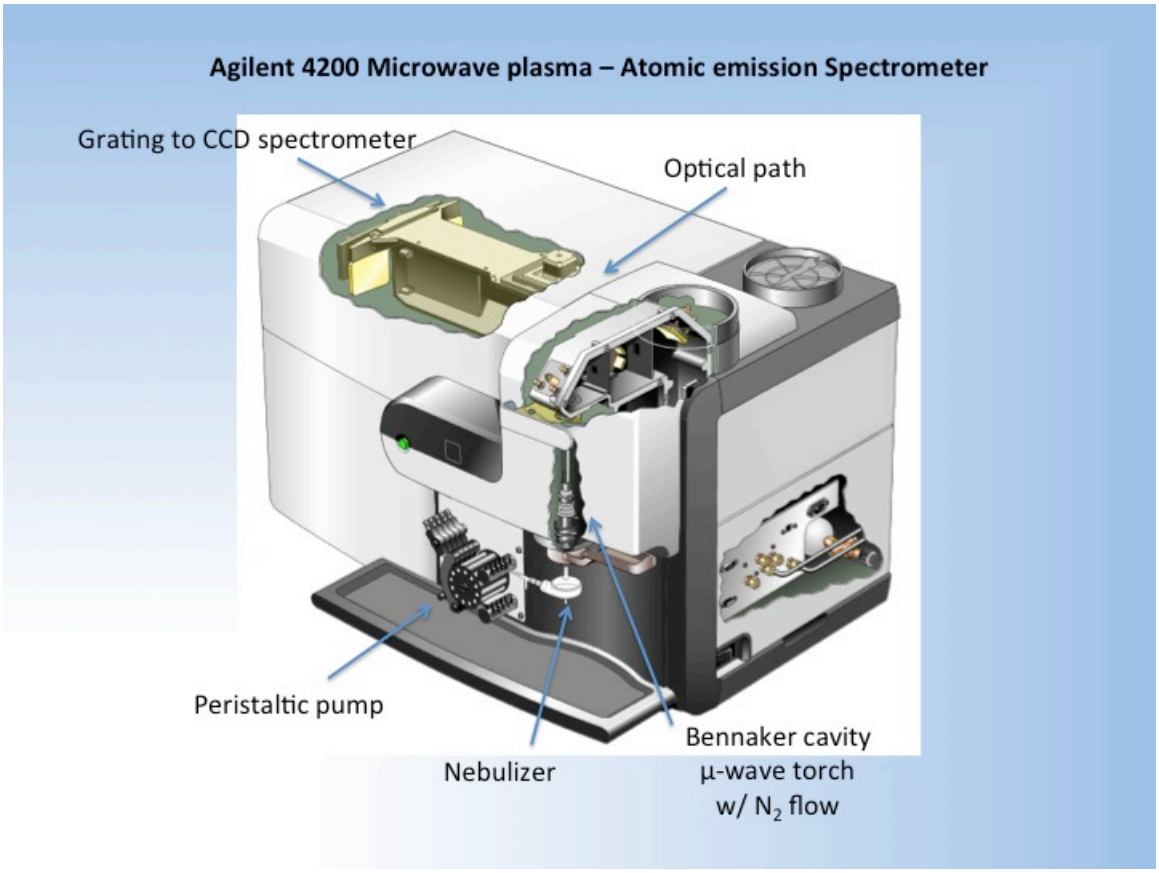
Milestone B: Gallium production improvements

The second milestone involves the production of gallium isotopes, ^{68}Ga and ^{66}Ga, from the irradiation of Zn targets. Again following the lead of the Swedish groups at

Uppsala and Lund, we have incorporated the thermally-assisted diffusion technique, again automated by Hector Valdovinos in a LabView driven separation system shown in the right had side of the dual mini-cell above. The concept is to carefully fabricate a thin, enriched zinc foil, using electro-deposition followed by extrusion in a jeweler's rolling mill to provide a target of about 50-100 mg/cm^2. Following irradiation at a shallow beam incidence angle on our -15^o beam line, the target foil is heated to about 400^0 C, just below the melting point of zinc. The gallium diffuses toward the surface of the foil in a matter of tens of minutes, where it can be harvested with very weak acid that leaves the zinc foil essentially un-affected. We have achieved about 70% gallium recovery, with less than 0.05% mass loss of the zinc foil, which is then directly suitable for re-irradiation. Since the thick target yield of ^{68}Zn(p,n)^{68}Ga is over 150 mCi/μA at saturation, this would permit the direct production of Curie levels of ^{68}Ga at high specific activities, far beyond the reach of any affordable ^{68}Ge/^{68}Ga generator. This project, and the gallium labeling of a number of novel PET agents, forms the focus of Hector Valdovinos' PhD dissertation project.

Milestone C: Trace metal determination of our products.

The third milestone of this quarter deals with the incorporation of specific activity assays for our ^{64}Cu and ^{89}Zr shipped out every Monday. This requires an additional several hours of lab work after the activity is delivered to FedEx, but it is a service that seems to be greatly appreciated by our off-site users, now numbering more than thirty. The ^{64}Cu specific activity is measured by competitive chelation against NOTA, while the ^{89}Zr is titrated against desferral. With this newly instituted discipline, our specific activities have now reached 10-20 Ci/μmol of Cu, and about 1-2 Ci/μmol of Zr. We have faced the need for a broad-range elemental analysis requested occasionally by some users needing CoA's for dealing with regulatory authorities, needed to find a solution to the firm reluctance of commercial labs to test our samples until all traces of radioactivity have decayed away. We have just taken delivery of an Agilent 4200 microwave plasma atomic emission spectrometer, shown below, that we are dedicating to the elemental analysis of our radioactive samples.



With this device, we can now quickly assay the detailed cold metal load in of our outbound Cu-64 and Zr-89, correlating this part-per-billion broad-element analysis with our effective specific activity measurements made by chelator titration.

Milestone D: Preparing for Y-86 production.

We have been supplying Y-86 to our local group of Prof. Weibo Cai, as well as a single shipment to users at Stanford. In both cases, the Y-86 was produced by proton irradiation of natural strontium, resulting in an initial Y-88 contamination of about 1% . Even these few microCuries of Y-88 are objectionable, given their penetrating high-energy gamma radiation and 106 day half-life. As a result, we have purchased several hundred mg of enriched Sr-86 carbonate, ready to irradiate when the demand develops.

Milestone E: Improving our I-124 production.

In the past, we have implemented the production of I-124 by the proton irradiation of enriched Te-124 in the form of aluminum telluride, followed by dry distillation.

We have tailored our -30° beam port on the vertical switching magnet of our PETtrace beam line for the production of volatile, low-melting targets, with He sweep gas cooling the target substrate and emerging to a water trap. However, the recent appearance of commercial I-124 at one-half of the previous $300/mCi brings the price of I-124 down below our production costs for the single-user demand that we could expect. For that reason, we plan to divert our vertically-directed beam line to serve our new demand for Br-76, made from selenium oxide.

Summary of the project activities for the entire period of funding.

Our original hypothesis was quite simple: that we could significantly upgrade our production of a number of radionuclides that are desired by a growing list of outside users by the acquisition of two shielded mini-cells to house our radio-metal processing modules. This had been our rate-limiting throttle point, and the arrival of the two RSI (Radiation Shielding Inc.) hot-cells resolved this problem immediately. With the heavily shielded space at hand, the construction of dedicated automated processing modules could be completed. The production of Cu-64, Zr-89 destined for national distribution, and Sc-44, Ga-66, Ge-69, Ge-71, and As-72 for local use increased as expected. The user list below has grown to ≈ 30 labs across the country, with roughly half of the destinations further distributing the Cu and Zr to multiple users inside their institutions.

AbbVie AECom Amgen Brigham and Women's Colorado State Emory GSK Harvard Johns Hopkins Invicro LANL Lantheus LBL Berkeley MD Anderson Mem Sloan Kettering Merck MPI Pittsburgh PNNL Stanford SW Texas UCLA UCSF U Minn U Missouri U North Carolina USC U Texas San Antonio Wake Forest

The problems encountered over the grant period stemmed mainly from the logistical difficulty of reliability of transportation, as FedEx enjoyed a monopoly position for transport of Dangerous Goods (HazMat; Yellow II) with the departure of DHL from the domestic scene. At its worst, 10% of our shipments were delayed by 1 day at the trans-shipment hubs of Indianapolis and Memphis. With the incorporation of DOT 7A-approved boxes, rather than our more substantial steel drums, this late (and lost) fraction dropped to less than 5%. Thus, on any given Monday, we make between 300 and 800 mCi of Cu-64, and ship out most of that to between 3 and 10 institutions. Our cost recovery price of $15/mCi (on departure), with a 30 mCi minimum, has not been raised since the initiation of our distribution a decade ago.

We are now gearing up for regulatory compliance for translational studies. Anticipating the need for certificates of authenticity (CoA's), we have instituted a routine measurement of effective specific activity, using NOTA titration for Cu-64, and desferal for Zr-89. Our users seem pleased with the added assurance, but have been reticent in asking for more detailed analysis. Nonetheless, we have now implemented broad range elemental analysis with our newly-acquired Agilent MP-AES, so as to be able to provide ppb assays of cold metal load in our outgoing product when requested.

Products developed under the award.

Refereed publications:

1. Severin, G W; Engle, J W; Valdovinos, H F, Barnhart TE, Nickles RJ. Cyclotron produced (44g)Sc from natural calcium. Applied radiation and isotopes Volume: 70 Issue: 8 Pages: 1526-30 Published: 2012-Aug (Epub 2012 May 24)

2. Xiao YL, Hong H, Matson VZ, Javidi A, Xu W, Yang YA, Zhang Y, Engle JW, Nickles RJ, Cai WB, Steeber DA, Gong SQ. Gold nanorods conjugated with Doxorubicin and cRGD for combined anticancer drug delivery and PET imaging. Theranostics **2**, 757-768, 2012.

3. Converse AK, Ahlers EO, Bryan TW, Williams PH, Barnhart TE, Engle JW, Nickles RJ, DeJesus OT. Positron emission tomography (PET) of radiotracer uptake and distribution in living plants: methodological aspects. JOURNAL OF RADIOANALYTICAL AND NUCLEAR CHEMISTRY **297** 2, 241-246 DOI: 10.1007/s10967-012-2383-9, 2013

4. Hong H, Zhang Y, Severin GW, Yang YN, Engle JW, Niu G, Nickles RJ, Chen XY, Leigh BR, Barnhart TE, Cai W. Multimodality Imaging of Breast Cancer Experimental Lung Metastasis with Bioluminescence and a Monoclonal Antibody Dual-Labeled

with Zr-89 and IRDye 800CW. MOLECULAR PHARMACEUTICS **9 ,** 8: 2339-2349, 2012. DOI: 10.1021/mp300277f

5. Orbay H, Zhang Y, Valdovinos HF, Song G, Hernandez R, Theuer CP, Hacker TA, Nickles RJ, Cai W. Positron emission tomography imaging of CD105 expression in a rat myocardial infarction model with (64)Cu-NOTA-TRC105. American journal of nuclear medicine and molecular imaging. 01/2013; 4(1):1-9.

6. Ellison, P., Converse, A.K., Williams, P., Ahlers, E., Lake, K, Nickles, RJ, Barnhart TE, DeJesus, OT. Imaging studies of copper uptake, transport and distribution in rapid growth Brassica oleracea JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS Volume: 56, Pages: S264-S264 Supplement: 1 MAY **2013**.

7. Ellison P, Ahlers E, Barnhart T, Converse A, Hetue J, Lake K, Nickles RJ, Williams P, DeJesus OT. Production, chemical isolation, and application of positron-emitting isotopes of arsenic for uptake and distribution studies in rapid growth Brassica oleracea JOURNAL OF LABELLED COMPOUNDS & RADIOPHARMACEUTICALS Volume: 56 , S222-S222

Conference proceedings:

1. Ellison, P.A.; Barnhart, T.E.; Engle, J.W, Nickles, RJ, DeJesus, OT. Production and chemical isolation procedure of positron-emitting isotopes of arsenic for environmental and medical applications 14th International Workshop on Targetry and Target Chemistry. AIP Proc, Vol 1509, 135-140, Playa del Carmen, Mexico, 26-29 Aug. **2012**

2. Engle, J., Gagnon, K., Ellison, P. A., Barnhart, T. E., Murali, D., DeJesus, O. T., Nickles, R. J. Production of electrophilic ^{34m}Cl for use in PET imaging. 7th International Symposium on Radiohalogens. Whistler, Canada, **2012**

3. Barnhart, T. E., Engle, J. W., Severn, G. W. Valdovinos, H. F., Gagnon, K., Nickles, R. J. Downward Dog: An After-Market, Five-Port Vertical Beamline Extension for the PETtrace. WTTC XIV, Playa Del Carmen, Mexico, **2012**

4. Engle, J. W., Gagnon, K., Severn, G. W., Valdovinos, H. F., Nickles, R. J., Barnhart, T. E. Flexible, Durable Proton Energy Degraders for the GE PETtrace. WTTC XIV, Playa Del Carmen, Mexico, **2012**

5. Barnhart, T. E., Engle, J. W., Valdovinos, H. F., Severn, G. W., Nickles, R. J. Prompt Radiation Detectors to Monitor Target Conditions In-Shootero. WTTC XIV, Playa Del Carmen, Mexico, **2012**

6. Engle, J. W., Lopez-Rodriguez, V., Gaspar-Carcamo, R. E., Valdovinos, H. F., Valle-Gonzalez, M., Trejo-Ballado, F., Severin, G. W., Barnhart, T. E., Nickles, R. J., Avila-Rodriguez, M. A. Highly Reactive $^{66/68}$Ga From Recycloted Zinc Targets for PET. WTTC XIV, Playa Del Carmen, Mexico, **2012**

7. Severin, G. W., Gagnon, K., Engle, J. W., Valdovinos, H. F., Farhoud, M., Barnhart, T. E., Nickles, R. J., ^{44g}Sc from Metal Calcium Targets for PET. WTTC XIV, Playa Del Carmen, Mexico, **2012**

8. Ellison, P. A., Barnhart, T. E., Engle, J. W., Nickles, R. J., Production and Chemical Isolation of Positron-Emitting Isotopes of Arsenic for Environmental and Medical Applications. WTTC XIV, Playa Del Carmen, Mexico, **2012**

Networks and Collaborations:

With the extended outreach made possible by the scale-up in production due to this DOE grant, a broad network of collaborators has been built up across the nation. We have been careful to not intrude into the protocols of our user community. We would rather provide them with the highest quality Cu-64 and Zr-89 that we can make, and then to trust in their research skills to carry out their studies. It is the nature of our collegiality that we ask only to be mentioned as the source of the tracer synthon in the methods section of resulting publications, with no expectation of co-authorship or other acknowledgements. At national meetings, this bonhomie is abundantly evident.

Computer modeling: None.