IGEMs/HERC Project Status Report
Idaho Incubation Fund Program
Final Progress Report
June 30, 2015

Proposal No.	**AHRC03**
P.I. Name:	**Dr. Alan Hunt**
Name of Institution:	**Idaho State University/ Idaho Accelerator Center**
Project Title:	**Development of Commercially viable accelerator produced Isotopes**

Proprietary Information – not for public review

Executive Summary:

During FY2015 the HERC/IGEMs funded project **Development of Commercially Viable Accelerator Produced Isotopes** at ISU/IAC succeeded in all of our milestones. With the release by the NRC of a production license for delivery of ^{67}Cu to researchers, we shipped multiple samples or revenue generating shipments to three different institutions. We have been contacted by other researchers requesting information and quotes to support their new grant proposals. The feedback from our deliveries has been excellent. Our product has exceeded quality at a lower price than the sporadic government supply and the process we developed allows "on demand" production. We were informed that based on our success, a government program to produce ^{67}Cu was shut down. The National Isotope Development Center will be profiling ISU/IAC in an upcoming bulletin. We strongly believe that the ^{67}Cu program will grow significantly year by year since a high quality dependable supply is now available.

To our knowledge, our program is the first in the nation to supply an isotope using an electron LINAC. The project has developed infrastructure and expertise allowing us to pursue other isotopes and grants with INL and private industry. Numerous proprietary techniques were developed in this program. We filed a full patent application, August, 2015, that will likely create at least two patents in the future.

PROJECT STATUS REPORT MILESTONES

This is the Final annual status report for FY 2015 for the IGEMs funded project, **Development of commercially viable accelerator produced isotopes**. The project proposal listed the following major project outcomes:

a. Have we established a commercially viable method of producing an isotope that is of economic potential and/or heretofore unavailable?
b. Have we created a technology, method or material that allows the creation of an isotope at a significant improvement in cost (either in direct material expense or capital requirements i.e. “fixed” costs)?
c. Are either a. or b. above proprietary, protectable and licensable to others with the objective of generating a positive return?
d. Have we trained a work force capable of advancing this industry and advancing our technology?

As we will detail below, we believe the answer to all of these questions is a resounding YES!

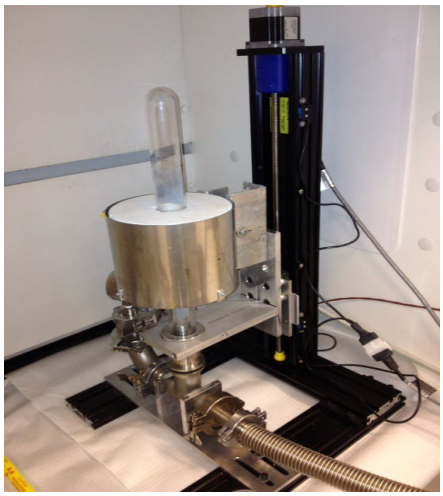
Final Report Milestone review

1). Simplify and improve the product separation processes suitable for operation in a commercial hot cell.

Summary:

This project developed a production process for separation of ^{67}Cu isotope from the accelerator activated Zn target. Several major challenges were overcome: 1). removing impurities from the final product without loss of the expensive target material, 2). separation of product quickly to allow shipment before decay of the isotope, 3). use low hazard materials and perform the separation in a low cost shielded hood. This equipment built and techniques developed are proprietary and patent pending.

a). **Sublimation:**



Figures 1 - Sublimation recovery furnace.

The first stage of the separation process is called sublimation, the low pressure step that vaporizes the target ^{68}Zn leaving behind the ^{67}Cu product. While sublimation processes are known in the metal industry, no commercial system or process had been created for radioactive isotopes. While the basic science is similar, the requirements are vastly different, forcing us to develop a novel approach. We designed, built and improved a furnace system and process for this first stage of isotope separation. Over the duration of this project, the sublimation equipment and process were substantially changed as we tried multiple materials and designs. As detailed in our patent application, we found a combination of heat zone design, temperature control, vacuum system, and automated furnace handling systems were critical in the sublimation furnace. In addition, the materials used inside the furnace including the tube, target holder, recovery collection scheme, and the recipe were critical in achieving >95% recovery of product and >>99% recovery of target material.

b). **Column separation:**

The second stage of separation is anion exchange column chromatography. In this step, the product from the sublimation process is dissolved in concentrated HCl, transferred, diluted, and pumped onto an anion exchange column (AG 1X8). Using varying molarities of HCl, we selectively elute impurities and the final product. Anion exchange chromatography is a well-known technique for purification, however, this step required a very large number of improvements and optimizations. Among the many factors we improved were the column volume, diameter and flow rate; all directly impact separation quality and eluate volume. Because of the requirement for minimal volume shipment, maximum yield and simplified processing, we ran multiple experiments and completed fractional analysis of eluate portions. Analysis of impurities (using the acquired ICP-MS) drove HEPA filtered environments around both the column and the radioactive hood. The overall results were improvements in yield collection to near 99% and a volume reduction (pre-drying) of 60%. We can now complete the entire column separation and drying process in a little over 3 hours with ICP-MS analysis.

Figure 2 Column chromatography with HEPA filter box

c). **Quality Control and Analysis:**

A very critical part of our process has been the determination of impurities and the final product specific activity (defined as the isotope radioactivity per unit of mass). Our ability to determine product quality and make incremental improvements was greatly enhanced this fiscal year by the purchase and installation of a used ICP-MS (PE DRCII) in our separation laboratory. The ICP-MS purchase was enabled by a separate grant from HERC/IGEMs (Figure 3).

Figure 3 ICP-MS installed in IAC radiochemical laboratory

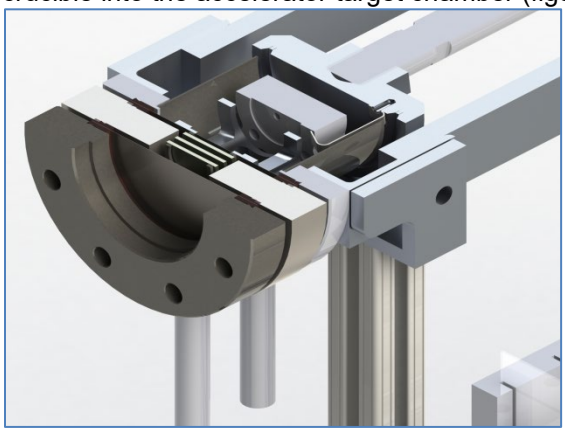
2). Complete all equipment for high power accelerator tests

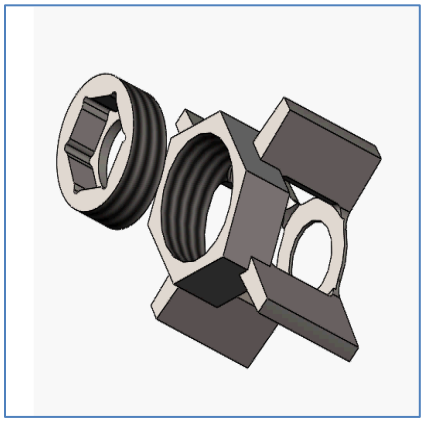
Summary: This project supported the design, construction and complete commissioning of a 40+ MeV electron linear accelerator for isotope production. Extensive modification and improvements were made to allow dependable operation for up to 1 day at > 5 kW of beam power. Target systems, shielding, cooling systems and a target extraction system were designed, built, and tested.

Accelerator and target extraction system improvements:

We greatly improved our systems for target irradiation, target cooling, target containment and target extraction.

A filled crucible is placed into a holder that holds a water tight lid on the crucible and centers the crucible into the accelerator target chamber (figures 9 and 10).





Figures 4 and 5. Figure 4 (left)) shows the target chamber with integrated 3 plate converter. Figure 5 (right) shows the target holder.

The target chamber integrates a 3 plate water cooled tungsten converter that is between the beam line and the target holder. The target is also water cooled. Figure 11 shows the target chamber assembly in place behind the accelerator beam exit window.

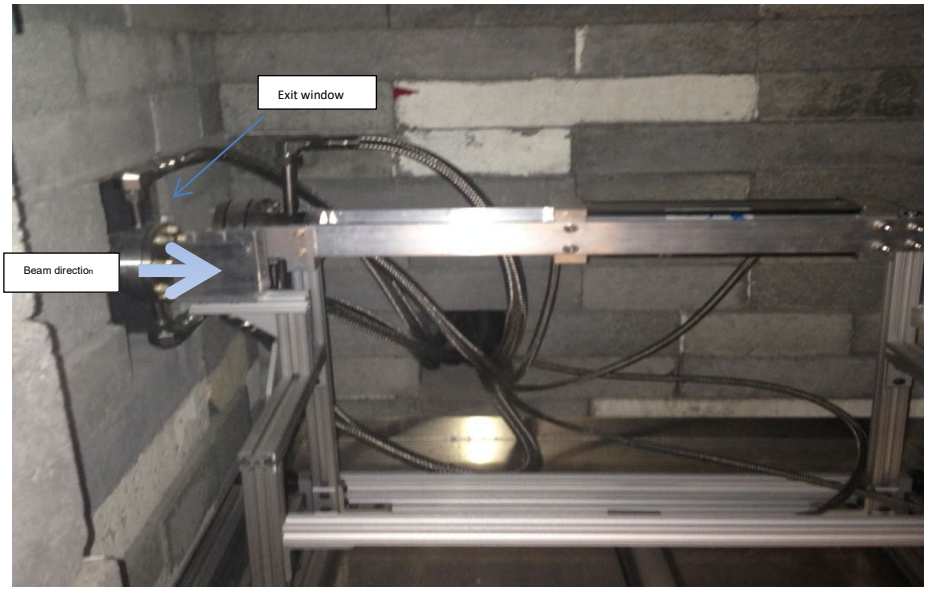


Figure 6. Target irradiation and holding system inside the accelerator radiation chamber and including a water cooled converter of 3 plates of a suitable bremsstrahlung converting material, This assembly also includes a water cooled target chamber that centers and cools the target during irradiation. A pneumatic ram extracts the target automatically after irradiation. Finally, the assembly translates to a position either aligned with the accelerator beam or away from the beam for beam diagnostics or other maintenance tasks.

In addition to the improved target assembly, we developed and tested an automated target shielding and target extraction system. The figure captions explain the operation.

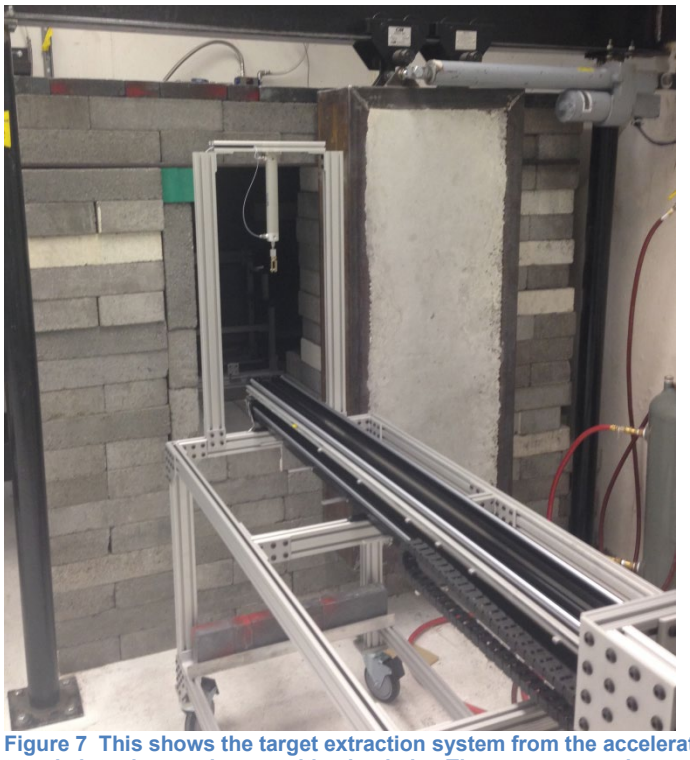


Figure 7 This shows the target extraction system from the accelerator after irradiation. A linear actuating arm travels into the accelerator with a lead pig. The target extraction ram drops the target into the pig then the linear arm removes the pig. Note that the irradiation cell is completely enclosed with an automatic door that only opens for target insertion or extraction – dramatically increasing worker safety.

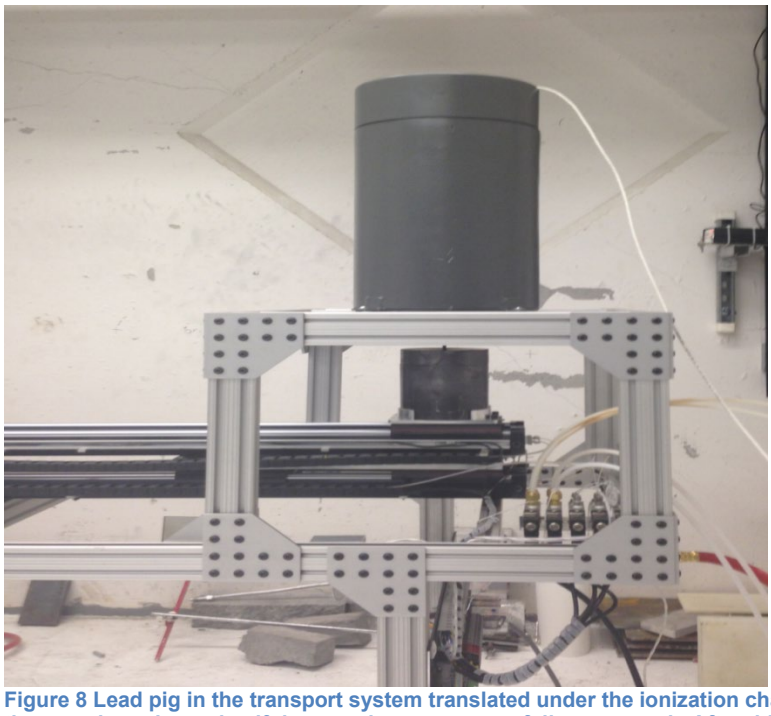


Figure 8 Lead pig in the transport system translated under the ionization chamber used to measure the activity of the sample to determine if the sample was successfully recovered. After this test, the lid is placed on the pig automatically.

3). Complete multiple full process tests

Summary:

The following graphs show the complete runs processed.

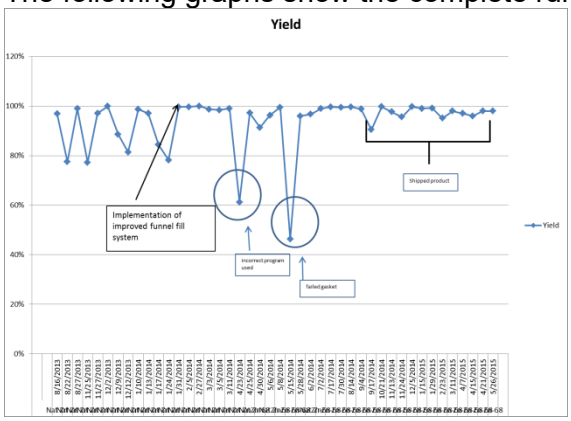


Figure 9. Graph shows the improvements in product yield made over a long sequence of full run processing. The points on the right of the chart include runs shipped to customers.

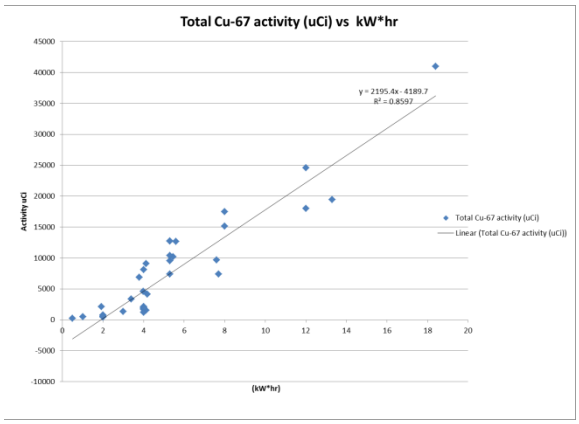


Figure 10. Graph shows the verification of total activity obtained over total power of irradiation. A linear relationship shows the consistency in processing and the ability to scale the activation to much higher power and time.

4). Delivery of approved quantities to researchers.

Summary:

In July of 2015 we received a production license from the NRC allowing us to ship product. Our first delivery was to the Beckman Research Center at City of Hope. Follows is Dr. David Cholcher's report on their results:

Labeling:

We assayed 12.13mCi. 50ul of 0.1N HCL was added to Cu67 to reconstitute brown powder in conical vial. 40ul (5.65mCi) was withdrawn and used for labeling a lot of our anti-CEA (M5A)-DOTA (0.5mg). Sample was pH adjusted to 5.0 and incubated at 43C for 45min. Reaction was chased by adding 10mM DTPA and the final sample was purified on a size exclusion Superdex 200 column. ITLC was 99.3% (Whatman paper progressed in saline) and the HPLC trace was 100%. Immunoreactivity with CEA antigen showed 100% immunoreactivity retained
93% labeling with 100%immunoreactivity. Great!

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We shipped product to two other customers: University of Texas, Southwestern Medical Center and Cal State Fullerton. Here is the initial report from UT Southwest:

I summarized a table for all labeling tests I did.

Reaction No.	Antibody amount*	^{67}Cu	Labeling yields
1	2.5 mg	1.45 mCi	>99%
2	125 µg	0.72 mCi	>99%
3	25 µg	0.72 mCi	>99%
4	2.5 µg	0.35 mCi	>99%
5	2 µg	0.72 mCi	54%
6	1 µg	0.72 mCi	32%
7	0.5 µg	0.72 mCi	13%
8	200 µg	6.1 mCi	>99%

* The antibody (NOTA modified Pertuzumab) amount was based on an estimation, and the accurate amount of antibody will be determined 1-2 weeks later.

I have my animal study going on, which will take more time to have the results out.

Based on the estimated antibody amount, ***the specific activity of your Cu-67 is much higher than previously reported***. You have done a really nice job on the purification.

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Dr. Maria Linder at Cal State Fullerton has also established an open purchase order with us for ongoing shipments, usually every ~4 weeks. While they have been cautious about sharing their project results with us, they are very pleased with the quality of the product. From this data we have concluded that our process is sound and producing high specific activity ^{67}Cu.

FINANCIAL

Summary: We believe we have been good stewards of the State's money. The following summary shows our expected zero balance at the completion of year 3 (June 30th) and use of

	HERC IGEM
Year 3 Budget	$516,084
Spent	$516,084
Remaining	$0
Spent in Salaries/Fringe	$354,610
Spent in Materials/Supplies/Beamtime	$158,851
Misc (travel, etc.)	$2,623

funds.

Intellectual Property and Commercial activity

Intellectual Property

We completed the filing of a patent which will most likely become at least two patents covering the methods we developed for producing and separating ^{67}Cu and the novel equipment in the activation and separation process. The patent application is before the PTO for examination.

Commercial Activity

Including our first shipment of material to City of Hope we have produced 169 mCi of ^{67}Cu in the commercial process. To date (our first ~ 9 months since acquisition of a NRC production license) we have shipped 85.2 mCi of ^{67}Cu to researchers in the US of which 43.7 mCi were free samples for evaluation. Our price per mCi is $100 plus shipping and container charges (approximately $200/shipment). Initially, we provided significantly more product to researchers than ordered so we could gain additional information on our product and engage them as long term purchasers. We also suffered shipping failures by our shipper (FedEx) due to weather and paperwork confusion. Because of the 2.5 day half-life of our product, we use overnight shipping and if the material does not arrive on time, we generally write off the sale. Due to these "teething" problems, our revenues are less than expected for our shipments. We have received a total of $1900 in revenues from the remunerated shipments. However, we have established a customer base that is pleased with our product and our ability to produce on demand. We established blanket POs with two customers and have quoted others. Researchers tell us that now that we are a credible supplier, they can approach funding agencies to support

new research programs. We believe we should double shipments this next year with potential for increased growth in the future.

Additional benefits:

Establishing a core capability in commercial isotope production at the IAC has raised our profile with other funding agencies. We are currently in progress on two government funded projects for national security on different isotopes (INL is a partner in these), with several additional requests for proposals expected. We have another commercial isotope possibility (^{123}I) request from our partner, International Isotopes, Inc. We have also been approached by cardiologists, radiologists, and a radio-pharmacy to begin producing proton isotopes at our facility for the Southern Idaho region from Jackson to Boise since no in-State supply exists. To that end we have been investigating a cyclotron that was donated to the IAC by the NIH to determine technology and business potential. This program could be started within a year with private sector backing. Our work in isotope production has also enabled new research into the chemistry and pharmacology of the drugs themselves. We have started research into the "linking" chemistry of isotopes to proteins utilizing the radiochemistry laboratory created at the IAC in support of the ^{67}Cu program. This is a unique facility and research being conducted jointly between the IAC and the College of Pharmacy of ISU could lead to new grants.

In closing, I'd like to note that this program is accomplishing what I believe the Higher Education Research Council envisioned: funding a research capability with strong ties to the private sector that creates long lasting intellectual property potential and economic possibilities. I'd like to thank the SBOE and HERC for establishing this funding opportunity and their support of our research. It has been a rewarding experience to be involved in this effort.

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