IGEMs/HERC Project Status Report
Idaho Incubation Fund Program

Annual Progress Report

June 30, 2013

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 FY2013 the IGEMs funded project **Development of Commercially Viable Accelerator Produced Isotopes** at ISU/IAC achieved substantial progress in the goal of providing a commercial supply of ^{67}Cu to the market. The manufacture of isotopes using an electron linear accelerator has not been attempted by any entity, public or private, to our knowledge. We selected an isotope in demand for cancer diagnostics and treatment and have developed proprietary methods to produce it. We are on the verge of shipping research quantities to an initial set of customers and then expanding that customer set as production capability increases. Over the last year we have completed 23 full process run tests, several hundred partial process tests and solved very difficult problems in high power accelerator operation, physical separation technology and chemical separation technology. Breakthroughs in these areas have shown that we can provide our product at roughly 10% of the "qualified researchers price" quoted by the United States Brookhaven National Lab. One of our key customers attended the June, 2013 Conference of the Society of Nuclear Medicine calling us immediately thereafter with a strong desire to receive ^{67}Cu as soon as possible. Shipment of samples to our customers is waiting on the installation and qualification of final quality assurance analytical equipment (an ICP-MS) at International Isotopes Inc, our commercial partner in the development and distribution of the isotope. FY2014 funding will allow us to complete the ramp up from sample quantities to volume production, provide a platform for full commercialization in Idaho, and start the work on developing additional isotope products.

PROJECT STATUS REPORT MILESTONES

This is the annual status report for FY 2013 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?

Our milestones are:

1). Simplify and improve the product separation processes suitable for operation in a commercial hot cell 2). Complete all equipment for high power accelerator tests 3). Complete multiple full process tests 4). Transfer separation and purification process to our commercial partner's hot cell, 5). Delivery of approved quantities to researchers for human trials.

<u>In addition to these milestones, we are employing full time or part-time 6 researchers and engineers and 2 students. Another full time hire of a Chemist, trained by us will be made in 2014.</u>

Each of these key milestones will be detailed below with progress.

PROJECT STATUS REPORT – Milestone review

For the year ending June 30th, 2013, (Q4 FY 2013), the following items were completed against the project plan:

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

Summary: During this year we have developed processes to separate and recover our product, ^{67}Cu, from the target material ^{68}Zn economically. These have been very difficult problems to find satisfactory solutions and have involved extensive experimentation and the development of proprietary equipment. We believe we now have a process that will recover approximately 90% of the product.

a). **Sublimation:**

Techniques to use vacuum sublimation to separate metals and radioactive materials were developed in the early 1950s. However, these methods were not utilized and improved through modern times and the use of vacuum sublimation for isotope separation required development from initial principles. Over the year we tested three types of furnaces, three types of vacuum systems, multiple configurations of heating crucibles, condensing apparatus and recovery systems. We had to find a solution to one of the most crucial issues of any separation process – high yields of the product and high recovery of the expensive starting material ($500/gram). Funding this work has allowed us to create a custom system for separation that we believe can be improved and scaled to high volume production. Figure 1 shows the yields we have achieved in sublimation along with annotations on equipment and process improvements:

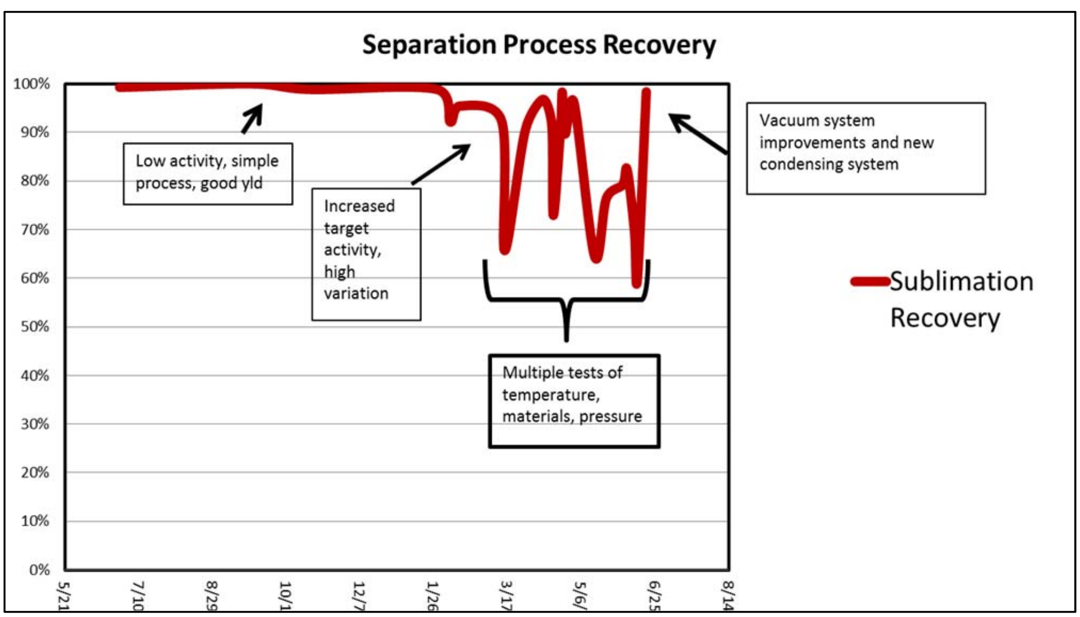

Figure 1 - Sublimation recovery process

Figure 2 shows pictures of the new equipment, pumping system and recovered material.

Figure 2 - left most picture is proprietary furnace, next picture is a small turbo pumping system, the last two pictures show recovered material after sublimation

b). **Column separation:**

Over the year we successfully developed a chemical column separation technique that allows us to further purify the ^{67}Cu product. We undertook the design and build of a custom pumping system to allow more automated dispensing of required acids and the movement of the product through the separation column. This pumping system has been used through many trials. We further modified the system with different speed motors and a PWM controller giving extremely precise dispensing of acids and product. This system is also designed for use within the hot cell.

We experimented with our separation chemistry to increase yields and lower cost. Our secondary purification system is an anion exchange column. The separation efficiency of the column is dependent upon the pH of the species introduced and the pH of elution. By changing column volumes and elution profiles, we found a process point that significantly improves product recovery with lower volume of carrier acid. This decreases the post separation volume reduction step, thereby decreasing the time of production and yields. Figure 3 shows the overall recovery of our column separation process through our trials. We are consistently achieving close to 100% recovery in this step.

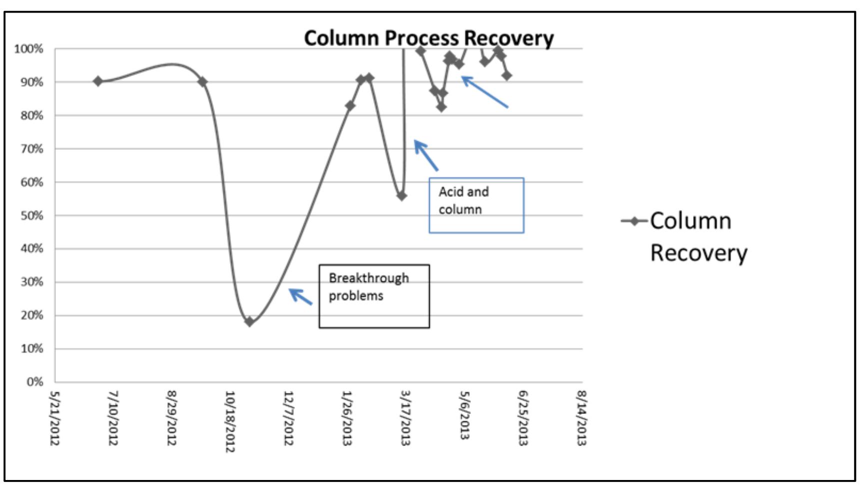

Figure 3 - Column % recovery

c). ^{68} **Zinc starting material**

We have purchased the very expensive starting material for our process – isotopically pure ^{68}Zn. This material cost approximately $480/gram, nearly 40% less than our initial expectation due to strong negotiations and the potential for a future market with the growth of this business. The material was purchased through Isoflex, USA who acquired the material from a Ukraine source. We are pleased that the specifications were better than we expected for impurities, however, we will still need to purify the material for final production. We undertook several experiments to determine purification technology for the starting material and have found that our sublimation apparatus with some changes to the process profile appears to be adequate to decrease background impurities by two orders of magnitude. This work involved extensive analytical chemistry using equipment at Idaho State University in the Chemistry Department (ICP-OES) and CAMAS (ICP-MS)

In addition, our efforts to improve the sublimation process have given us a good method to recovery >95% of the starting material after each run. However, we still need to improve the total recovery of the expensive ^{68}Zn to greater than 99%. That work will continue in FY2014.

d). **Analytical testing**

A customer requirement is a Certificate of Analysis of our final product procured by a suitable analytical instrument. Previously we reported on the development of a method using an Ultra-Violet (UV) spectrometer. However, our customers want verification of all potential impurities to a very high level, and therefore we began testing using the ISU CAMAS Inductively Coupled Plasma Mass Spectrometer (ICP-MS). We completed 3 extensive analyses of various combinations of separated product using the ICP-MS. As a result, we have started work with our partner, International Isotopes on the installation of International Isotopes own ICP-MS for final product verification. A dedicated ICP-MS will be necessary because the material we are producing is radioactive and therefore the equipment must be isolated for a single application. International Isotopes has stopped using this >$100,000 value equipment in its normal production operation so that it can be relocated for ^{67}Cu product development and production.

Next quarter actions:

Continue improvement in overall process recovery. Analyze product and produce quality assurance documents, ship samples to researchers.

2). Complete all equipment for high power accelerator tests

Summary: The production rate ^{67}Cu or any isotope using a linear accelerator is generally proportional to the energy and current (total power). We have had to develop the accelerator for production and work out the many issues in high utilization at high power. These issues included reliable accelerator operation, control of key parameters like energy, current, temperature, and radiation background. In addition we have had to develop high power targets and handling equipment. This has been a very challenging part of the overall project and we have now achieved a level of operation suitable for sampling product.

Accelerator:

The accelerator we developed for isotope commercialization was built internally by IAC engineers from parts donated over several years. The advantage of this approach is the extremely low cost of the final equipment. The disadvantage is the necessity to develop and characterize every single control system from scratch. A partial list of systems that were engineered and characterized over the year include:

1). Guide temperature control systems. These included water cooled loops for both operating guides, the target area and a main (and separate) chilled water system that feeds the secondary systems. See Figure 4:

Figure 4 - picture on left is the end station cooling system, center picture is the first guide cooling system, the last picture is the second cuide cooling system

2). Operational safety systems: These include valves to shut down the beam line in the case of vacuum failure in the target area. We experienced several types of failure over the year of testing and we have addressed each with a separate system.

Figure 5 - fast reaction valve in case of target driven vacuum leaks

3). Radiation target shielding and automated equipment handling: This includes equipment that we developed to remotely remove the target from the process area after product has been made and shielding of the target area during irradiation. See pictures in Figures 6 and 7:

Figure 6 - Pictures of shielding around the production target area. The concrete bricks provide radiation shielding and the black iron is part of a rolling door and framing system

Figure 7 - Left picture is the designed handling system to remotely remove the production product, the center and right pictures are of the constructed handling equipment.

5. Target centering and temperature control: We experimented, designed, developed, and characterized, numerous systems to measure and handle the target during irradiation. A key control point is the temperature of the target, the accelerator window and converter during operation. Software and hardware were developed so we could do real time temperature measurements of these parameters. We also procured a high capacity compressor to deliver cooling air flow for the low power <3 kWatt experiments. See pictures in Figure 8:

Figure 8 - the picture on the left is the target and converter on the end of the accelerator. The converter is water cooled, the target is air cooled currently, but, will switch to water cooling for production. The center picture is the control system developed to monitor energy during production and temperature of the target. The right picture is the high capacity compressor.

<u>Temperature vs power and accelerator temperature control</u>.

We completed extensive characterization of temperature of the target during operation. This is a critical parameter for both safety and the speed of production. Higher production rates require more power which heats the target, perhaps to failure if the parameters are not tightly controlled.

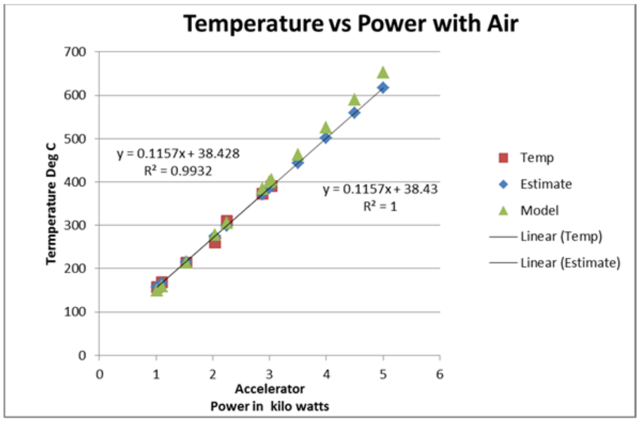

Figure 9 - graph of target temperature vs accelerator power.

<u>Next quarter actions:</u>

Complete additional higher power testing to work out bugs in shielding, target handling, accelerator reliability and production yield. Our long term goal is to increase the overall power of the accelerator by another 10%, an increase in total yield of at least that much.

<u>3). Complete multiple full process tests</u>

<u>Summary</u>: We have now completed more than 23 full process tests and hundreds of small scale tests of our process. We have increased our production activity level by one order of magnitude and intend to increase by 2 more orders as we move the process to full production. Figure 10 shows the activity from full scale tests we have done as well as the production yield (in product activity vs input power). Our results continue to improve and we believe sample shipments of product are possible.

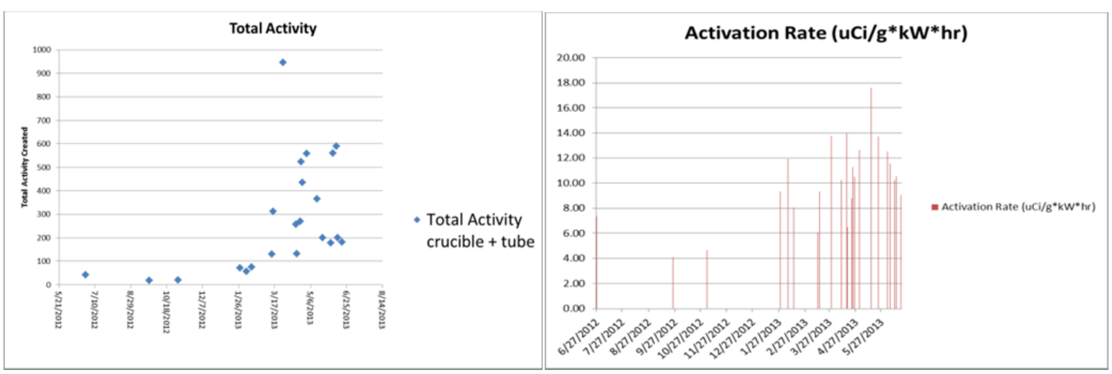

Figure 10 - left graph is total activity created and rright graph is ate of activity. These graphs represent trials over months of tests and multiple configurations of targets and converters among other variables.

4). <u>Delivery of approved quantities to researchers for human trials.</u>

Summary: We have made contact with four major customers for ^{67}Cu. We are now in the enviable, but, pressure packed position of meeting their requests for delivery. As mentioned earlier, we are constrained in shipment by the need for production quality assurance equipment. That is now being installed and we anticipate samples to go out to our customers next quarter.

FINANCIAL

Summary: We believe we have been good stewards of the State's money. We have completed most of our goals well within our budget and with the remaining budget spent in FY2013, and carryover into FY2014 we will be successful in meeting our initial goals.

Project Budget/Financial Status as of June, FY 2013

Budget Item	Revised Budget (SBOE approved)	Actual spend to date	Variance/Explanation
Salary + Tuition + Fringe	345,710	304,158	We believe this will be completely spent on final year close
Consulting	60,590	60,590	Remaining on spend plan
Travel expenses	4,100	1,100	Below budgeted spend
Materials and Equipment	160,300	138,439	Below budgeted spend, however, some items remain to be delivered at end of June, 2013 and early July, 2014
Beam time	100,000	48,500	Does not include all of June, 2013 use. Expected below plan, but will increase as samples prepared

Intellectual Property and Commercial activity

So far our customer base includes City of Hope Cancer Research Center, Fred Hutchinson Cancer Research Center, Harvard Medical Center, and the University of Texas Southwestern Medical Center. We have received very positive feedback on a new dependable supply of this isotope. Our customers want delivery. We have discussed the logistics of supply with our partner, International Isotopes Inc. of Idaho Falls and they are partnering with us to get samples into our customer's hands. They have expressed concern that quality and delivery are very dependable. Researchers have had high hopes for years, only to be disappointed when the supply was unavailable for human trials. We are endeavoring to be fully prepared to meet the customer expectations.

We have done extensive modeling of the commercial economics of this project. We have been encouraged by our customer's response not only with demand, but, with our planned pricing. We have received pricing from the only other supplier to this market, Brookhaven National Labs. Their pricing is (and this is discounted for researchers) $300 per miliCurie. Considering that for most therapies, the dose will be in the range of 50 to 100 miliCuries, the expected cost for the isotope alone from BNL would be $15,000 to $30,000. Our customers tell us that price is unsustainable in the market, however, our suggested pricing of approximately $50 per miliCurie would be enthusiastically accepted. We believe our model can lead to a successful Idaho based business and significant future market growth in this and other isotopes. We look forward to 2014.

Intellectual property has been maintained as trade secret for our technology. There are several reasons for this:

1). There is a lack of budget for patent filings at our University. This is being addressed and we believe budget will be made available in 2014 for those proprietary inventions that we believe will be well protected by patent filings.

2). Patent disclosures may decrease the licensing value of our know how. It is difficult and expensive to protect patents through litigation. We believe that what we have learned would be very costly for others to develop and implement. The safer course is to keep our information private and only disclose to partners and licensed partners.

3). Our know-how is evolving. We believe that the final production process will include potentially even more valuable IP than has been developed to date. The value of our IP increases with the establishment of a market supply. We believe we are increasing the overall value through silence at this time.

Summary: We have made very significant progress in achieving our goal of a commercially viable process for producing ^{67}Cu for cancer therapy and establishing methods for other isotopes. We remain committed to our goal and have a strong team of our industrial partner, International Isotopes, and our top quality researchers and engineers on this project. We have solved many key issues and are poised for sample deliveries.

Prepared by Jon Stoner
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