DOE-DUKE-8775-1

PRODUCTION OF ASTATINE-211 AT THE DUKE UNIVERSITY MEDICAL CENTER FOR ITS REGIONAL DISTRIBUTION

Final Technical Report

Period Covered: August 1, 2012 – November 30, 2014

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A. OBJECTIVES AND SPECIFIC AIMS

Systemic targeted radiation therapy and radioimmunotherapy continue to be important tools in the treatment of certain cancers. Because of their high energy and short path length, alpha particle emitters such as ^{211}At are more effective than either external beam x- ray or *in vivo* beta radiation in delivering potentially curative doses of radiation. The 7.2-hour half-life radiohalogen Astatine-211 has long been considered one of the most promising α-particle emitting radionuclides for targeted radiotherapy; however, radiochemistry, preclinical and clinical investigations with ^{211}At have been severely hampered by the lack of availability of this radionuclide. At Duke, we have been fortunate to be able to produce ^{211}At on our CS-30 Cyclotron in support of our own research programs, which have led to new ^{211}At labeling methods, radiopharmaceuticals and one clinical trial.

Coupled with DOE's commitment to identify and help establish a network of regional production and distribution sites for radionuclides in critical need, the primary objective of this project was to ramp up our ^{211}At production and purification capabilities so that this radionuclide can be supplied to researchers at other institutions throughout the US. In order to address this objective, the following **Specific Aims** were pursued:

Primary Specific Aim: To fix, upgrade or replace those subsystems and components of the Duke University CS- 30 Cyclotron that will yield an instrument capable of running ≥ 60 μAp α-particle beam on target for durations of not less than 4 continuous hours of operation multiple times per week. This will allow us to reliably and routinely produce ^{211}At at a reasonable cost and with irradiation periods that would not interfere with other obligations of this machine, including its use in support of our clinical PET center.

In order to address radiation safety issues resultant from higher ^{211}At levels and more frequent production runs, and to maximize the efficiency of target processing, we also proposing the following additional specific aims in order to decrease radiation absorbed dose to personnel and also increase reliability and efficiency of ^{211}At production to best meet the emerging needs at other academic institutions, and hopefully biotechnology companies, for this promising radionuclide for alpha particle targeted radiotherapy.

Specific Aim 2: To design, fabricate and deploy a solid target recovery system (TRS) that is compatible for used with the natural bismuth internal target installed on the CS-30 cyclotron.

Specific Aim 3: To procure a charcoal-filtered hood/glove box designed for target processing and ^{211}At recovery.

Specific Aim 4: 4) to design, fabricate and deploy a more efficient dry distillation apparatus that would permit more reliable distillation yields and shorter synthesis times without increasing release of ^{211}At into the environment.

With these modifications in place, we are confident that we shall be able to reliably and routinely produce ^{211}At at sufficient activity levels to supply users at other institutions in a cost effective manner.

B. STUDIES AND RESULTS

Project Highlights from April 15, 2013 Report (Dr. Gerald Bida, Project Manager)

During the week of 2/25-29/13, we were visited by Fred Ramsey of Carroll-Ramsey Associates as part of the overall CS-30 Cyclotron evaluation process. It was determined that most of the Cyclotron's subsystems are in reasonably robust condition, with the exception of the Ion Source Power Supply (ISPS). We have experienced frequent ISPS component failures during this reporting period. Investigation of the cause(s) of these failures is ongoing.

Given the generally favorable state of the accelerator and Mr. Ramsey's location plus schedule, we decided to shift a large portion of the identified tasks from Fred Ramsey to Collin McKinney of M2 Innovations. Mr. McKinney is an electrical engineer who used to work in the Duke Cyclotron Facility. He and his company are located here in Durham. Along with FRamsey, his primary objective during the current reporting period (Q3 of FY13) was to identify a suitable ISPS alternative to the OEM device.

The most important forecasted milestone that slipped start date was CS30 subsystem evaluation. Given our in-house diligence in moving forward in those areas where we can, coupled with Mr. Ramsey's visit in February, we have achieved this important milestone completion date. Some of the equipment that was recommended we purchase (for example, chilled water pump) has been received, but not installed or tested. This status has no impact on the project at this time.

Finally, during this review period, we have been able to provide sufficient alpha production in support of Dr. Zalutsky's At-211 research program. Also, during his visit, Fred Ramsey helped us to install a deflector for the purpose of extracting external beam needed to support other At-211 related research projects here at Duke.

In summary, the primary concern as of this writing was with the viability of the circa 30yo ISPS. It is the case that DOE funds are available to this project for procurement of a newer device. That said, it is not a simple case of locating one off-the-shelf. What came with the machine has not been commercially available for many years. A 5-amp device into a negative resistance presents a challenge. Further, some manufacturers have arc suppression built in, which could mean an inability to even strike a source arc. Some level of custom fabrication may be necessary. For these reasons, plus the general good health of the machine, we decided to abandon purchase of two pieces of capital equipment, i.e., a gate valve and a diffusion pump. Instead, we rebudgeted for purchase of a rebuilt mechanical pump and a turbomolecular pump. This will free up some resources in the event they are needed for the ISPS purchase.

Project Highlights from July 15, 2013 Report (Dr. Gerald Bida, Project Manager)

In last quarter's report, it was noted that frequent Ion Source Power Supply (ISPS) component failures were occurring and that an investigation into the cause(s) of these failures was ongoing. The primary cause of these failures was traced to an aged (almost 30 years) 25kW power tetrode in the ISPS. This tetrode was essentially operated as a variable voltage resistance capable of handling large currents at high voltages. Over time, they tend to leak to atmosphere and performance declines accordingly.

It was also noted in the last report that Mr. Collin McKinney of M2 Innovations had as his primary objective during Q3FY13 identification of a suitable ISPS alternative to the OEM device. After several measurements of the ISPS performance and behavior post tetrode replacement, a commercially available power supply has been identified. This device will require an add-on, custom built inductor and some user interfacing. These projects will continue to be handled by Mr. McKinney.

A major objective of this project was to achieve the ability to run sustained alpha currents at or above 60 uAp. As noted in the Request for Initial Packet of Information, preliminary thermal modeling of the situation suggested that bismuth melting could be a problem. During this reporting period, additional calculations were performed and the results reported in a poster presented at the Eighth International Symposium on Targeted Alpha Therapy. Briefly, a conjugate heat transfer analysis supports 1) a modification to the aluminum support for the Bi target material and 2) a better top-to-bottom centering of the beam strike along the alpha path across the support. Some work during Q4FY13 will address if and how the latter may be achieved. This will be discussed in greater detail in a subsequent section of this Final Report.

In summary, the primary concern as of this writing has less to do with the course and conduct of the project and its milestones, but more with the fate of the Duke CS-30 Cyclotron and its support personnel, to include myself (Dr. Bida).

Project Highlights from October 15, 2013 Report (Dr. Gerald Bida, Project Manager)

The Ion Source Power Supply (ISPS) replacement for the OEM device was received mid-September. The custom built inductor that was mentioned in the last report is due during the first half of October.

Drawings were completed, reviewed and approved for fabrication of seven different components that will comprise the Target Retrieval System (TRS). These parts are currently scheduled for an early November delivery.

During the course of inspecting and calibrating some of the major power supplies for the CS-30 Cyclotron, it was discovered that the digital readout for the main magnet current was too low by nearly 35 amps. This translated to limited, or nearly, no headroom in the operation of the OEM magnet shunt. Magnet current regulation is accomplished via feedback from this water-cooled, current sensing (actually sensed as a voltage) shunt. At the high currents required to accelerate alpha particles, solder connections in the shunt can, and have been, compromised. Thus, a more robust solid-state current transducer was installed during this reporting period.

In summary, the ISPS replacement proved to be a sizeable challenge. It was anticipated that we should have data by mid Q1FY14 indicating that the power supply and inductor combination will be a reliable source for the anticipated high alpha beam currents that will be needed to reliably produce high levels of Astatine-211 in support of the central objective of this project.

Project Highlights from January 15, 2014 Report (Dr. Gerald Bida, Project Manager)

A significant amount of time was spent during this quarter testing the Ion Source Power Supply (ISPS) replacement for the OEM device received last September. In addition, we needed to determine if the custom built inductor that was mentioned in the last report would perform as anticipated. Our findings are summarized below under the ***New ISPS Progress*** Section below. Finally, a custom-built interface unit has been fabricated that allows the operator to control the new ISPS in a manner similar to the OEM configuration. That testing is about three-fourths complete, but so far is not yielding any unforeseen complexities.

Drawings were completed, reviewed and approved for fabrication of seven different components that will comprise the Target Retrieval System (TRS). Due to circumstances at the vendor end, these parts are currently scheduled for a mid-February delivery.

In summary, ss indicated above and in the ***New ISPS Progress*** Section below, the new ISPS/inductor combination testing was proceeding smoothly. We will probably transition to a ten-fold larger inductance in order to assure protection of the ISPS circuitry. Placement of an order for the fume hood has taken longer than anticipated, primarily due to a need for re-quotation. At this time, we believe we can purchase one new and one previously owned hood for the same price as originally budgeted/funded.

New ISPS Progress. The existing, original ISPS is a linear analog type which utilizes a very large vacuum tube as the main current regulating element. The tube is rated for an o rder of magnitude higher power than it supplies in the ISPS circuit and is therefore fairly impervious to changes in the load. When the plasma is normally formed in the ion source, at least one arc event occurs (and sometimes many arcs actually occur) before the p lasma is formed and sustained. The existing power supply only has a continuous overcurrent protection shutdown, and although these arc events may exceed the threshold current, the event does not last long enough to trigger a shutdown. Figure 1 shows three arc events (green trace) that occurred during the normal lighting of the ion source. The measurement is made across a 1Ω current sense resistor in the power supply. The magnitude and duration of these events is determined by the output capacitance and inductance of the power supply but it represents the amount of energy that is expended during a typical arc event.

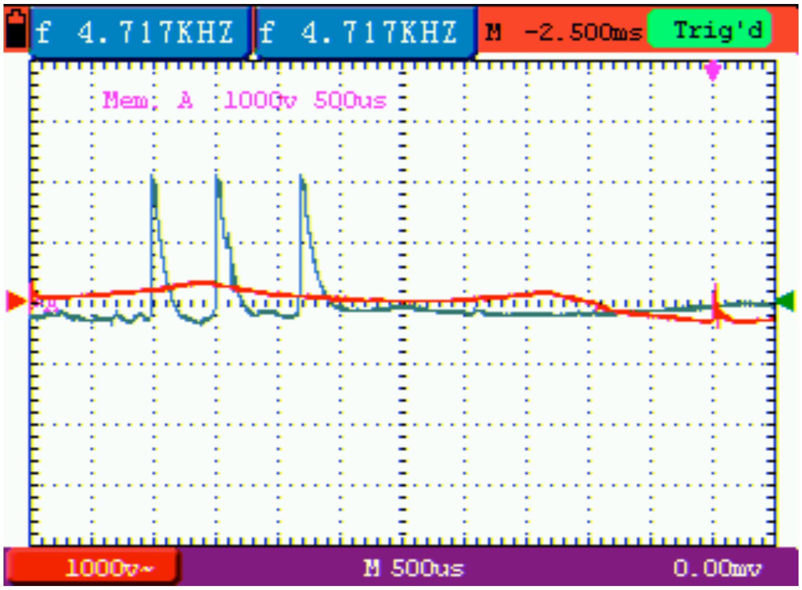

Figure 1. Arc events during normal lighting of ion source (hydrogen) using existing vacuum tube power supply.

Modern switching- type power supplies, such as the one chosen as a replacement for the existing vacuum tube supply, generally have very tight controls on overcurrent conditions. The specific MagnaPower unit can sense very short duration arc events and actually counts the number of events. If the total integrated power over a number of such events exceeds a threshold or if the number of events counted per unit time exceeds a preset value, the power supply is shut down to protect the output capacitors and semiconductors from damage. It is therefore desirable that the power supply does not shut down during the normal lighting of the ion source. The MagnaPower power supply was specified with additional output capacitance and more robust capacitors due to the likelihood of arc events occurring. However, as indicated previously, if these arc events exceed the potential storage capacity of the capacitors, the output voltage will sag and the protection circuitry will activate. Therefore, we have elected to add a power inductor in series with the output of the power supply to store current in reserve to overcome the arc events. The calculation for the size of the inductor is as follows:

From Figure 1:

Peak current in one arc event:

$I + V/R = 2500V/ 1\Omega = 2500 A$

Peak instantaneous power (Max applied voltage = 3kV):

$$P = E * I = 3000V * 2500A = 7.5E6\ W$$

Number of Joules in one arc event (simplify to a rectangular pulse 3µSec wide) :

J = P * T = 7.5E6W * 300µSec = 2250 J

Calculate the inductance of an inductor to store this amount of energy:

L = 2J/I2 = (2 * 2250 J)/(2500) 2 = 0.7 mH

To allow for headroom, a 10 mH inductor was specified. The results of testing the MagnaPo wer unit with and without this inductor when striking a hydrogen arc are shown in Figures 2 and 3. In this case a 0.1 Ω series current sense resistor was used for the measurement.

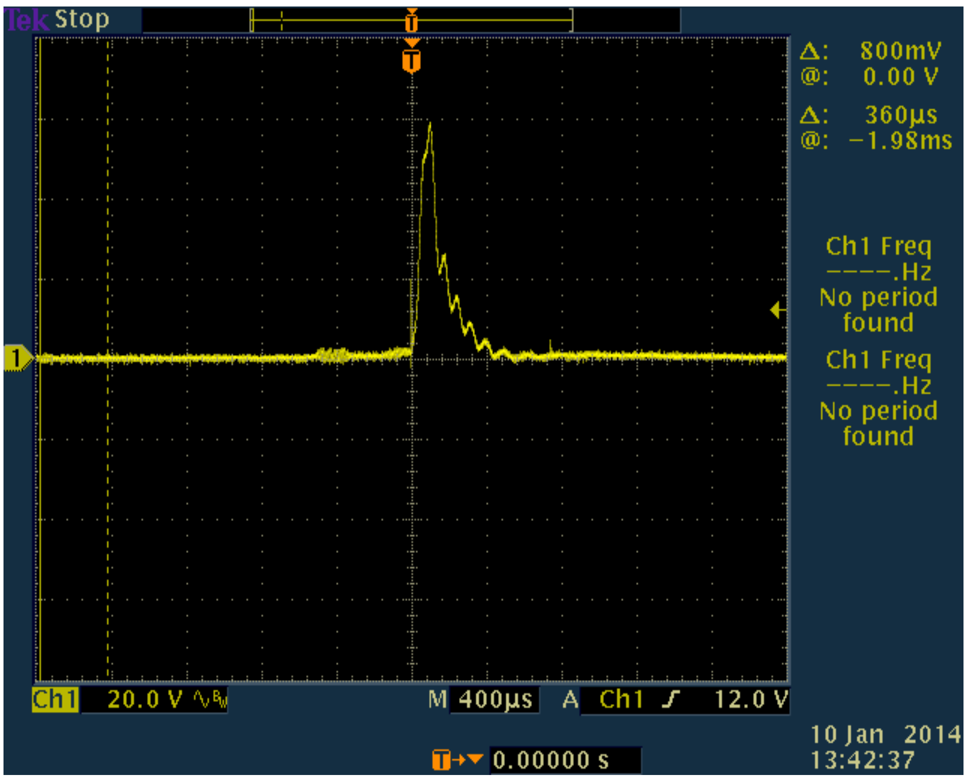

Figure 2. MagnaPower power supply peak current during an arc event (60V/0.1Ω = 600A) with 10mH series inductor.

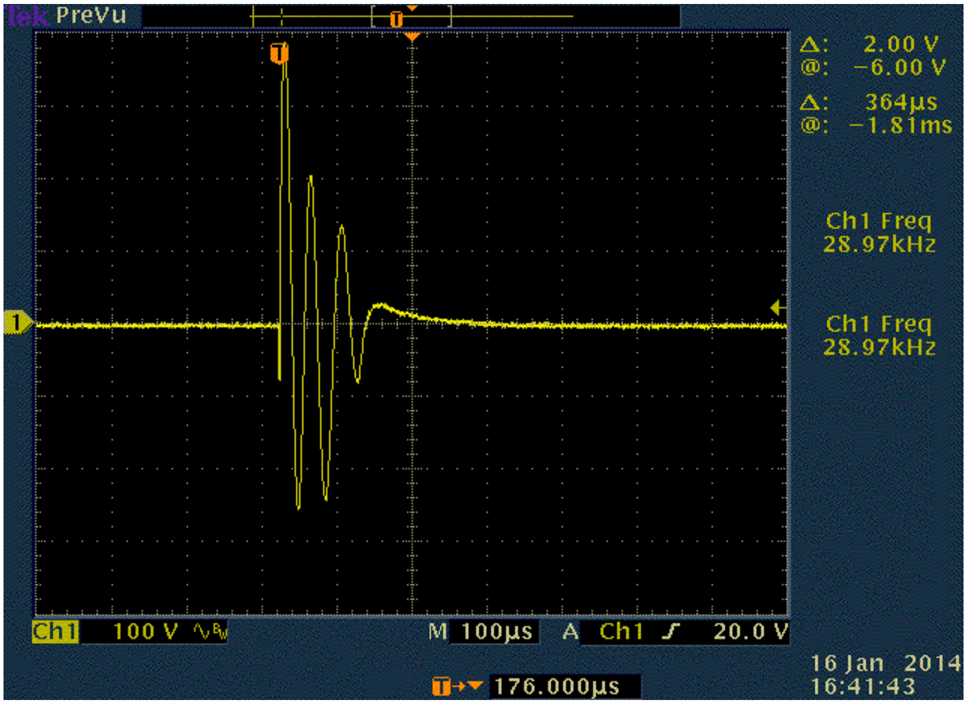

Figure 3. An arc event occurring without the use of the inductor which causes the transient current to be bipolar, significantly higher (6500 Amps), and also causing ringing on the output.

Project Highlights from April 15, 2014 Report (Dr. Gerald Bida, Project Manager)

We are transitioning to a ten-fold larger inductance in order to assure protection of the ISPS circuitry, as noted in the previous report. This component has yet to be delivered due to the long lead time for the ferrite core used in the process.

Delivery of two fume hoods for the purpose of post-irradiation ^{211}At recovery are scheduled for delivery within the next two weeks. The two units have been purchased for less than the originally budgeted request for a single unit.

A reasonable amount of progress was made this period on the Target Retrieval System (TRS). Some minor effort remains in the operation of the servo motor motion control. In addition, some time will have to be spent in modifying the internal target control system to accommodate operation of this hardware. To minimize lengthy component descriptions, a before and after picture of the TRS is presented below in Figure 4 on the left and right, respectively. On the right, the TRS is shown bolted to the bottom of the vacuum cross, isolated via a gate valve.

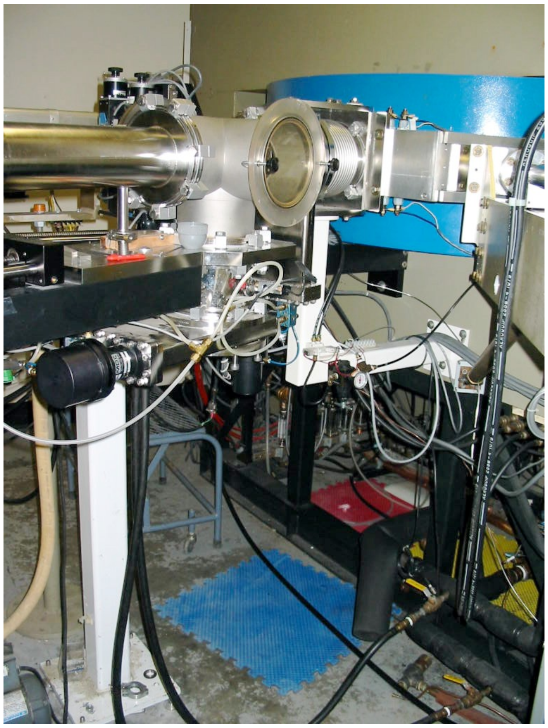 

Figure 4. Current status of Target Retrieval System before (left) and after (right).

Simulation Delivered Changes for Increased Production of ^{211}At

Historically, production of ^{211}At via the ^{209}Bi(α,2n)^{211}At by bombarding natural bismuth metal targets with ≥28 MeV α-particles has been below 60 μAp. The target capacity is limited by the relatively low melting point of the metallic bismuth target medium(~500°F). A computational model has been developed for the target medium, target holder and cooling water system. The objectives for this study are to predict the power level where melting will occur in the original design and to detemine if any incremental gains in thermal margin can be realized through design modifications.

The prepared target consists of a uniform thickness of metallic bismuth bonded to a curved depression in an aluminum target holder. The beam strike area was approximated using measurments from an irradiated aluminum target (no plating). Beam intensity was assumed to be uniform over the entire beam strike. The heat input was modelled using a conservative surface heat flux boundary condition. Measurements of 14 prepared targets indicated an 85 μm average thickness of the bismuth layer and a maximum thickness of 116μm. The maximum thickness was selected as the limiting case for the computational model. A conjugate heat transfer analysis was employed using Solidworks Simulation 2012. Maximum temperature for each part of the assembly was determined, as well as the maximum heat input to result in melting of the bismuth (Figure 5). Figure 6 shows the surface temperature of the bismuth exceeding the melting point with a heat imput of approximately 1500 W, or 107 μA. The simulation indicates that no melting will occur at or below 1400 W, or 100 μA.

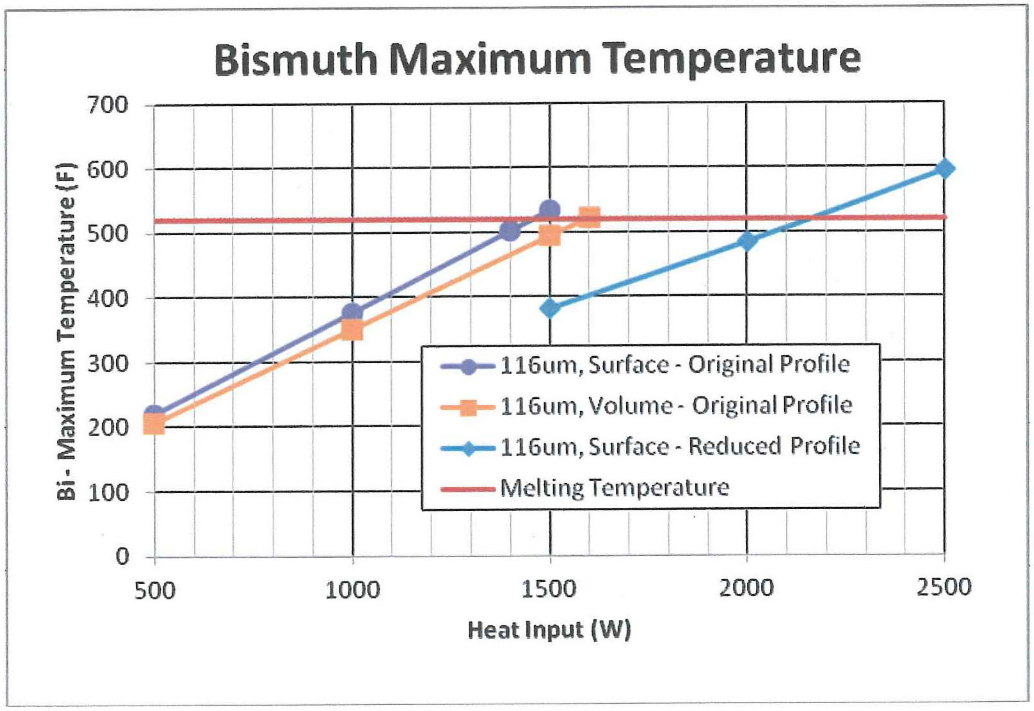

Figure 6. Model determination of maximum temperature on the bisbuth target as a function of heat input in comparison to the melting point of bismuth.

The position of maximum temperature occurs at the edge of the target, where the conduction length from the target to the cooling water is greater. The target holder was modified to eliminate the beam striking near the edges of the assembly. This results in a significant increase in thermal margin, with a maximum temperature of 390°F at 1500 W (Figure 7). The reason for this more favourable profile is that the outer edges of the target were located beyond the coverage area of the cooling channels.

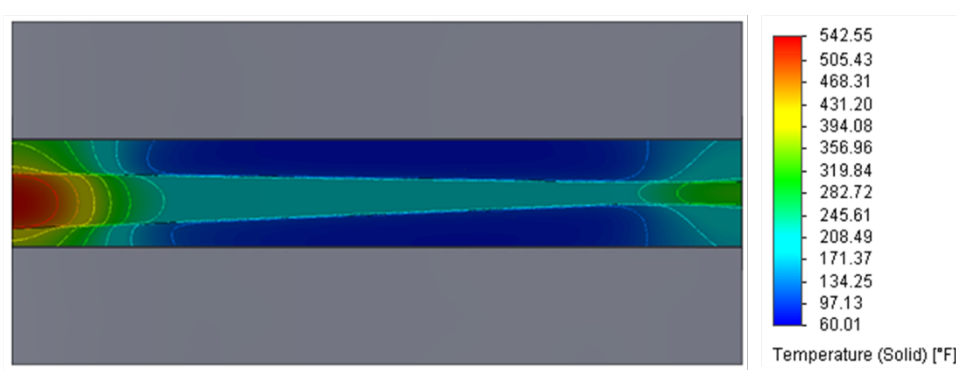

Figure 6. Bismuth temperature profile distribution on the surface of the bismuth layer at 1500 Watts for the original profile target.

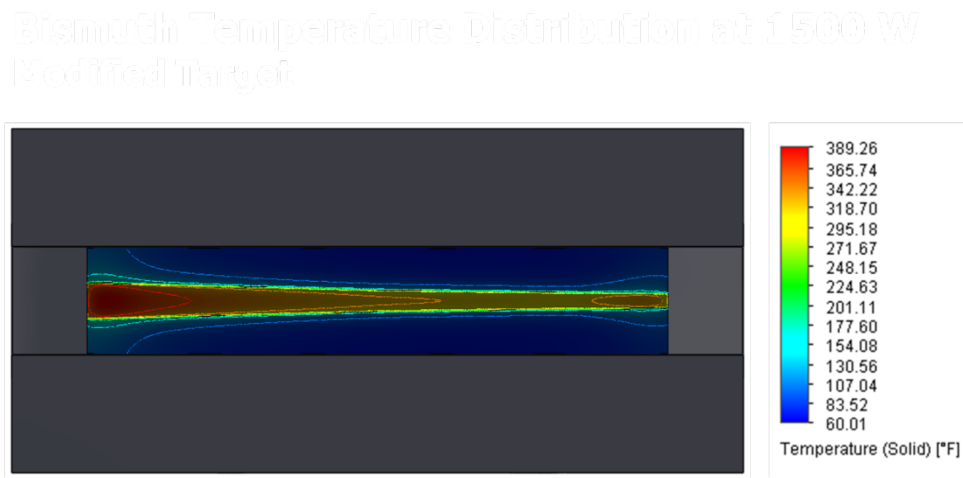

Figure 7. Bismuth temperature profile distribution on the surface of the bismuth layer at 1500 Watts for the modifiedl profile target.

In summary, this simulation indicates that the bismuth melting temperature will not be exceeded at power levels up to 1400 W. The maximum power can be increased to roughly 2100 W, or about 25%, by implementing the chamfered aluminum target holder, permitting the use of beam currents as high as 120 µA.

C. SUMMARY: ASTATINE-211 PRODUCTION AND PURIFICATION MODIFICATIONS IMPLEMENTED AS A RESULT OF THIS PROJECT

Cyclotron Production

In an effort to enhance ^{211}At production at the Duke CS-30 cyclotron, there were cyclotron subsystem improvements leading to increased production and reliability. The original ion source power supply was replaced with a new Magna-Power Electronics Model TS3000-4.8 power supply. The new supply utilizes solid-state components rather than obsolete, hard to find components and it doesn't have to be water-cooled. It provides more alpha beam current capability at lower ion source currents as well as cleaner ion source operation. As a result, there is less ion source cathode deterioration and a decreased likelihood of a cyclotron failure.

With the Duke CS-30 cyclotron, one previously existing limitation to the production of At-211 was the tendency of the solid Bi-209 target material plated on the aluminum target blank to melt at alpha beam currents as low as 40uA electrical. By reducing the amount of Bi-209 plated over a ¾ x 4 inch area of the face of the target blank from 1.25 grams to a range of 0.011-0.200 grams, there is no evidence of melting on sustained one hour runs at beam currents as high as 120uA electrical (60uA particle).

There are several additional benefits of this modification. The thinner layer of bismuth conforms to the radial curvature of the aluminum target blank and the natural curvature of the alpha beam. As a result, the target cooling water more efficiently cools the bismuth target layer at the beam strike area. With better cooling, the target is able to withstand higher beam currents. Thus, a run of 100uA electrical, as opposed to the prior limit of 40 to 50uA electrical, will yield 75mCi per hour of ^{211}At or 0.75mCi/µA-hr. The 75mCi/hr production rate is a decay corrected calculation corrected back to end of bombardment (EOB) after performing a one hour run at 100 µA and measuring the solid target in a Capintec CRC-7 after waiting 2 half lives (7.2hours= ½ life). This production rate has been consistent over a series of production runs. The maximum amount of ^{211}At that has been produced to date is approximately 200 mCi after an irradiation period of 156 minutes.

Additionally, at that production rate, a 75mCi production run can be performed on the afternoon of day one and the distillation can be completed the next morning yielding about 10 mCi of ^{211}At in solution. This capability is quite beneficial for ^{211}Astatine distribution to other facilities on the East Coast because it will allow time for delivery of the product to the desired location and provides evidence that a predictable and usable quantity will be available. Logistically, this allows time to accommodate cyclotron failures in a timely manner with time to spare to successfully complete a run for distribution. Furthermore, with regard to the radiation safety rule of ALARA, it is very helpful.

With the elimination of target melting, it is now possible to wipe the face of the target clean with a Chemwipe and acetone prior to distillation and remove all of the discoloration and signs of heat related residue from the face of the target, which helps to promote a cleaner post-distillation ^{211}Astatine product. This is one of many improvements involving the distillation process.

Distillation Process

Several changes in the distillation process have yielded a higher degree of reliability. Other changes have made elution of the ^{211}At in the cold trap easier. The overall goal for Astatine distribution is to be able to predict end of distillation and eluted distributable ^{211}At production quantities. Repeated distillations have shown that these changes have achieved this measure.

The tubing used for the cold trap to capture the volatile ^{211}At has been changed from 6 feet of 0.040" ID x 1/16" OD PEEK tubing to 6 feet of Zeus Item # 183847 0.0625" ID x 1/8" OD clinical grade PTFE. The large diameter prevents flow restriction of the argon push gas that carries the volatile ^{211}At to the cold trap. With the PEEK, the tubing would clog. If the quartz still starts to experience overpressure, ^{211}At could escape from the still and not condense into the cold trap tubing. Secondly, because the PTFE is flexible, it can be placed in the cold bath in an oval pattern that submerges all of the tubing down into the cold bath and helps ensure the product condenses before exiting the cold trap. With PEEK, the tubing is rolled in a small 3-inch circle and only half of the tubing is in the cold bath. With the larger ID PTFE, the cold bath temperature can be reduced to -77^{0}C and will not clog. The argon pressure is increased from 50mL/min to 110mL/min once distillation starts to accommodate the increased dead volume and push the volatile ^{211}At from the quartz still into the cold trap. This decreases the likelihood that the product will deadhead at the exit of the still and be deposited on the walls of the still or on the transition fitting connecting the still to the cold trap. Around 5% of the pre-distillation activity makes it past the cold trap and into the waste bottle.

The transition fitting between the still and the cold trap also has been changed. As high temperature ¼" ID x 1/16" ID PTFE fittings are expensive and increasingly difficult to find, the Plasmatech 02F42 ¼' x 1/8" ID PTFE High Temperature compression fitting is currently used. It has demonstrated that it withstands the 700^{0}C quartz still temperature without deformation or leakage and can be used multiple times. Furthermore, 99% of the product that condenses inside the fitting is easily recovered in the product vial via elution.

The ideal maximum distillation temperature has been changed from 715 to 700^{o}C in order to prevent the aluminum target blank from melting. This prevents loss of product in the quartz still, possible extraneous volatile contaminants in the product from the aluminum alloy target blank, and also irreparable damage to the still and the quartz target blank support. Movement of the volatile ^{211}At into the cold trap has been noted to occur near 650^{o}C. Therefore, distillation is well underway prior to reaching 700^{o}C. No noticeable additional product appears be trapped at the higher temperature. Roughly 10-15% of the starting activity on the target remains on the target at the end of distillation.

Next, is the topic of the changes with collecting the product from the cold trap once it's removed from the distillation apparatus. When eluting the ^{211}At from the cold trap, the clear flexible PTFE tubing allows the elution solvent to be visible as it is pushed thru the trap with a tuberculin syringe followed by 5 psi of argon gas. This ensures that all of the solution is recovered and yields 95% of the product into the product vial using as little as 250 µl of solvent. The Plasmatech transition fitting and the cold trap tubing are eluted simultaneously into the product vial.

To date, these changes have not interfered with desirable lab results following product usage. End of distillation quantities of 60 mCi of usable in solution ^{211}At produced from a 120 minute run can be achieved on a reliable basis. The end-of-distillation yields consistently fall within the 55-65% range and have yet to result in a failed distillation.

D. PUBLICATIONS

None