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CRADA Final Report: CRADA Number NFE-19-07859 with Purist, Inc.



Leila Safavi

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OAK RIDGE NATIONAL LABORATORY
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1. Abstract

Cooperative Research and Development Agreement (CRADA) NFE-19-07859 between Oak Ridge National Laboratory (ORNL) and Purist Inc. (Purist) focused on developing a technology for production of high purity radioisotopes using small-scale underutilized research nuclear reactors. Purist is developing a novel production mechanism that will produce, and efficiently isolate radioisotopes with high specific activity at small-scale research reactors. The goal of this technology is to enable underutilized smaller scale reactors, typically not capable of producing medical grade radioisotopes, to be utilized as a production supply source. Such radioisotope production facilities will complement production efforts of the few larger production facilities to reduce and prevent risk in the medical isotope supply chain. The work done under this CRADA explored target development, to maximize isotope production and separation using Purist's technology to ultimately obtain a radioisotope product with high specific activity for use in medical applications. Furthermore, under this CRADA post production, capture, concentration and encapsulation of the radioisotope product was studied by developing post irradiation milli to microscale processes to capture, store and release the separated radioisotopes from large volumes of the capture matrix after production, via automated High-Pressure Ion Chromatography (HPIC) and microfluidic purification/separation systems. This will enable concentration of the radioisotope product obtained into small volumes, which will aid in packaging and transporting the final radioisotope product to users.

2. Statement of Objectives

Fulfilling the stated objectives and relevant tasks were heavily impacted by the pandemic and COVID19 restrictions. Therefore, adaptations and pivots were implemented appropriately. Following CRADA approval in the 4th quarter of 2019, target development efforts were initiated. In the first quarter of 2020, under the advisement of Dr. Mike Zach, efforts were focused on training on the Ion Sputter Beam Deposition tool and fabricating holmium thin film targets. Furthermore, in February 2020, an ad was placed for hiring a post-bachelor's research associate to help carry out the efforts of the CRADA. This recruitment was halted in the wake of the COVID19 pandemic. Following the pandemic and lab shutdown, efforts were shifted and adjusted to fulfill objectives accordingly. The objectives of the CRADA, and their relevant accomplishments are as follows:

Objective 1: Irradiation Target Development and Fabrication

Description: Purist's radioisotope production and separation technology relies on recoil of the radioisotope from the target upon neutron capture, which enables separation and isolation of a high specific activity radioisotope product. Therefore, the aim for this task was design and development of targets that enable maximum radioisotope production, separation and isolation while withstanding exposure to the radiation field without degradation.

The goals of this task include the following:

1.1: Define target characteristics that will maximize radioisotope production yield and separation, while minimizing the effects of radiation induced degradation and undesired activation.

1.2: Target design.

1.3: Target synthesis and fabrication.

1.4: Target Characterization.

Next Steps:

1.5: Target Stability studies under various conditions mimicking the radioisotope production process in the reactor. (e.g. atmospheric conditions, aqueous conditions, various temperatures and radiation exposure conditions)

1.6: Address any target design and fabrication challenges that may arise during development characterization and testing phases of the target.

Objective 2: Computer modeling and simulation of Purist's radioisotope production process

Description: The irradiation process carried out at the University of California Irvine's Nuclear Reactor Facility operates at a neutron flux on the order of 10^{11} n/cm².s. Currently irradiations run for between 20-60 minute time intervals, with an ultimate goal of scaling up to 8-hour time intervals. As a part of this process, the target is simultaneously exposed to: (i) neutrons (ii) the radiation field and environment of the nuclear reactor core and (iii) a capturing matrix for radioisotope separation. The objective of this task was to develop a computer model of the proposed radioisotope production and separation concept simulating Purist's process.

The tasks for developing a computer model of Purist's radioisotope production and separation process includes the following:

2.1: Complete introduction to MCNP6 training course offered by Los Alamos National Laboratory.

2.2: Determine irradiation input parameters: core configuration, neutron flux profile, irradiation time, target characteristics, irradiation vessel parameters, capturing medium flow profile, etc.

Next Steps:

2.3: Develop computer model.

2.4: Understand the performance sensitivity and correlation between the irradiation target and various input parameters (i.e. irradiation time, neutron flux, etc.)

2.5: Use the computer model to optimize target development, prototype design, and irradiation conditions to maximize radioisotope production and separation.

2.6: Validate the computer model experimentally at the UCI Nuclear Reactor Facility.

2.7: Use the validated computer model as a foundation to develop computer models for additional reactor facilities that Purist plans to employ for radioisotope production.

Objective 3: Target irradiation and radioisotope production studies.

Description: Following target design and fabrication, targets that pass the initial testing and characterization studies and show promising potential for radioisotope production, using Purist's proposed technology, were irradiated at the UCI nuclear reactor facility under a separate complementary project.

Objective 4: Development of Midi to Microscale Processes to Capture, Store and Release Small Quantities of Radioisotopes from Large Volumes of Solution.

Description: This objective investigates the separation and concentration of radioisotopes enabled through automated separation techniques such as HPIC and microfluidics. Specifically, separation technologies for concentrating microcurie amounts of lanthanide elements, such as holmium, samarium, and lutetium, from aqueous solutions with volumes up to 100 mL. This objective focuses on developing a system that enables miniaturization, integration, and automation of the radioisotope post-production process while reducing waste, radiation exposure and maximizing product recovery.

To achieve the project goals, this work is divided into three main tasks.

4.1: Define radioisotope separation platform characteristics

4.2: Design and fabrication of the platform to optimize sample loading

4.3: Testing the HPIC guard column and/or the microfluidic platform using radioactive solutions to determine maximum sample loading, concentration, and elution.

3. Benefits to the Funding DOE Office's Mission

The proposed technology supports the mission of DOE's isotope development program. The mission of the DOE Isotope Development and Production for Research and Applications program (DOE Isotope Program) is to support isotope production, and research into novel technologies for production of isotopes to assure availability of critical isotopes that are in short supply, to address the current and future needs of the Nation. The proposed technology will benefit DOE's isotope program, by development of a technology that ensures: an increased portfolio of isotope products, more cost-effective and efficient production/processing methods, a reliable supply of isotopes, and reduced dependence on foreign supplies.

4. Technical Discussion of Work Performed by All Parties

For target development we started working with the ion beam sputter deposition tool to make thin films. The goal of this objective was to study if the transition from a powder target to thin films or nanowires, will increase separation yield, due to the increased probability of the radioisotope escaping the surface of the target, and into the capture matrix, as opposed to being retained in the target due to limited recoil range and increased

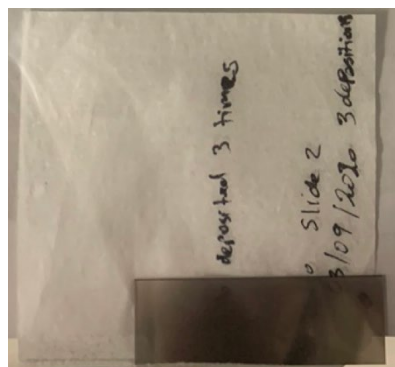


Figure 2: Thin film deposition of Holmium on pre-cleaned slide.

collisions with surrounding atoms. Ideally the

thickness of the irradiation target should be in the nanometer to micrometer range with a large surface area covered with the target atom, such that when the target is in contact with the capture matrix, there is an increased probability the recoil range of the radionucleus exceeds the thickness of the target and escapes into the capture matrix, resulting in increased radioisotope enrichment and separation yields.

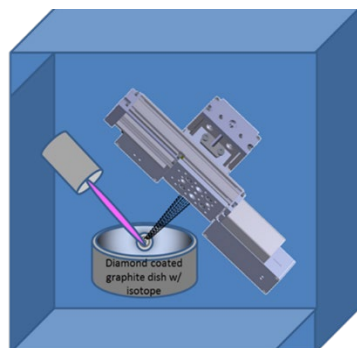
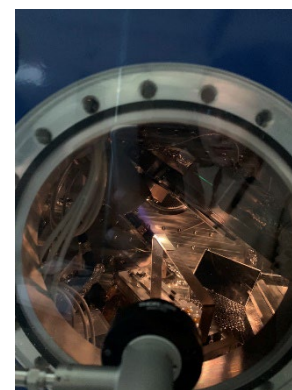


Figure 1: Ion Beam Sputter Deposition tool. The target substrate will fit onto the 2D stage which gets rastered back and forth while the sputtered ions project upon its surface.



The ion beam sputter deposition (IBSD) tool (Fig.1) utilizes 5 – 100 mg pellets as targets of enriched isotopes to make high quality thin to thick film targets with >80% efficiency. IBSD is a compact, right-sized tool that can provide suitable targets using a narrow plume of sputtered atoms while minimizing the losses due to deposition upon surfaces other than the desired target. The chamber attaches onto an argon inert atmosphere glovebox so that reactive materials can be deposited without oxidation loss. The first thin film we prepared was a holmium thin film using a holmium foil as the sputtering target. The sputtering settings and results are summarized in **table (1)**.

Table 1: Summary of sputtering setting and results of holmium deposition.

Substrate	Deposition	QCM rate 1 (Å/s)	QCM time 1 (s)	Deposition rate (Å/s)	Deposition time (s)	QCM rate 2 (Å/s)	QCM time 2 (s)	Neutralizer	Deposition thickness (nm)
Slide 1	1	0.87	97	0.27	203	N/A	N/A	On	15.36
Slide 1	2	1.61	60	0.33	240	N/A	N/A	off	24.08
Slide 2	1	1.33	76	0.33	204	1.96	20	off	27.1
Slide 2	2	2.14	60	0.36	210	2.6	30	off	42.13
Slide 2	3	2.38	60	0.30	210	2.7	30	off	49.98

This work resulted in two holmium thin films deposited on pre-cleaned microscope slides (Fig.2). The total deposition thickness on slide 1 was 39.36 nm corresponding to an atomic thickness/layers of 91.1 atoms. The total deposition thickness on slide 2 was 119.08 nm corresponding to an atomic thickness/layers of 275.6 atoms.

In addition to thin films we also investigated nanowires as thin high surface area targets. For development of nanowires Purist collaborated with Dr. Catherine J. Murphy (C.J. Murphy) at University of Illinois Urbana Champaign. The Murphy group's extensive expertise and advancements in nanowire and nanomaterial fabrication motivated this collaboration. C. J. Murphy and her group have developed the syntheses of gold and silver nano-rods and nanowires over the last 20 years; these synthetic methods use water as a solvent and can be scaled up to provide solid milligram quantities.

Initially, the elongated gold nanostructures synthesized by the Murphy group was a starting point for this study (Fig. 3). To utilize these materials as irradiation targets, two criteria must be met. First, they need to be of nanoscale dimensions to maximize their surface area and provide a large surface of Au metal for radioisotope generation. Second, the targets must be large enough (~ 20 microns) to avoid being lost to the filter membrane.

To grow the gold nanowires, a multi-step seed-mediated procedure, was adapted. Gold nanorods with strong twinning features were synthesized and purified as shown in Figure 3. Unfortunately, some shape impurities and size dispersity are still present in the seed solution which could affect the resulting wire product. When utilizing a 40 mL batch for the growth of wires, different seed concentrations were used to grow varying wire sizes. The original procedure states increasing the overall volume of the growth solution while keeping the seed concentration the same, so instead different amounts of seed solution was used while keeping the growth volume the same. As shown in Figure 4, the Murphy group were able to push the size of the wires to 10 microns, but unfortunately decreasing the seed concentration further, results in the thickness of the wires starting to increase. It is likely a result of the above-mentioned issues with the gold nanorod seeds.

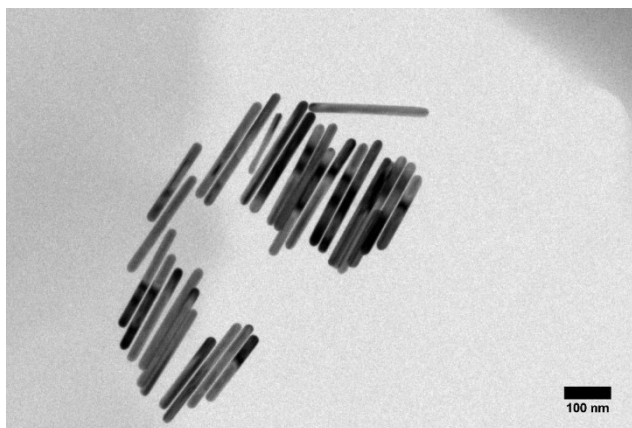


Figure 3: The produced gold nanorod seeds which were used subsequently to grow large wires.

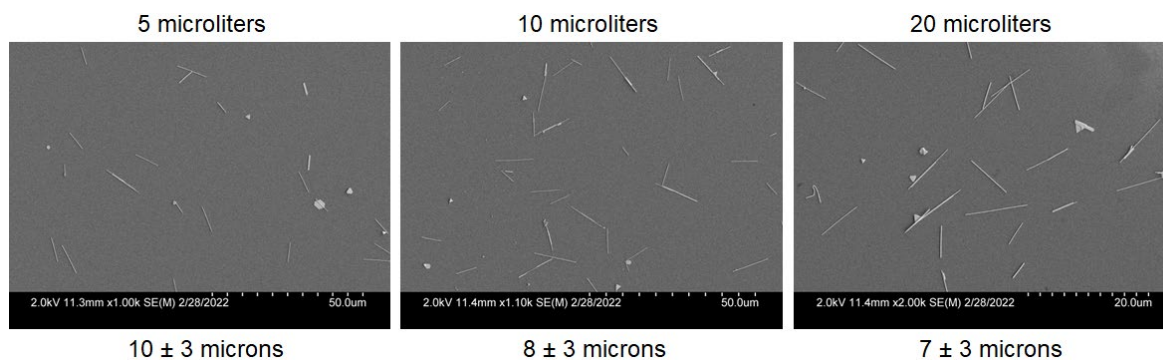


Figure 4: The resulting gold nanowires from using different amounts of seed solution (on a 40 mL scale) and their average length distributions.

The gold nanowires, while still being hard to get above 10 microns in length, do show nanoscale widths of 70-100 nm, which is necessary for the radionuclide generation. Additionally, there are visible twinned planes on the tips of the gold nanowires meaning they were generated correctly from the penta-twinned rod seeds.

Finally, in hopes to increase the yield of wires the HCl concentration in the wire growth was increased. Doing so reduces the reducing potential of the ascorbic acid and slows the overall growth of the wires and is a typical method in the literature to make high quality anisotropic nanoparticles. However, further increases in acid concentration effectively shut off the growth of wires and yield large spherical and triangular particles. This is further evidence that the size of the wires is likely not as tunable as expected because the gold rod seeds have size/shape dispersity to them.



Figure 5: Proof of the skinny nature of the wires (<100nm) with visible twin planes.

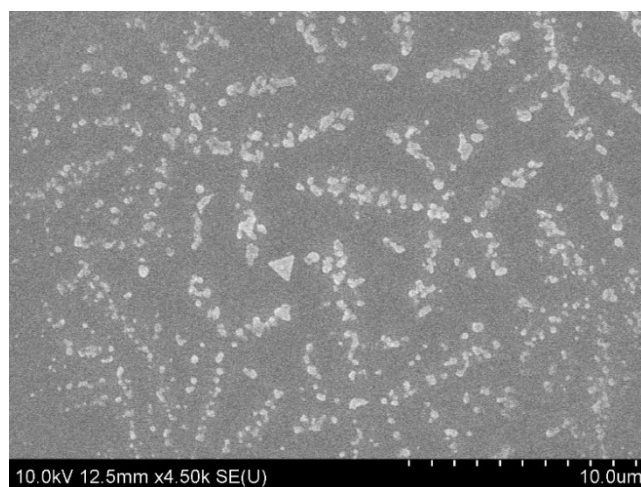


Figure 6: Addition of double the HCl induces sphere growth only and doesn't allow the growth of wires.

To assess whether the particles could be scaled up – a large 4-liter batch was prepared. The most difficult part to scaling up the procedure is that the purification becomes non-trivial. It was necessary to use a siphon and careful hands to steadily remove the supernatant and perform the steps. However, as can be seen in Figure 7, the wires are of similar quality and size as the same parameters but scaled down. Following synthesis, the film was purified several times and dried out to a powder – this powder will be used in the generation of radioisotopes. Despite the fact the wires contain many particles which are much smaller than the pore size of the membrane, extensive rinsing and drying of the particles should ensure they are in an extremely aggregated and irreversible state. Hopefully, a significant number of particles will not leach through the membrane.

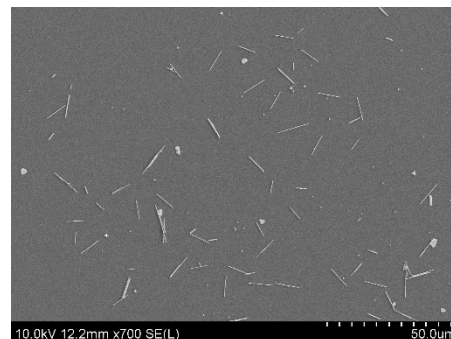


Figure 7: 4-liter batch of wires following purification.

The growth of gold nanowires has been done to synthesize nano-sized targets for Au radionuclide generation. The gold nanowires were grown using a method from the literature and were subsequently scaled up to give several hundred milligrams of wires in a single batch. It is difficult to produce high quality nanowires at the size range of 20 microns, however 10 micron wires were easily prepared and will be used as a solid powder target for radioisotope generation due to the ease at which aggregation occurs.

The second objective was to develop a computer model of the proposed radioisotope production and separation concept simulating Purist's process. For this purpose, the MCNP software was licensed from ORNL, and an introductory MCNP course offered through Los Alamos National laboratory was completed in November 2020. Following the course, it was concluded that the modeling and simulation were more complex than initially anticipated and required relevant technical expertise beyond what was learned in the introductory MCNP course. Discussions with modeling and simulations groups at ORNL and University partners were initiated but ultimately did not result in a collaboration.

For target irradiation and isotope production studies seven target candidates (copper resin, holmium foil, holmium 8-hydroxyquinolate, lutetium 8-hydroxyquinolate, samarium oxide, holmium oxide, molybdenum foil, and hydroxyapatite) were designated, and irradiation experiments were carried out at the University of California Irvine research reactor facility. The results of these experiments further indicated the need for targets that have a large surface area and have a nanoscale thickness to achieve the desired yield and separation of the radioisotope product. Currently three target candidates are in the pipeline for testing, and collaboration with nanomaterial experts for target development needs is being explored. All irradiated samples were successfully analyzed for radioisotope content, and radioisotope separation of up to 53% was witnessed depending on the target and irradiation conditions. Targets and irradiation samples still need to be analyzed for stable isotope content. Therefore, enrichment factors have yet to be determined. Based on our previous studies, enrichment factors of up to 15.29 were obtained, resulting in a decrease in the amount of isotope required for a typical medical procedure by 93%. Based on the preliminary data obtained from the irradiations, we anticipate surpassing the previous studies in terms of enrichment factors and specific activity – this will be verified once we determine the stable isotope content of the samples.

The fourth objective focused on developing a system that enables miniaturization, integration, and automation of the radioisotope post-production process while reducing waste, radiation exposure and maximizing product recovery. This work focused on evaluating the column capacity of a commercial

cation-exchange column (IonPac® CS10, Thermo Scientific) and testing the concentration of small, medium, and large Lanthanide surrogate solutions. Cerium was selected as a case study due to its characteristic absorbance spectrum, which allows the determination of the column capacity and testing the sample concentration using ultraviolet-visible (UV-Vis) spectroscopy. Surrogate studies minimize the generation of radioactive waste during the early stages of the project while providing useful information on system response.

Current successes of the project include:

- determination of CS10 standard bore guard column (CS10GC) capacity;
- concentration of small, medium, and large cerium solution volumes using a CS10GC into 1- or 2-mL aliquots; and
- determination of hydrochloric acid concentration required to elute Ce from CS10GC.

Concerns for the proposed system include:

- breakthrough of radioactive solution from CS10GC due to column saturation with cold target material, and
- integrity of CS10GC during concentration, handling, and shipping due to radiolysis.

HPIC is a useful technique to concentrate radioisotopes from large volumes. Using a cation-exchange column, CS10GC, different Ce solutions were concentrated into 1- or 2-mL aliquots. This shows the potential to concentrate radioactive solutions by 2- to 100-fold factors. Sample loading into the CS10GC column can be carried out at flowrates of 1–3 mL/min. It is important to maintain the flowrate below 3 mL/min based on the recommendations from the vendor for the CS10GC column. This case study shows the potential of using HPIC with a CS10GC column to concentrate radioisotope solutions that can be delivered to customers. Although there is significant opportunity to increase the activity of radioisotopes that can be concentrated with HPIC, nonradioactive target material may saturate the column and cause radioisotope breakthrough.

5. Subject Inventions (As defined in the CRADA): None.

6. Commercialization Possibilities

The increasing demand and growth of the radioisotope market, particularly the medical radioisotope market, has provided new opportunities to develop solutions in this space. Based on the results obtained from this work, as we have not yet been able to reach the radioisotope specific activity required for medical applications, Purist's short-term commercialization goal is to focus on using its technology to cater to the R&D radioisotope market.

7. Plans for Future Collaboration

Further research into target development and capture and concentration of the produced radioisotope could potentially yield the improvements to the specific activity and purity of the radioisotope product. Therefore, future collaboration with the Radioisotope Science and Technology Division (Stable Isotope Materials & Chemistry Group) and the Enrichment Science and Engineering Division at ORNL will be considered upon synergy of projects and availability of funding.

8. Conclusions

During this CRADA, we demonstrated: i) Development of robust irradiation targets ii) Production of radioisotopes using Purist's production technology iii) Initial studies on computer modeling of Purist's radioisotope production system iv) Development of midi to microscale processes to capture, store and release small quantities of radioisotopes from large volumes of solution.