Final Technical Report for DOE Grant DE-SC0007348

Project Name: ***Accelerator Production and Separations for High Specific Activity Rhenium-186***

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Principal Investigator: Silvia S. Jurisson (University of Missouri)

Sub-contract PI: D. Scott Wilbur (University of Washington)

Federal Program Manager: Dennis Phillips

Work-scope Highlights: This project was carried out at both the University of Missouri (Jurisson, Cutler, Ketring) and the University of Washington (Wilbur). This project was collaborative with Dr. Kevin John, Michael Fassbender and their collaborators at Los Alamos National Laboratory (LANL) through their separate award. The three institutions were involved to different degrees on each of the specific objectives (listed below) based on infrastructure and expertise/capabilities. The chemistry graduate students and postdoctoral fellows working at the various sites participated in limited internships at the other sites for both training and project translation/facilitation. The anticipation was that completion of the objectives would lead to the determination of the best method for producing high specific activity ^{186}Re on a cyclotron, including identification of the target material giving the highest yield of ^{186}Re and the minimum amount of radioactive impurities, the method for recovery of enriched target material for reuse, a method for separating the ^{186}Re from target material, and evaluation of the no carrier added ^{186}Re and impurities (chemical and radiochemical) by ICP-MS and gamma spectrometry.

Specific Objective 1*: Production of HSA ^{186}Re.* The goal of this objective was to evaluate different target materials and cyclotron irradiation approaches to produce radionuclidically pure ^{186}Re in high specific activity, and obtain data to determine the optimal production rate.

Specific Objective 2*: Separation of ^{186}Re from its target.* The goal of this objective was to evaluate methods of isolating ^{186}Re from target materials to obtain data on the isolation yields of ^{186}Re and recovery yields of the enriched target materials. The ^{186}Re must be of sufficient specific activity and purity (radiochemical, radionuclidic and chemical) for radiolabeling peptides and other biological targeting molecules.

Specific Objective 3*: Training of Graduate and Postdoctoral Students.* The goal of this objective was to train graduate students and postdoctoral students in radiochemical methods, both for production of radionuclides and isolation/separation of the radionuclides from their target material.

Brief summary of activity issues, concerns, successes: Tungsten (W) and osmium (Os) target materials were evaluated for the production of high specific activity ^{186}Re. Separation methods were developed to isolate the high specific activity ^{186}Re and recover enriched W and Os target materials. Three postdoctoral fellows, two graduate students and three undergraduate students were directly involved in this project and were trained

in the radiochemistry involved. Several manuscripts and meeting abstracts have been (or will be) published. Several talks and poster presentations were made at national and international conferences.

***Year 1 milestones*:**

University of Missouri

(a) *Identify graduate student to work on the high specific activity ^{186}Re production project.* Matthew Gott, a fourth-year graduate student at Missouri, joined the Jurisson group in January 2012. Matt Gott interned at Los Alamos National Laboratory (LANL) with Dr. Michael Fassbender and Dr. Beau Ballard from May 15th to August 15th, 2012. He was a recipient of the Seaborg Institute Summer Research Fellowship, which provided support while he was at LANL. Matt Gott interned at Brookhaven National Laboratory (BNL) with Dr. Suzanne Smith from January 21st, 2015 to May 21st, 2015; a Department of Energy, Office of Science Graduate Research Fellowship (SCGSR) provided support while he was at BNL. First year graduate student Timothy Phelps joined the project in May 2015.

(b) *Identify postdoctoral fellow to work on the high specific activity ^{186}Re production project*. Dr. Don Wycoff worked on this project. He was involved with the Os targetry (electroplating) and separations.

(c) *Determine the quantity and optimal conditions for natural W targets from the metal (foil and powder) and WO_3.* $^{nat}WS_2$ targets were prepared and irradiaed at 11 and 14 MeV. WO_3 targets proved too brittle and thus our focus was with WS_2 targets.

(d) *Irradiate natural W targets to determine the optimal irradiation conditions including beam characteristics with foils and geometry*. Three ^{nat}W metal foils (with monitoring foils) were irradiated at BNL to determine foil placement for ^{186}Re production in the BNL target array.

(e) *Obtain an enriched ^{186}W target (foil, metal powder or oxide)*. Enriched $^{186}WO_3$ was purchased from Isoflex USA.

(f) *Begin optimizing the separation method to isolate high specific activity ^{186}Re and recover enriched ^{186}W using neutron irradiated Re and W.* BioRad's AG 1-X8 anion exchange resin, IBC Advanced Technologies' AnaLig Re-02 ion exchange resin and Eichrom's TEVA anion exchange resin were examined to isolate rhenium from tungsten. BioRad's AG 1-X8 demonstrated the best separation characteristics.

University of Washington

(a) *Identify Postdoctoral Fellow to work on the high specific activity ^{186}Re production project*. Dr. Katherine Gagnon (now at the University of Edmonton) and Dr. Ethan Balkin (now at the DOE) worked on this project.

(b) *Determine the quantity and optimal conditions for preparing 13 mm thick target disks from ^{nat}W metal, $^{nat}WO_3$, $Al_2(^{nat}WO_4)_3$ and ^{nat}Os metal powders.* This milestone was successfully completed for metallic W targets and has progressed well for the Os targets (OsS_2 is likely the best target form).

(c) *Irradiate ^{nat}W metal, $^{nat}WO_3$, $Al_2(^{nat}WO_4)_3$ targets at 15, 17, 20 and 24 MeV deuterons for short periods to determine the optimal energy for ^{186}Re production with each target material*. This milestone has been successfully completed. Target stability issues during irradiation resulted in a focus on the construction of physically stable pressed target pellets using W metal as the target material with graphite to augment structural stability.

(d) *Irradiate ^{nat}W metal, $^{nat}WO_3$, $Al_2(^{nat}WO_4)_3$ targets at optimal energy for production of ^{186}Re*. The best target form was determined to be enriched metallic ^{186}W, which can be reclaimed from the waste streams of previous experiments using enriched material and then recycled using a chemical and high-temperature conversion process. The irradiation was conducted under the previously established optimal beam energy of 22 MeV (~18 MeV incident energy on target material) and current of 27 μA. Post isolation assessments of production yield and radiochemical purity were made. This milestone was completed.

(e) *Begin optimizing the dry distillation method to isolate high specific activity ^{186}Re from irradiated ^{nat}W metal*. It was determined that a resin based column elution approach is a better alternative isolation method to dry distillation. This milestone is complete.

***Year 2 milestones*:**

University of Missouri

(a) *Irradiate small natural Os metal targets (encapsulated in Al) to determine the feasibility of the $^{189}Os(p,\alpha)^{186}Re$ reaction and its proton energies*. Natural OsS_2 targets were irradiated and several isotopes of iridium and rhenium were quantified. Several Ir radioisotopes are co-produced with the ^{186}Re.

(b) *Begin optimizing the separation method to isolate high specific activity ^{186}Re and recover enriched ^{189}Os using neutron irradiated Re and Os*. Liquid-liquid extraction and chromatography studies were performed to isolate rhenium from osmium and iridium. The best approach is to distill osmium tetroxide away from unwanted iridium isotopes for recovering enriched Os target material.

(c) *Develop analytical methods to evaluate high specific activity ^{186}Re for radionuclidic and radiochemical purity, non-radioactive metal impurities, and labeling efficiency*. HPGe analysis and ICP-MS analysis are the methods of choice for determining radionuclidic purity and specific activity, and were used.

(d) *Obtain an enriched ^{189}Os metal target (preferably a foil)*. Enriched (99.65%) ^{189}Os was purchased from Isoflex USA.

(e) *Irradiate the enriched ^{189}Os target and determine/confirm the optimal conditions (irradiation time, target geometry, cross section, and energy) for producing ^{186}Re*. A ^{nat}Os metal target was irradiated at BNL and quantified for radioactivity and for other radioactive products formed (i.e., Ir radioisotopes).

(f) *Determine the best separation method for isolating high specific activity ^{186}Re and recovering the enriched ^{189}Os target*. The best separation scheme and recovery of target for reuse is shown below.

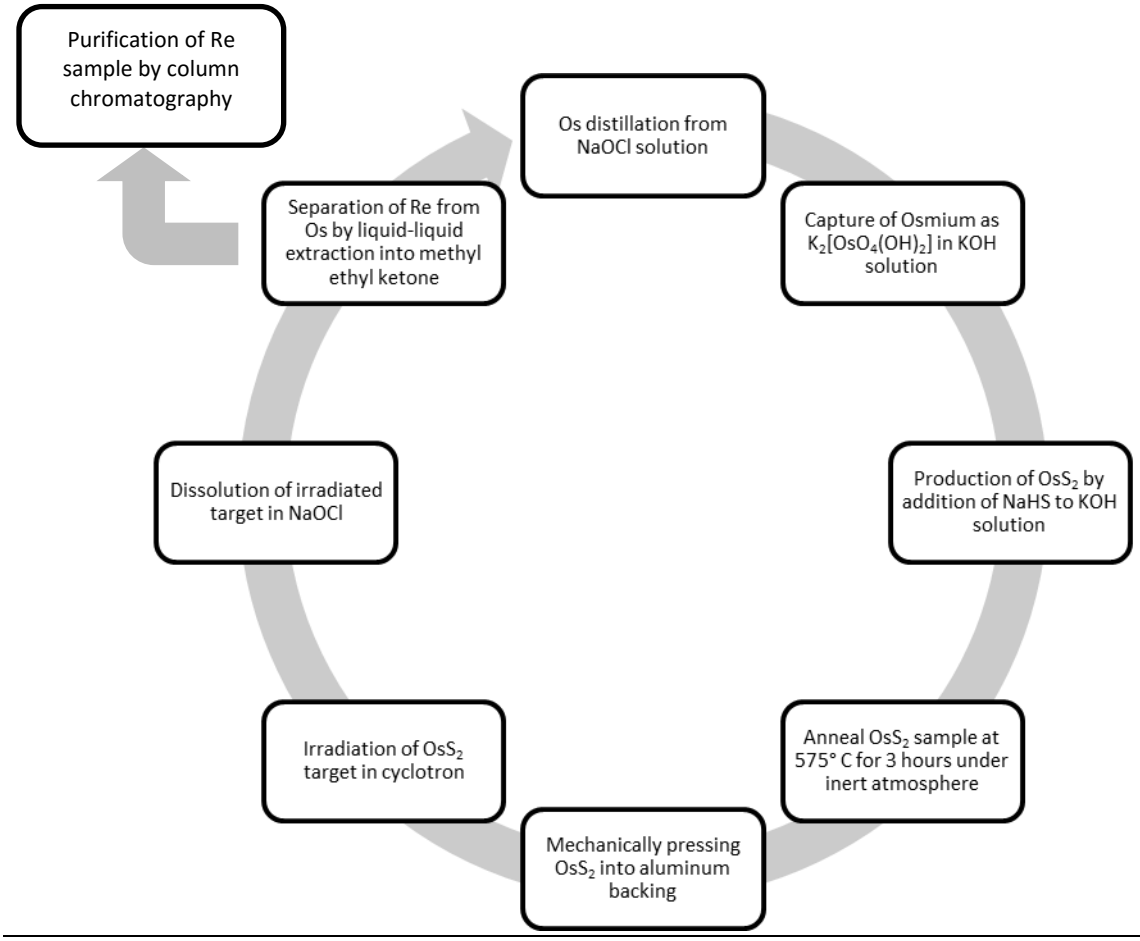

Figure 1: Updated Proposed "Full Circle" Re production process using OsS_2

University of Washington

(a) Irradiate ^{186}W metal, $^{186}WO_3$, $Al_2(^{186}WO_4)_3$ targets with deuterons at optimal energy using 10, 20 and 30 μA beams. This objective was completed.

(b) Optimize dry distillation separation for ^{186}W metal and begin optimizing method for separation of ^{186}Re from $Al_2(^{186}WO_4)_3$. As reported above, we switched to the use of a resin based column elution approach as an alternative isolation method to dry distillation. Additionally, we abandoned the use of aluminum based target material due to the quantity of long-lived contaminants produced during the deuteron bombardment of aluminum. We instead focused our efforts on ^{186}W metal target material.

(c) *Irradiate ^{nat}Os and ^{189,192}Os metal targets with 15, 20, 25, 30 and 35 MeV protons for short periods to determine the feasibility of the ^{189}Os(p,α)^{186}Re or*

$^{192}Os(p, \alpha 3n)^{186}Re$ reaction. Due to the number of Ir radioisotopes co-produced, this route was abandoned for now.

(d) *Optimize method for separation of ^{186}Re from $Al_2(^{186}WO_4)_3$*. See milestone (*b*) above.

(e) *Choose ^{186}W target that is best for deuteron irradiations and optimize conditions in production runs of ^{186}Re from ^{186}W.* See Year 1 milestones and associated detailed progress reported above. One production run was conducted by irradiation of a recycled ^{186}W metal target encased in graphite using a deuteron beam at 17 MeV and 26 uA for 2 hours.

(f) *Irradiate enriched ^{189}Os target with the optimal proton beam energy at 20, 30 and 40 μA and ship irradiated targets to MU*. See milestone (*c*) above.

Education and Training:

Postdoctoral Fellows: Katherine Gagnon (UW), Ethan Balkin (UW), Don Wycoff (MU)

Graduate Students: Matthew Gott (MU), Timothy Phelps (MU)

Undergraduate Students: Connor Hayes (MU), Nicole Moore (MU)

Published Papers and Manuscripts in preparation/submitted

(1) M.D. Gott, B.D. Ballard, L.N. Redman, J.R. Maassen, W.A. Taylor, J.W. Engle, F.M. Nortier, E.R. Birnbaum, K.D. John, D.S. Wilbur, C.S. Cutler, A.R. Ketring, S.S. Jurisson, M.E. Fassbender, "Radiochemical Study of Re/W Adsorption Behavior on a Strongly Basic Anion Exchange Resin", *Radiochimica Acta* **2014**, 102(4), 325-332.

(2) M.D. Gott, C.R. Hayes, D.E. Wycoff, E.R. Balkin, B.E. Smith, PJ Pauzauskie, CS Cutler, AR Ketring, DS Wilbur, SS Jurisson, "Accelerator-Based Production of the Diagnostic ^{99m}Tc/ Therapeutic ^{186}Re Pair using Metal Disulfide Targets (MoS_2, WS_2, OsS_2)", *Applied Radiation and Isotopes* **2016** (submitted).

(3) E.R. Balkin, K. Gagnon, K.T. Strong, B.E. Smith, E. Dorman, R. Emery, P. Pauzauskie, M.E. Fassbender, C.S. Cutler, A.R. Ketring, S.S. Jurisson, D.S. Wilbur, "Deuteron irradiation of W and WO_3 for production of high specific activity ^{186}Re. Challenges associated with thick target preparation", *Applied Radiation and Isotopes* **2016** (submitted).

(4) E.R. Balkin, K. Gagnon, E. Dorman, R. Emery, B.E. Smith, K.T. Strong, P. Pauzauskie, M.E. Fassbender, C.S. Cutler, A.R. Ketring, S.S. Jurisson, D.S. Wilbur, "Structural Enhancement of Pressed W Metal Targets With Graphite Facilitates Thick Target Preparation, Facile Isolation, and Efficient Recycling of Target Material Used in the $^{186}W(d,2n)^{186}Re$ Reaction", to be submitted to *Radiochimica Acta* **2016**.

Presentations at Meetings/Conferences

"Radiochemical Study of Re/W Sorption Behavior on a Strongly Basic Anion Exchange Resin", M. Gott, B. Ballard, L. Redman, M. Fassbender, E. Birmbaum, K. John, S. Jurisson, presented (oral) at the 245th American Chemical Society National Meeting, New Orleans, LA, March 2013.

"Radiochemical Study of Re/W Sorption Behavior on Strongly Basic Anion Exchange Resin", M. Gott, B. Ballard, L. Redman, M. Fassbender, E. Birmbaum, K. John, A. Ketring, C. Cutler, S. Jurisson, presented (poster) at the 2013 International Symposium on Radiopharmaceutical Sciences, Jeju, South Korea, 12-17 May 2013.

"Targetry investigation of ^{186}Re production via proton induced reactions on natural osmium targets", M. Gott, D. Wycoff, M. Fassbender, D. S. Wilbur, A. Ketring, C. Cutler, S. Jurisson, presented (oral) at the 246th American Chemical Society National Meeting, Indianapolis, IN, 8-12 September 2013.

"Thick target preparation and isolation of ^{186}Re from high current production via the ^{186}W(d,2n)^{186}Re reaction", E. R. Balkin, K. Gagnon, E. Dorman, R. Emery, B. E. Smith, K. T. Strong, P. Pauzauskie, M. E. Fassbender, C. S. Cutler, A. R. Ketring, S. S. Jurisson, D. S. Wilbur, presented (oral) at the Workshop on Targetry and Target Chemistry WTTC15, Prague, Czech Republic, 18-21 August 2014.

"Challenges associated with thick target preparation of WO_3 for high current production of ^{186}Re via deuteron irradiation", E. R. Balkin, K. T. Strong, B. E. Smith, K. Gagnon, E. Dorman, R. Emery, P. Pauzauskie, M. E. Fassbender, C. S. Cutler, A. R. Ketring, S. S. Jurisson, D.S. Wilbur, presented (oral) at the Workshop on Targetry and Target Chemistry WTTC15, Prague, Czech Republic, 18-21 August 2014.

"Targetry Investigations of ^{186}Re Production via Proton Induced Reactions on Natural Osmium Disulfide and Tungsten Disulfide Targets", M. D. Gott, D. E. Wycoff, E. R. Balkin, B. E. Smith, M. E. Fassbender, C. S. Cutler, A. R. Ketring, D. S. Wilbur, S. S. Jurisson, presented (oral) at the Workshop on Targetry and Target Chemistry WTTC15, Prague, Czech Republic, 18-21 August 2014.

"New Radiometal/Radiometalloid Chemistry for Potential Radiopharmaceutical Applications", S. S. Jurisson, presented at the 55th Midwest Regional American Chemical Society Meeting, 19-21 November 2014, Columbia, MO (invited oral).

ER Balkin, K Gagnon, E Dorman, R Emery, B Smith, K Strong, P Pauzauskie, M Fassbender, CS Cutler, AR Ketring, SS Jurisson, DS Wilbur, "Structural enhancement of W metal targets with graphite facilitates thick target preparation, facile isolation, and high current production via the ^{186}W(d,2n)^{186}Re reaction", presented (oral) at the 21st International Symposium on Radiopharmaceutical Sciences (ISRS2015), Columbia, MO, 26-31 May 2015.

M. Gott, D. Wycoff, E. Balkin, C. Cutler, A. Ketring, M. Fassbender, D. S. Wilbur, S. S. Jurisson, "Investigation of Accelerator-Based Production of High Specific Activity ^{186}Re", presented (poster) at the 21st International Symposium on Radiopharmaceutical Sciences (ISRS2015), Columbia, MO, 26-31 May 2015.

"An introduction to theranostic radionuclides", S. S. Jurisson, presented at Pacifichem 2015, 15-20 December 2015, Honolulu, HI (invited oral).

"Production of ^{186}Re at the Brookhaven Linac Isotope Producer via proton induced reactions on natural tungsten and osmium targets", M. D. Gott, C. Cullen, L. Muench, J. Napela, C. S. Cutler, A. R. Ketring, D. S. Wilbur, S. S. Jurisson, S. V. Smith, presented (oral) at Pacifichem 2015, 15-20 December 2015, Honolulu, HI.

Additional Information

The scientists (including trainees) from the three sites (MU, UW, LANL) will held joint research meetings 1-2 times per year (as deemed necessary) to discuss the progress on the project, update any objectives, assist with translation between sites, etc. Meetings rotated between the three sites so that all involved on the project will have first hand knowledge of the facilities and capabilities at the other sites. This allowed us to adjust and update our work between the sites as needed to best achieve the results described.

Matt Gott was awarded a DOE SCGSR fellowship to perform additional studies at Brookhaven National Laboratory (BNL) and worked with Dr. Suzanne Smith to evaluate W/Os targets at much higher beam currents and higher proton energies.

Matt Gott successfully defended his dissertation research on 8 July 2015. The title of his dissertation is "**ACCELERATOR-BASED PRODUCTION OF HIGH SPECIFIC ACTIVITY RADIONUCLIDES FOR RADIOPHARMACEUTICAL APPLICATIONS**".

Matt joined the group of Jorg Steinbach and Constantin Mamat at the Helmholtz Institute in Dresden, Germany as a postdoctoral fellow starting 1 October 2015.

Dr. Michael Fassbender irradiated a W-186 target at LANL in November 2015 and sent MU and UW purified high specific activity Re-186 for evaluation.

Graduate student Timothy Phelps submitted (and was just awarded) a DOE SCGSR fellowship proposal in December 2015 to work at Brookhaven National Laboratory with Dr. Cathy Cutler to further develop methods for the production and evaluation of ^{72}Se and ^{72}As, and for $^{186/189}$Re production/scale-up. He will be at BNL from 06/01/16-09/30/16.

Dr. Ethan Balkin has accepted a position in the Isotope Program at the DOE and began his new position on 1 February 2016.