Early Career Award Final Report
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Project Title: Direct production of ^{99m}Tc using a small medical cyclotron
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1. Introduction and Research Progress

a. Overview

This project describes an investigation towards the production of ^{99m}Tc with a small medical cyclotron. This endeavor addresses the current urgent problem of availability of ^{99m}Tc due to the ongoing production reactor failures and the upcoming Canadian reactor shut down. Currently, ^{99m}Tc is produced via nuclear fission using highly enriched uranium which is a concern due to nuclear proliferation risks. In addition to this, the United States is dependent solely on currently unreliable foreign sources of this important medical isotope. Clearly, a need exists to probe alternative production routes of ^{99m}Tc. In the first year, this project measured cross-sections and production yields of potential pathways to ^{99m}Tc and associated radionuclidic impurities produced via these pathways using a small 15 MeV medical cyclotron. During the second and third years target systems for the production of ^{99m}Tc via the most promising reaction routes were developed and separation techniques for the isolation of ^{99m}Tc from the irradiated target material will be investigated. Systems for the recycling of the enriched target isotopes as well as automated target processing systems were examined in years four and five. This project has the potential to alleviate some of the current crisis in the medical community by developing a technique to produce ^{99m}Tc on location at a university hospital. This technology will be applicable at many other sites in the United States as many other similar, low energy (<20 MeV) cyclotrons (currently used for a few hours per day for the production of [^{18}F]fluorodeoxyglucose) are available for production of ^{99m}Tc though this method, thus leading to job creation and preservation.

The specific aims of this project were as follows:

1. Measure cross sections of possible low energy nuclear reaction pathways and those associated with radionuclidic impurities to produce ^{99m}Tc: at various incident proton and/or deuteron energies.
2. Develop solid targetry systems for the production of ^{99m}Tc via the most promising nuclear reaction route(s).
3. Develop processing systems for the routine production of ^{99m}Tc and recycling of enriched target material.

The overarching goal of this project is to develop the in house capability to routinely produce ^{99m}Tc for nuclear medicine patient procedures and to translate this capability to other nuclear medicine departments. Additionally during the course of this project, we aimed to develop new target materials and separations methods that can be used in a variety of isotope production areas.

Personnel involved with the project

i. **Suzanne Lapi** is the Principal Investigator on this proposal and was be responsible for the oversight and design of all experiments. She has expertise in isotope development and characterization.

ii. **Vernal Richards** was a postdoctoral fellow with experience in materials chemistry and chemical vapor deposition of thin films. He was focused on preparation of high power targets

and separation/purification methods for the preparation of ^{99m}Tc and other isotopes. He is now a staff scientist at Zevacor Molecular.

iii. **Andrew (Lake) Wooten** was a biomedical engineering graduate student (supervisor Lapi) who is involved in the automation of the separation chemistry. He is now a staff scientist at Zevacor Molecular.

iv. **Tara Mastren** was a chemistry graduate student (co-supervisors Lapi/Sobotka) who was involved in the measurement of cross sections related to this project. She has training in nuclear chemistry including gamma spectroscopy and calculation of theoretical cross section calculations using commercially available software. She is now a postdoctoral fellow at Los Alamos,

In addition to these individuals other members of the Lapi group and of the Radiochemistry Laboratory and Cyclotron facility were available for consultation and general assistance where appropriate.

b. Research Highlights

We have conducted studies of the ^{100}Mo(p,2n)^{99m}Tc reaction on a medical cyclotron using $^{100}Mo_2C$. This is the first report of this compound being used as a target for this reaction. $^{100}Mo_2C$, a refractory carbide with high thermal conductivity, properties which underscore its use on a cyclotron, was synthesized using $^{100}MoO_3$. Its ease of oxidation back to $^{100}MoO_3$ under air at elevated temperatures facilitates the use of thermo-chromatography, a high temperature gas phase separation technique for the separation and isolation of ^{99m}Tc. Activity yields for ^{99m}Tc averaged 84% of the calculated theoretical yields. Additionally, the percent recovery of MoO_3, the precursor for Mo_2C, was consistently high at 85% ensuring a good life cycle for this target material. In the second phase of the project, we have expanded our studies using metal carbide targets to include tungsten carbide as a target material for the production of ^{186}Re.

c. Research Outcomes

The principle investigator on this proposal, Suzanne Lapi is currently heavily involved with the production, characterization and scale up of many radionuclides including ^{99m}Tc. During the first phase of this work at Washington University in St. Louis, systems were developed for the production, separation and quality control of cyclotron produced ^{99m}Tc.

Initial work focused on production of ^{99m}Tc via the ^{100}Mo (p,2n)^{99m}Tc reaction, using a ^{100}Mo target material of Mo_2C. Previous work at Washington University used $^{94}MoO_3$ to produce ^{94m}Tc via the ^{94}Mo(p,n)^{94m}Tc reaction and the highly efficient thermo-chromatographic method to separate the ^{94m}Tc from the ^{94}Mo target material(1). MoO_3 has a lower melting point and low thermal conductivity. Thus we chose to use $^{100}Mo_2C$ as an alternative target material. This compound has been synthesized from $^{100}MoO_3$ and has ideal properties that make it suitable for use on a cyclotron. Its melting point is 50 °C below that of Molybdenum metal, and being an interstitial carbide it maintains metal-metal bonds(2), which along with other factors gives it a high degree of thermal conductivity. Pressing into well compacted powdered targets can be achieved at room temperature. In addition, it lends itself to be processed by the well-established and efficient

thermo-chromatographic technique, as it re- oxidizes to the oxide at temperatures above 500 °C facilitating easy separation of the ^{99m}Tc and collection of the $^{100}MoO_3$ starting material.

Hexamethyltetramine (HMT) and 28% aqueous ammonia ($NH_3.H_2O$) were purchased from Aldrich USA (St. Louis, MO) and used as received. $^{100}MoO_3$ was purchased from Isoflex USA (San Francisco, CA) and used as received. MDP-BRACCO^{TM} was purchased from Triad Isotopes, Inc. (Orlando, FL) and used as received. Isoflurane was purchased Baxter (Deerfield, Il) and used as received.

Synthesis of Ammonium heptamolybdate(3)
Enriched $^{100}MoO_3$ was used as the molybdenum source for the synthesis of ammonium molybdate. The full isotopic composition of the material as given by the supplier (Isoflex USA, San Francisco, CA) was ^{92}Mo (0.09%), ^{94}Mo (0.06%), ^{95}Mo (0.10%), ^{96}Mo (0.11%), ^{97}Mo (0.08%), ^{98}Mo (0.55%) and ^{100}Mo (99.01%). 1.00 g of $^{100}MoO_3$ was dissolved in 10 ml of 28% aqueous ammonia ($NH_3.H_2O$) solution while stirring. The resulting clear solution was evaporated slowly to dryness at 40 °C.

Synthesis of Ammonium heptamolybdate –HMT complex and Molybdenum carbide(4)

$$(NH_4)_6Mo_7O_{24}\cdot 4H_2O + \text{excess } (CH_2)_6N_4 \rightarrow (NH_4)_4(HMT)_2Mo_7O_{24}\cdot 4H_2O$$

0.800 g of ammonium molybdate and 0.900 g of hexamethyltetramine (HMT) were dissolved in 20 ml of 28% NH_3 solution while stirring. The solution was allowed to evaporate to dryness under air at room temperature after which the resulting solid was subjected to drying under vacuum at 40 °C for 3 hours. The solid obtained (1.550 g) was crushed to a fine powder using a mortar and pestle, after which it was loaded in a quartz boat and placed inside a quartz tube of a horizontal furnace. Heating was carried out under argon flow.

$$(NH_4)_4(HMT)_2Mo_7O_{24} \rightarrow 7/2\ Mo_2C_{(s)} + 17/2\ CO_{(g)} + 7/2\ H_2O_{(g)} + 3NH_{3(g)} + 9/2N_{2(g)}$$

The temperature of the furnace was increased by step by step heating at a rate of 10 °C per minute until a temperature of 700°C was reached. Heating was maintained at this temperature for 2 hours after which it was increased to 900°C and heating continued for an additional 2 hours. On cooling the powder was removed, ground with a mortar pestle and stored in air at room temperature for further use.

The process was repeated starting with recycled $^{100}MoO_3$ (from previous irradiation and sublimation separation) resulting in a yield of 93 %. This recycling process illustrates that this chemistry is amenable to the recycling life cycle that is necessary if this method of ^{99m}Tc production is to be economically viable. Elemental analysis (Galbraith Laboratories, Knoxville TN) showed the following composition Mo – 87%, C – 7.2%. Theoretical composition was calculated to yield, Mo – 93%, C – 6.2%. The X-ray diffraction (XRD) pattern is shown in Figure 1. The major component is Mo_2C, and matched ICDD card 04-008-1889.

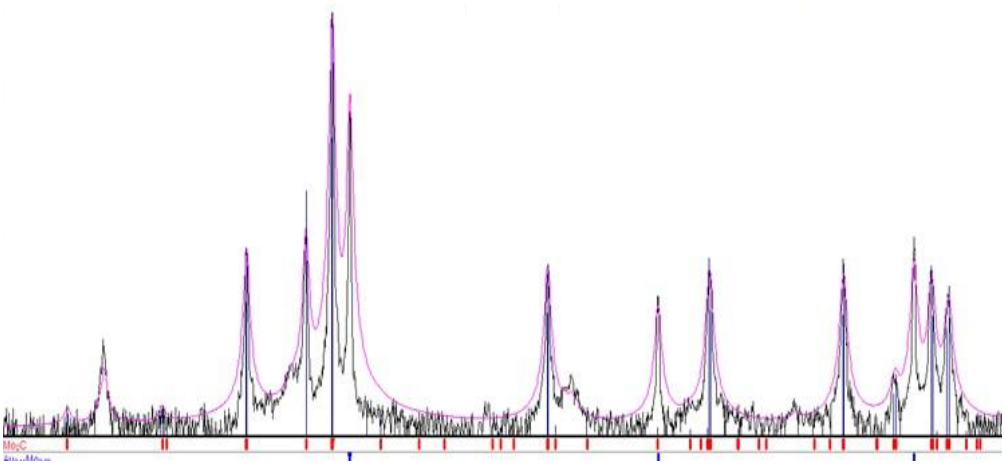

Figure 1. XRD pattern for Mo_2C sample.
Overlay of purple spectra indicates Mo_2C reference standard

Target preparation and irradiation
A platinum disc with a diameter of 19 mm, and a thickness of 0.16 mm, containing a dimple with diameter of 6.35 mm and height of 1.01 mm. (Electronic Space Products International) was used as the target holder for the cyclotron bombardment of $^{100}Mo_2C$. Approximately 50 mg of $^{100}Mo_2C$ was transferred to the cylindrical dimple located in the center of the platinum disc. The powder was pressed at 5000 psi for 30 seconds to secure it in place, after which the target was mounted into the cyclotron for bombardment. Proton irradiations were carried out using the CS-15 at Washington University. Production runs were conducted in the 15→ 10 MeV energy window determined by SRIM software(5, 6), and at 3, 4 and 5 µA currents. For each µA, the total µAhr was varied from 1 to 3 in successive runs. The integrity of the powder was preserved during bombardment period.

Target Processing
After bombardment, the target was allowed to decay for two hours before being processed in order to allow short lived isotopes (^{100}Tc, ^{96m}Tc) to decay.

To extract the ^{99m}Tc from the irradiated target material, a sublimation method described by Vleck *et al*.(7, 8) was employed. Custom quartz glassware based on the design put forward by Roesch *et al*.(9) was used for the separation. The individual pieces and the complete arrangement of the apparatus are shown in Figure 2. The assembled glassware with the target in the location was inserted into a preheated furnace at 850°C. Moist air was pumped into the apparatus, via the spout- like opening on tube B. Moist air was obtained by pumping air through a water-filled bubbling tube. Heating under these conditions continued for 20 minutes and the ^{99m}Tc and ^{100}Mo compounds were deposited in tubes D (~ 250 °C) and C respectively. The deposition is temperature dependent, thus ^{100}Mo deposits lower down in tube C at a higher temperature zone (~500 ºC). Heating under these conditions converts the $^{100}Mo_2C$ to $^{100}MoO_3$. As a safety measure, a small piece of glass wool was placed over the opening of tube D to ensure that small radioactive particulates were not released into the atmosphere. After the process was complete, Tube D containing the ^{99m}Tc compound was allowed to cool for ~ 5 minutes, after which it was washed with 8 ml of hot 1.0×10^{-4} M NaOH.

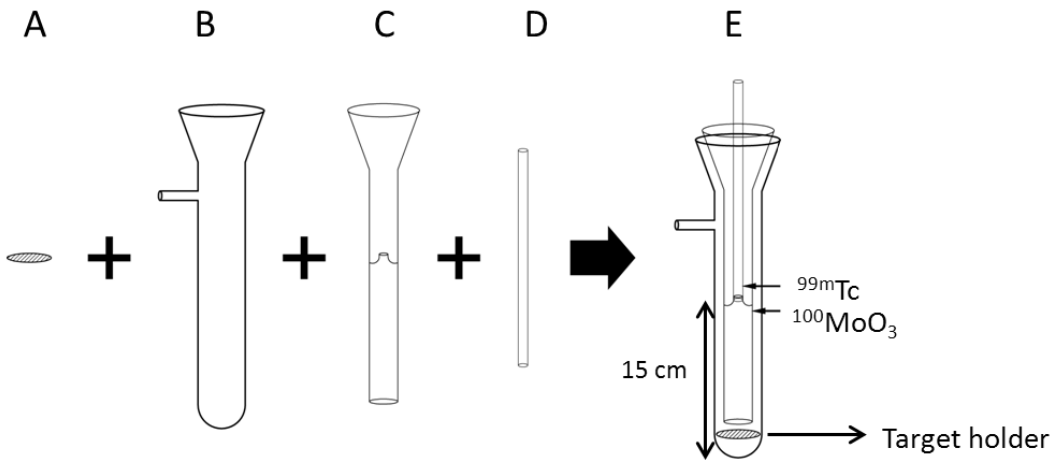

Figure 2. Apparatus used for target processing. Platinum target holder (A), outer (B), middle (C) and inner (D) quartz tubes, along with the assembled apparatus (E).

While processing the target by thermal chromatography using moist air, hot $^{100}MoO_3$ (yellowish) is deposited below the constriction in tube C, and ^{99m}Tc as pertechnetate ($^{99m}TcO_4^-$) was deposited in tube D. Confirmation of the yield of ^{99m}Tc deposited in tube D was confirmed post thermo-chromatography by using a dose calibrator. The depth to which the thermo-chromatography apparatus was lowered into the vertical furnace was 15 cm as indicated in Figure 2. This ensured maximum deposition of ^{99m}Tc in tube D and washing tube D with hot (~ 100 °C) NaOH resulted in near quantitative recovery of ^{99m}Tc.

The total processing time typically less than 45 minutes, with 20 minutes required for the thermal chromatography process.

In order to examine the efficiency of recovery of ^{99m}Tc through the sublimation process, a separate target was bombarded under identical conditions as those processed and entirely dissolved in 10 ml of 30% H_2O_2 . 10 µL of this raw target peroxide solution was then subjected to dilution and Ge gamma spectrometer analysis. Calculated activities for H_2O_2 processed targets show good agreement with activities for thermal chromatography processed targets indicating near quantitative recovery as shown in Table 1.

Table 1. Recovered Radioactivity/Percent Recovery

	3µA	4µA	5µA
1 µAhr	$7.4x10^7$ Bq/66%	$7.4x10^7$ Bq /66%	$7.4x10^7$ Bq /66%
2 µAhr	$1.9x10^8$ Bq /83%	$1.9x10^8$ Bq /83%	$2.1x10^8$ Bq /97%
3 µAhr	$3.1x10^8$ Bq /97%	$3.1x10^8$ Bq /97%	$3.1x10^8$ Bq /97%

Radionuclidic and Radiochemical purity analysis
10 µL of the resulting solution was diluted to 1000 µL using Millipore water and analyzed on a high purity Ge gamma spectrometer (Canberra) 5 minutes after obtaining the NaOH solution. Using the peak areas and peak efficiencies, radioactivity quantities were subsequently determined and back calculated to end of bombardment (EOB). To determine the identities and quantities of long lived radionuclidic impurities, the solution was allowed to decay for a minimum of 72 hours after which the analysis was repeated where peak data was collected for 6 h.

Analysis of radionuclidic impurities
The gamma–ray spectrum in Figure 3A shows the characteristic 140 keV peak for ^{99m}Tc. Table 1 lists the calculated activities corrected to EOB along with the percent recovery for the various parameter settings employed. Radionuclidic impurities were identified following a 6 hour scan on samples where ^{99m}Tc was allowed to decay for 72 hours post irradiation. A gamma-ray spectrum of an analysis for long-lived impurities is shown in Figure 3B. In addition to the peak at 140 keV other peaks at various energies became more conspicuous. Based on their energies peaks were assigned to ^{95}Tc and ^{96}Tc. Those associated with ^{95}Tc occurred at the following energies, 204 keV and 765 keV, with branching ratios of 63% and 94% respectively. Peaks at 778 keV, 812 keV, 850 keV and 1127 keV were assigned to ^{96}Tc, with branching ratios of 99%, 82%, 97% and 15% respectively. The percentages of these impurities expressed relative to ^{99m}Tc are shown in Table 2.

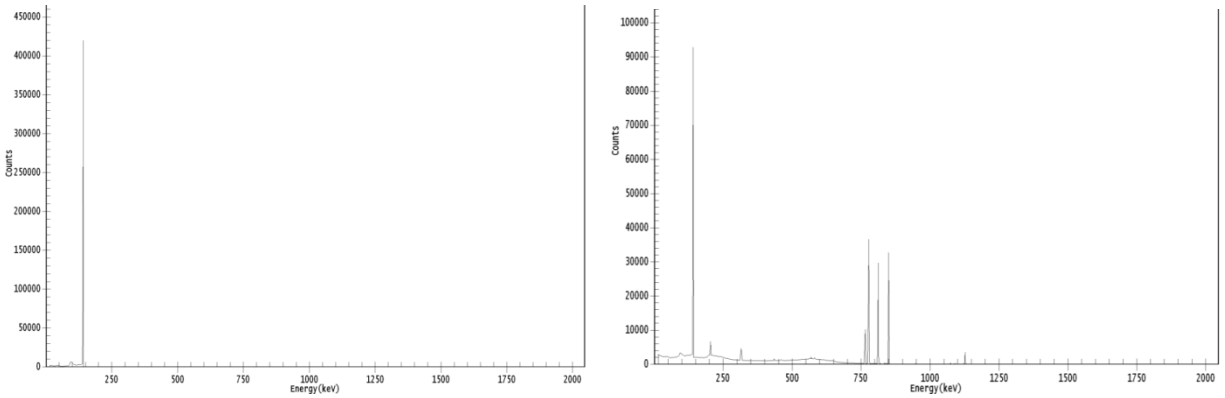

Figure 3. A. Gamma Spectroscopy plot for ^{99m}Tc sample at 4 hours post EOB. **B.**Gamma Spectroscopy plot of ^{99m}Tc, ^{96}Tc and ^{95}Tc at 85 hours post EOB. Scan time was 6 hours.

Table 2. Average Isotopic Impurities at EOB.
Values expressed as a percentage relative to ^{99m}Tc

^{99m}Tc	^{96}Tc	^{95}Tc
100%	0.08 %	$8.6*10^{-6}$ %

Radiochemical purity of the $^{99m}TcO_4^-$ in NaOH was determined by instant radio-thin layer chromatography (ITLC) using Alumina oxide TLC plates and acetone as the developing solvent. Analysis was performed on a Bioscan System 200 imaging scanner running the WinScan 3 software. Sep-Pak Light alumina N cartridges (Waters, Milford, MA) were used to purify and concentrate the $^{99m}TcO_4^-$ for radiochemistry. The column was first conditioned with 8 ml of acidified Millipore water (pH 2). The water was acidified with 2 M HCl by drop wise addition until the desired pH was reached. After conditioning, 8 ml of NaOH containing $^{99m}TcO_4^-$ was then slowly passed through the column, followed by elution with 400 µL of saline solution resulting in the final purified product. Radiochemical purity of the final product was also determined by radio-ITLC.

Radio-ITLC analysis performed on the recovered ^{99m}Tc revealed that a small amount of $^{99m}TcO_3$ (5%)was present along with $^{99m}TcO_4$ -. Purification of the wash with a Sep-Pak light alumina N cartridge conditioned by acidified Millipore water (pH 2) resulted in only pertechnetate. Eluting this cartridge with 400µL saline solution was effective in releasing the pertechnetate with a 71% to 75% activity recovery.

Preparation of ^{99m}Tc-medronic acid (^{99m}Tc-MDP)

^{99m}Tc-MDP was prepared using commercially available kits. 3.9 mg of a sterile lyophilized powder containing medronic acid as the main constituent, under the trade name MDP-BRACCO™ was dissolved in 135 µL saline solution. . From this solution 10 µL was pipetted and added to the 400 µL of 1.6 x10^8 Bq (4.3 mCi) $^{99m}TcO_4^-$ containing saline solution. Radio-ITLC results of the saline solution of methylene diphosphonate conjugated $^{99m}TcO^{4-}$ and showed 100% labeling. In vivo imaging of normal mice at various time points showed uptake of the ^{99m}Tc in the bones as expected.

Target Recycling

As the thermal chromatography process results in a conversion of the $^{100}Mo_2C$ target material to $^{100}MoO_3$ we aimed to develop a life cycle recycling process. This is illustrated in Figure 4. To maximize the mass of $^{100}MoO_3$ recovered after distillation, tube B was used for at least three trials before any attempt was made to recover this material. Removal was effected by gentle scraping. However scraping was not enough to get all the material so tube B was washed with 28% NH_3(aq) to dissolve the material and this ammonia solution was stored for further use in the synthesis of $(NH_4)_6Mo_7O_{24}.4H_2O$. The recovered $^{100}MoO_3$ was heterogeneous, containing powdery and spindle-like phases. MoO_3 was converted to Mo_2C as described above with an average efficiency of 85%. In the synthesis of $(NH_4)_6Mo_7O_{24}.4H_2O$ using recovered $^{100}MoO_3$, the spindle-like crystals were not readily soluble in the ammonia solution so heating to 50 °C became necessary for complete dissolution. On using $^{100}Mo_2C$ obtained from recycled $^{100}MoO_3$, activities were identical to those obtained using fresh $^{100}MoO_3$.

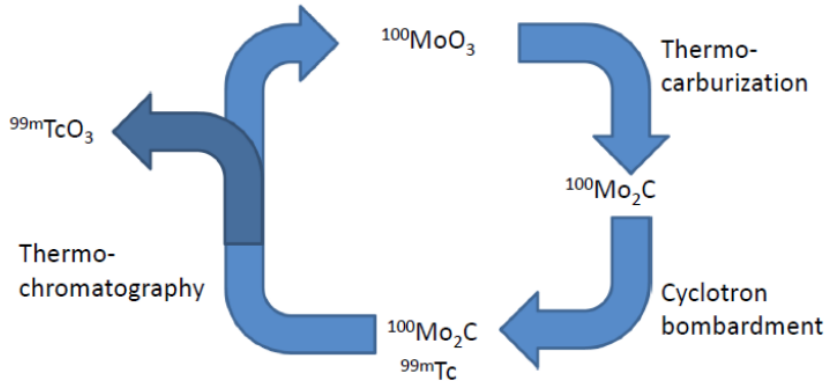

Figure 4. Life cycle of MoO_3 in the $^{100}Mo(p,2n)^{99m}Tc$ reaction production method

Use of the material $^{100}MoO_3$ for the sustainable cyclotron production of ^{99m}Tc was not considered ideal for a number of reasons. The first and foremost issue is that MoO_3 has a low melting point of 778 °C, thus its utilization at high currents and consequently high temperatures may preclude its use. At high temperatures sublimation of target material could occur during irradiation creating contamination and loss of product. Secondly, the low thermal conductivity of MoO_3 means that heat dissipation upon bombardment would be low. At room temperature MoO_3 is an insulator due to its fixed ions in its ionic lattice. As temperature rises, thermal conductivity in insulators fall leading to local thermal hotspots, which in the case of MoO_3 would facilitate sublimation of the oxide. Additionally, if the target holder being used is not sufficiently inert, such hotspots could possibly be the starting points for a chemical reaction between the MoO_3 and the target holder. The third and perhaps most important issue is one of stoichiometry. Each unit of MoO_3 has one in every four atoms being ^{100}Mo, thus the percentage of target atoms is considerable lower than that of other materials.

Ideally, one would want to use elemental metal ^{100}Mo as the target material for the cyclotron production of ^{99m}Tc. ^{100}Mo has a high melting point of 2850 °C and has a high thermal conductivity. Additionally this target material contains 100% ^{100}Mo nuclei. Whereas one can readily obtain ^{100}Mo powder for cyclotron bombardment, pretreatment of this starting material by sintering and melting are necessary for maximum adherence to a metallic backing and also for a sufficiently dense structure(10, 11). The wet chemical processing techniques that are used are multi-chemical, multi-step(10, 11) and at times multi-column operations to a purified pertechnetate. Similarly, the recovery of the target material entails a multi-step high temperature hydrogen reduction(10). The production of $^{94m}TcO_4^-$ using $^{94}MoO_3$ piqued our interest because of its simplicity in arriving at the purified pertechnetate solution and recovery of the starting material(1).

Mo_2C was seen as a viable alternative to MoO_3 because of its unique properties. These include its high melting point of 2800 °C, which compares favorably with elemental Mo. Also the high degree of chemical stability of Mo_2C means that handling at ambient conditions is possible. The high thermal conductivity also aid with heat dissipation during bombardment. Unlike insulators where thermal conductivity decreases with temperature, Mo_2C as an interstitial carbide

experiences an increase in thermal conductivity caused by strong scattering of electrons and phonons by the carbon vacancies(12). Unlike MoO_3 where only 25% of the nuclei are Mo, Mo_2C has a much higher percentage of Mo nuclei, 66.66%.

$^{100}MoO_3$ was obtained from Isoflex USA in, 99.01% purity. This high isotopic purity of ^{100}Mo minimizes contamination from other Technetium species post bombardment. The synthesis method used in the preparation of Mo_2C begins with MoO_3, which is highly soluble in an alkaline aqueous environment, and thus readily forms ammonium heptamolybdate tetrahydrate when dissolved in aqueous ammonia. Further reaction of the heptamolybdate with HMT results in ligand exchange taking place, where two of the ammonium ligands are replaced by HMT. Whereas elemental analysis was not performed on this complex, steric factors posed by the size of HMT may be used to explain why there was not total ammonium ion replacement even when HMT was used in stoichiometric excess. The presence of the ammine in bonding sphere facilitated the easy reduction of Mo from the +6 oxidation state to the +2 state while the excess HMT acted primarily as the carbon source while being heated. Before being subjected to heat, care was exercised in the drying of the HMT-Mo complex. The presence of water in the HMT-Mo complex acts as an extra oxygen source for the formation of an oxide. Elemental analysis reveals that some oxide was still present in the Mo_2C while XRD identified the phase as Tugarinovite MoO_2, which matched ICDD card 01-074-6246. Others have used a reducing gas, such as 4% H_2, Ar mixture while subjecting the material to heat(13). Although not attempted in our studies, one could theorize that the hydrogen gas would preferentially combine with any oxygen atom thus making it unavailable for metal oxide formation. One could also envisage that if the present heating of the HMT- Mo complex were to occur in a ball mill, fresh new surface would be rapidly exposed to heat, and since this reaction is a solid state reaction, there would be a greater frequency of Mo ions coming into contact with carbon, decreasing the likelihood for Mo to remain bonded to oxygen. Although faced with minute amounts of oxide through the present synthesis convention, this particular method of using a single source precursor eliminates the use and need for temperatures in excess of 1000 °C, or the need for alkali earth carbides such as calcium carbide to be used as the carbon source(14). Using such carbides under inert atmospheres would greatly reduce the presence of metallic oxides but would no doubt create a contamination issue, by introducing a metallic contaminant.

Processing and purification was carried out on the bombarded target material in the shortest time period possible. Thermo-chromatographic separation has proven itself as an efficient method for the separation of Mo and Tc species (1, 7-9, 15) . Dash *et al*. list the high radio-nuclidic purity of ^{99m}Tc attained, the repeated use of the same set up and the ready recycling of target material as some of the strengths of using this separation method(15). Under these conditions, Mo_2C undergoes oxidation to MoO_3 which then readily sublimes at a lower temperature than Mo_2C would, thus enhancing the feasibility of this process. It should be noted that under these processing conditions platinum was an ideal target holder material due to its inert nature and high melting point.

Tc was recovered by rinsing the glassware with 0.1mM NaOH. Radio-ITLC analysis of the recovered ^{99m}Tc revealed that a small amount of $^{99m}TcO_3$ (5%)(9, 16) was present along with $^{99m}TcO_4^-$. Purification of the wash with Sep-Pak light alumina N cartridge conditioned by acidified Millipore water (pH 2) resulted in only the TcO_4^- species. The acidified and hence positively charged column holds the negatively charged pertechnetate ion and allows any neutral technetium species to readily pass through. Eluting this cartridge with 400µL saline solution was

effective with a 71% to 75% activity recovery. Gamma spectroscopic analysis allowed for the calculation of the activities produced at the end of bombardment. Unfortunately, although several groups have measured the ^{100}Mo (p,2n)^{99m}Tc cross section, significant variability is noted among the values reported (17-21). To compare our results to theoretical values, cross section values were chosen for those plots that showed greater agreement between each other. Thus the cross section values for, Sholten(20), Takas(21) and Khandaker(18) were used in the determination of the theoretical yields. Actual yields for this study were determined to be an average of 84% for the various currents employed. These high yields indicate that Mo_2C is an effective target material for the ^{100} Mo (p, 2n) ^{99m}Tc reaction. In addition to the high yields, the radionuclidic impurities produced in this reaction, ^{95}Tc and ^{96}Tc were relatively low.

The majority of this research progress was published in Nuclear Medicine and Biology.

Changes in bombardment parameters were also tested, both to increase the activity of the ^{99m}Tc produced and to assess the integrity of the starting material under more demanding conditions.

Over a series of runs, the current of the proton beam used for bombardment was gradually increased from 5 μA to 20 μA, the maximum bombardment current at which the CS-15 cyclotron operates. The bombardment time was also increased from a maximum of 45 minutes in the previous year, to over two hours. In order to secure the $^{100}Mo_2C$ powder for bombardment at these parameter settings, pressed powder targets were prepared, however the design of a new platinum target holder was necessary. After the powder was pressed in the dimple, it was covered with aluminum foil that was held in place by a screw top lid for safety during this testing period. Figure 5 shows all three components of the new target set up.

Figure 5. Redesigned target holder for ^{99m}Tc production from Mo_2C and Mo target material

Pressing of the $^{100}Mo_2C$ gave a relatively compact powder, however methods were investigated so as to yield a more compact structure. Based on conversations with other groups in the field, low temperature sintering was carried out by heating the pressed powder under vacuum at 600 °C. The vacuum conditions employed ensured that heat would not be lost by thermal currents to any surrounding gas molecules. Initial studies show that upon bombardment of 50 mg targets,

sintered targets were shown to produce somewhat higher activity than non-sintered targets and shown in Table 2.

Table 3. Comparison of target yields from sintered and unsintered targets

Bombardment parameters, 20 μA, 40μAhr	
Un-sintered powder 46 mCi	Sintered powder 56 mCi

Under both conditions, sintered and unsintered, the integrity of the powder was maintained.

Cyclotron production of ^{99m}Tc using elemental ^{100}Mo powder target material

While $^{100}Mo_2C$ targets gave promising results, we hypothesized that elemental Mo target material would give higher yields and initiated an investigation into the use of this material for production of ^{99m}Tc.

We adapted our thermo-chromatographic method of separation to be amenable to elemental ^{100}Mo targets and developed and implemented an effective recycling method for ^{100}Mo. Mo metal oxidizes at 500 °C to MoO_3 facilitating sublimation at higher temperatures, indicating the utility of this method of processing and separation. The thermo-chromatographic method converts the target material to $^{100}MoO_3$. In order to effect an efficient recycling of the ^{100}Mo, $^{100}MoO_3$ was converted to ammonium heptamolybdate tetrahydrate ($(NH_4)_6Mo_7O_{24}.4H_2O$) by its room temperature reaction with 28% NH_3(aq). $(NH_4)_6Mo_7O_{24}.4H_2O$ was then converted to a HMT-molybdate complex ($(NH_4)_4(HMT)_2Mo_7O_{24}.4H_2O$) by its reaction in 28% NH_3(aq) with hexamethyltetramine (HMT). (22) Stepwise heating of the dried HMT-molybdate complex in 4% hydrogen/argon mixture up to a temperature of 1100 °C yields Mo metal. Both XRD(ICDD card 04-001-0379) and elemental analyses confirm the formation of Mo metal. The full reaction is shown below.

$$(NH_4)_4(HMT)_2Mo_7O_{24} \rightarrow 14Mo(s) + 10NH_3(g) + 23CO(g) + 7N_2(g) + H_2O(g) + C(s)$$

Bombardment of elemental ^{100}Mo powder, sintered at 800 °C for 16 hours, with cyclotron parameters of 20 μA at 40 μAhr yielded a maximum activity of 68 mCi, thus confirming much higher yields can be obtained with the elemental target material.

Cyclotron production of ^{186}Re using $^{186}W_2C$ powder

Encouraged by our successes with molybdenum carbide and understanding that there existed a need for cyclotron target materials for production of ^{186}Re, we aimed to use our developed techniques for production of this important therapeutic isotope.
Natural isotopic abundance WO_3 was reacted with hexamethyltetramine under reflux in aqueous ammonia to form a $[(W_7O_{24})(NH_4)_4(HMT)_2]_2$.$11(H_2O)$ complex . The structure of this complex is shown in Figure 6.

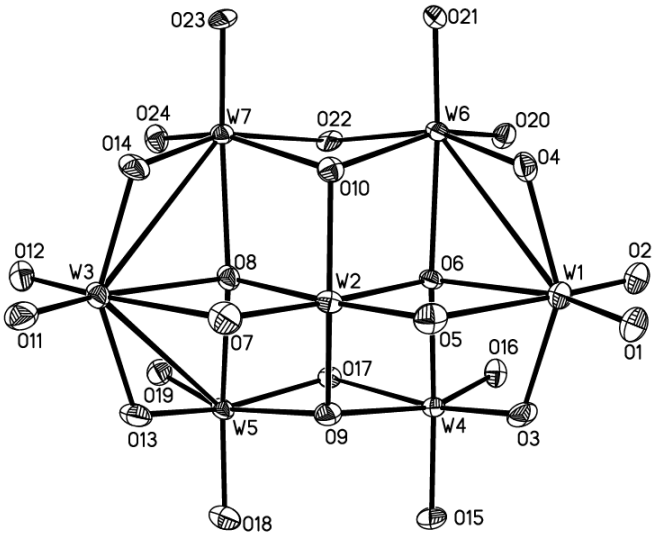

Figure 6. Projection view of one of the two unique clusters of $[(W_7O_{24})(NH_4)_4(HMT)_2]_2$.$11(H_2O)$. Anions and water omitted for clarity

This complex was dried and heated in 4% hydrogen/argon mixture at a temperature of 1100 °C for four hours to covert the material to the tungsten carbide. The percentage yield of W_2C from WO_3 was approximately 95%. X-ray diffraction and elemental analysis indicate the formation of W_2C. X-ray diffraction confirmed the major component of our produced material matches W_2C ICDD card 01-089-2371, Figure 7.

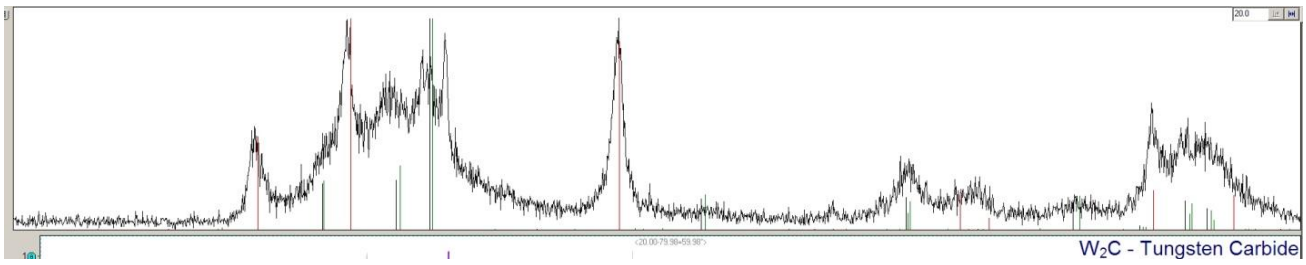

Figure 7. XRD pattern of synthesized W_2C

Enriched $^{186}W_2C$ was obtained from Isoflex, (^{180}W <0.01%, ^{182}W <0.01%, ^{183}W <0.01%, ^{184}W=0.1±0.05%, ^{186}W=99.90 ± 0.1%). We have prepared enriched [^{186}W]W_2C as above and have begun irradiating sintered targets produced with this material. Post bombardment processing has been conducted via thermochromatograpy at 1100 °C as with the ^{99m}Tc recovery(23) and previously reported (24). To date our preliminary low current experiments have resulted in the recovered yield of 0.24 mCi, which is 40% of the calculated end of bombardment activity based on gamma spectroscopy data. When compared to the theoretical yields calculated from cross section data, our end of bombardment activity stands at only 20% of this value. A log plot of a gamma spectrum of the produced ^{186}Re is shown below in Figure 8. The characteristic peak of ^{186}Re is shown at 137 keV, with the main impurity being ^{182}Re (half-life of 12.7 hours), with its characteristic peak at 1121 keV. The end of bombardment radionuclidic purity of ^{186}Re was > 95%.

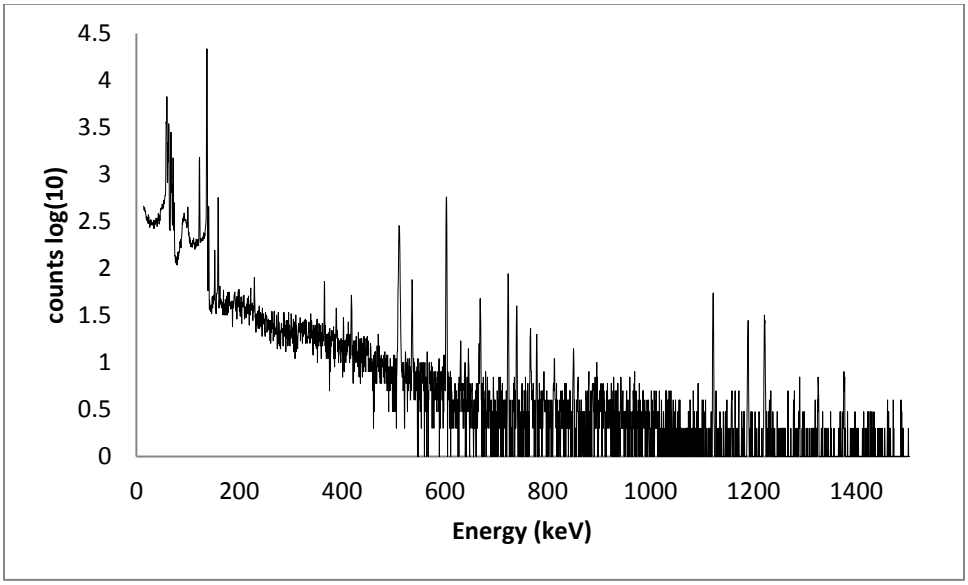

Figure 8. Gamma Spectroscopy of ^{186}Re at 4 hours EOB. Scan time of 10 minutes.

Design of an automated module for dry distillation purification of ^{99m}Tc

Based on our previous work we have designed a remote purification system for the isolation of ^{99m}Tc. The proposed automated distillation technique is similar to the process which our group currently employs to purify ^{76}Br from irradiated enriched $^{63}Cu_2{}^{76}Se$ cyclotron targets.

The purification module consists of a high temperature compact furnace (4.25” heated length) with a tapered quartz processing tube for dry distillation, an auxiliary peltier cooler adjacent to the furnace, a 4 way valve and a vacuum to direct the flow of liquid and argon, and a heater where the recovered TcO_4^- solution could be brought to dryness under an argon stream. Activity in the system would be tracked using silicon diode probes coupled with a Carroll & Ramsey radiation detector. The ^{99m}Tc would be recovered by dry distillation by heating the target at 850°C as previously described. Rapid cool down of the system would be expedited through the use of a

vortex cooling tube or peltier cooler. The distilled ^{99m}Tc would be condensed in the 2.5" cooled section of the quartz tube. The distilled activity can be eluted with deionized water or dilute ammonium hydroxide after cooling. A schematic of the proposed distillation automation apparatus is shown in Figure 9.

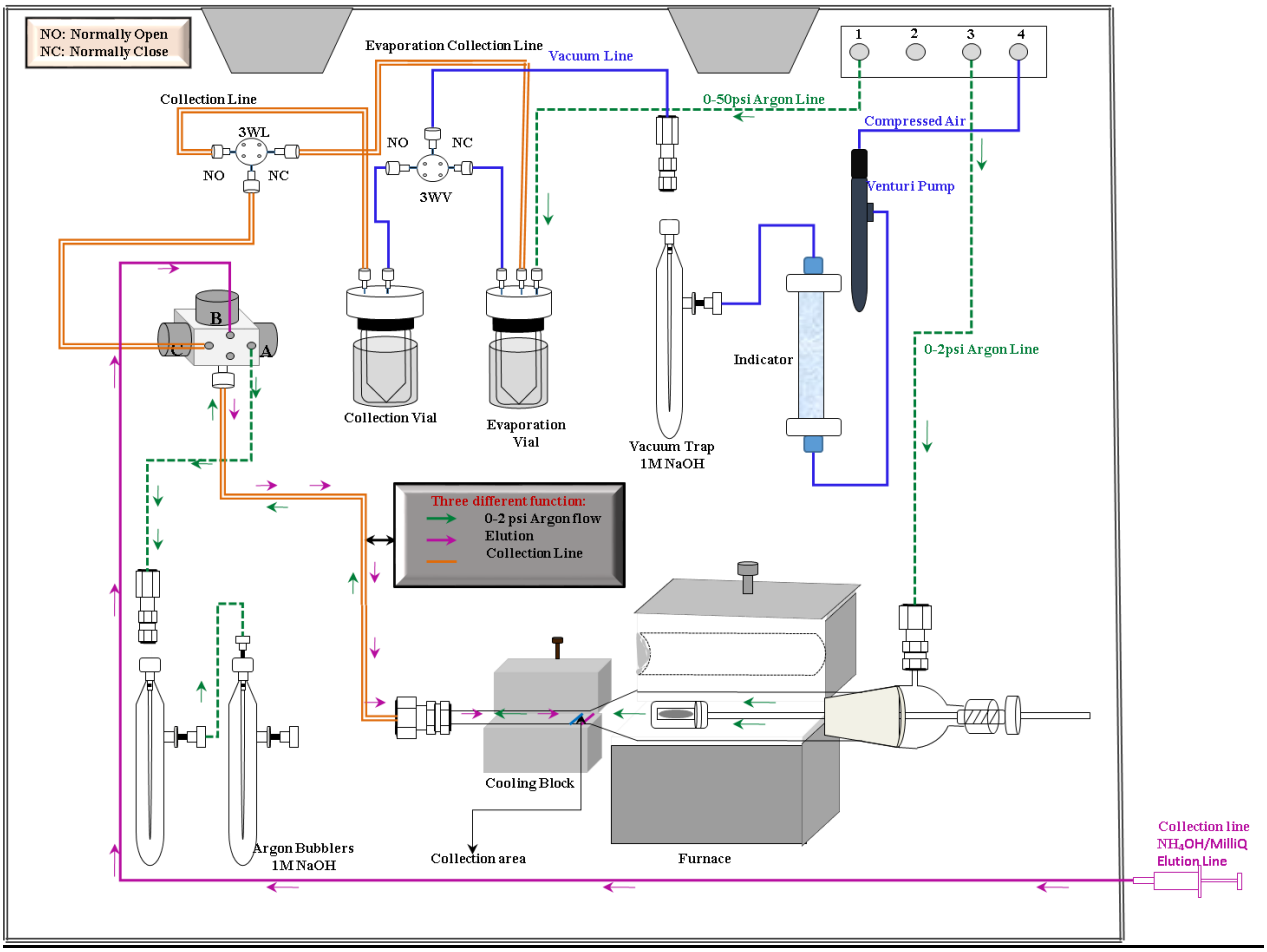

Figure 9. Design of remote automated purification system for ^{99m}Tc

2. Additional Benefits

This grant resulted in advanced training opportunities for one postdoctoral fellow and two graduate students:

Tara Mastren – Chemistry Graduate Student 2011-2014
Currently Postdoctoral Fellow at Los Alamos National Lab
Andrew (Lake) Wooten - Biomedical Engineering Graduate Student 2012-2015
Currently Staff Scientist at Zevacor Molecular
Vernal Richards - Postdoctoral Fellow 2012-2015
Currently Staff Scientist at Zevacor Molecular

This grant also resulted in the publication of two peer-reviewed manuscripts

Richards VN, Mebrahtu E, Lapi SE. Cyclotron Production of 99mTc using 100Mo2C targets. Nuclear Medicine and Biology. 2013;40(7):939-45.

Richards V.N., Rath N., Lapi S.E. (2015) Production and separation of 186gRe from proton bombardment of 186WC. Nuclear Medicine and Biology 6:530-5

Additionally our group was able to participate in the IAEA coordinated research project (CRP) "Accelerator-based Alternatives to Non-HEU production of Mo-99 / Tc99m" 2012-2016 which resulted in a widely distributed publication:

Cyclotron based Production of Technetium-99m, (2017) International Atomic Energy Agency, Vienna, Austria 2017 available at: http://www-pub.iaea.org/books/IAEABooks/10990/Cyclotron-Based-Production-of-Technetium-99m

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