Implementation of Multi-Curie Production of ^{99m}Tc by Conventional Medical Cyclotrons

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^{99m}Tc is currently produced by an aging fleet of nuclear reactors, which require enriched uranium and generate nuclear waste. We report the development of a comprehensive solution to produce ^{99m}Tc in sufficient quantities to supply a large urban area using a single medical cyclotron. **Methods:** A new target system was designed for ^{99m}Tc production. Target plates made of tantalum were coated with a layer of ^{100}Mo by electrophoretic deposition followed by high-temperature sintering. The targets were irradiated with 18-MeV protons for up to 6 h, using a medical cyclotron. The targets were automatically retrieved and dissolved in 30% H_2O_2. ^{99m}Tc was purified by solid-phase extraction or biphasic exchange chromatography. **Results:** Between 1.04 and 1.5 g of ^{100}Mo were deposited on the tantalum plates. After high-temperature sintering, the ^{100}Mo formed a hard, adherent layer that bonded well with the backing surface. The targets were irradiated for 1–6.9 h at 20–240 μA of proton beam current, producing up to 348 GBq (9.4 Ci) of ^{99m}Tc. The resulting pertechnetate passed all standard quality control procedures and could be used to reconstitute typical anionic, cationic, and neutral technetium radiopharmaceutical kits. **Conclusion:** The direct production of ^{99m}Tc via proton bombardment of ^{100}Mo can be practically achieved in high yields using conventional medical cyclotrons. With some modifications of existing cyclotron infrastructure, this approach can be used to implement a decentralized medical isotope production model. This method eliminates the need for enriched uranium and the radioactive waste associated with the processing of uranium targets.

Key Words: ^{99m}Tc; cyclotron; radioisotope production; molybdenum

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After 5 decades of use, the ^{99}Mo/^{99m}Tc generator remains the principal source of radioisotopes for nuclear medicine. ^{99m}Tc is an ideal single-photon emitter (*1*), because of its favorable half-life, photon energy, and radiopharmaceutical chemistry (*2*). ^{99m}Tc is used in 30,000–40,000 procedures per day in the United States, with estimates of global consumption topping 40 million scans per year (*3*). The use of ^{99m}Tc continues to grow worldwide (*4*).

The fragility of ^{99}Mo supply for ^{99}Mo/^{99m}Tc generator production was highlighted by recent shutdowns at 2 of the leading production sites for ^{99}Mo (*4,5*). The Canadian Chalk River nuclear reactor, which supplies 35%–40% of the global demand of ^{99}Mo, will terminate its isotope production service in 2016 (*6*). Other reactors supplying ^{99}Mo are typically more than 40 y old and are at risk of prolonged or permanent shutdown within a few years, creating a risk for loss of a long-term, stable supply of ^{99}Mo for medical purposes.

The fission of enriched ^{235}U was a cost-effective approach to produce large quantities of high-specific-activity ^{99}Mo using legacy research reactors. However, the cost of building new nuclear reactors for isotope production is extremely high. The international community has recommended, through the Nuclear Energy Agency of the Organization for Economic Co-operation and Development, to implement full cost recovery on radioisotope production, which will lead to higher ^{99}Mo pricing in upcoming years (*7*). This price increase will be compounded by the effects of a shift from highly enriched uranium to low enriched uranium targets for ^{99}Mo production (*8,9*).

Alternative methods for ^{99}Mo and ^{99m}Tc production have been known for years (*10*). These include nuclear reactors for neutron enrichment of ^{98}Mo (*11*), accelerators to produce spallation neutrons for enrichment of ^{98}Mo, linear accelerators for the fission of ^{238}U or the ^{100}Mo(γ,n)^{99}Mo reaction (*12*), and the direct production of ^{99m}Tc through the ^{100}Mo(p,2n) ^{99m}Tc reaction (*13–15*). This latter method was pioneered by Beaver and Hupf in 1971 (*13*), and experiments were later conducted by Lagunas-Solar (*16*), Takacs et al. (*17*), and others (*18*) to measure the cross-sections for the ^{100}Mo(p,2n)^{99m}Tc reactions (*19*).

Despite some successes with low-current irradiations, the implementation of a robust production system for routine, large-scale production of ^{99m}Tc has remained elusive to date. We report the results of our successful experiments in designing a fully engineered solution for high-yield production of ^{99m}Tc by conventional medical cyclotrons.

MATERIALS AND METHODS

Cyclotron System

The experiments were conducted on a 19-MeV cyclotron (300 μA, TR PET cyclotron; ACSI) at the BC Cancer Agency. This cyclotron had 2 beam ports, one connected to a target selector and the other to a switching magnet to direct the beam to either a solid target station or a target selector positioned horizontally for conventional targets. The cyclotron configuration is illustrated in Figure 1. In addition to the

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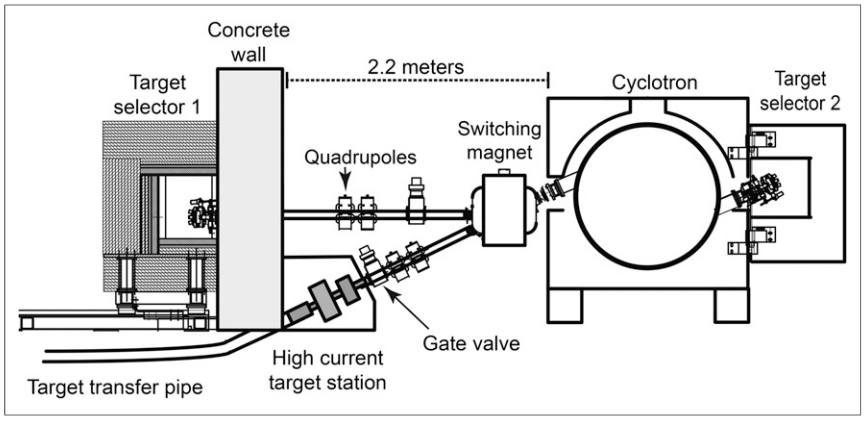

FIGURE 1. Cross-sectional view of BC Cancer Agency TR-PET cyclotron showing beamline facilitating both standard 4-port target selector and solid target station for high-current ^{100}Mo irradiations.

concrete shielding of the vault, both target selectors and the solid target station were surrounded by mobile local shields.

Target System Design

Two target systems were designed for ^{99m}Tc production. The initial design consisted of an aluminum target holder accommodating a 10 × 20 mm plate with an aluminum cold finger at the back to dissipate heat from the target plate (cold finger target, further described in the supplemental data [supplemental materials are available at http://jnm.snmjournals.org]). The target plate was automatically dropped into a shielded container after irradiation.

The second target holder was designed for high-current irradiations over a larger surface (referred to as the large target) (Fig. 2). This target station accommodated a capsule containing the target plate. This capsule could be automatically connected to, and retrieved from, the target station. The assembly is described in the supplemental data section. The target station alignment and the beam collimator adjustments were performed by irradiating blank aluminum or tantalum target plates, exposed to radiographic film (Gafchromic EBT2; International Specialty Products) to measure the beam distribution on the target plate.

Target Plate Preparation

Tantalum target-backing plates were mechanically etched at the target surface by introducing shallow grooves to maximize adhesion of the target material. The targets were prepared by electrophoretic deposition (EPD) of ^{100}Mo on tantalum plates as described by Gutierrez et al. (*20*). The deposition of ^{100}Mo was achieved within minutes. Two lots of ^{100}Mo were tested (99.01% and 97.4% ^{100}Mo content) (Table 1). The third batch (99.8%) listed in Table 1 was not irradiated but is included to highlight the specifications of enriched material that is now available. After EPD, the targets were placed in a sintering oven (CTF 18/300; Carbolite) and heated to 1,700°C for 5 h. Electron microscopy images of the target were obtained on a Hitachi S-2300 instrument.

Target Irradiations

The targets were irradiated at progressively higher currents to test their ability to withstand the proton beam. The energy was 18 MeV for all irradiations. The cold finger target was irradiated at 20, 30, and 50 μA. For the large target, experiments were performed at beam currents of 100, 200, and 240 μA. The current was progressively ramped up over a period of approximately 15 min, followed by constant current. The total irradiation time ranged from 1.3 to 6.9 h.

Target Dissolution Process and Apparatus

The small target plates were dissolved into a beaker containing 30 mL of 30% H_2O_2 preheated to 50°C. In early experiments, the dissolved target solution was mixed with 2 M NaOH and evaporated to dryness. The dry powder was then reconstituted in 4–6 mL of water. For later experiments, the dissolution mixture was first evaporated to dryness while heating the beaker at 80°C, and 7 mL of 2 M NaOH were added as a final step to dissolve the residue.

The target capsules were directly used as dissolution vessels to extract ^{99m}Tc from the target plates (supplemental data). The target dissolution containing the dissolved ^{99m}Tc and approximately 1 g of ^{100}Mo was reconstituted in 4 M NaOH.

Pertechnetate Purification

The ^{99m}Tc pertechnetate purification followed our published solid-phase extraction procedures (*21*). Several resins were compared for the separation of pertechnetate from molybdate, including the ABEC-2000 resin (Eichrom Technology) and the AnaLig Tc02 resin (IBC Advanced Technologies).

The ABEC-2000 resin was used as previously described, with the exception that potassium hydroxide was replaced by NaOH (*21*).

Initial experiments with the AnaLig TcO2 resin were performed manually to optimize separation conditions at low activity levels using a solution of 1.8 g of molybdenum metal powder dissolved in 15 mL of 30% H_2O_2. The solution was evaporated to dryness and dissolved in 7 mL of 2 M NaOH. A small amount of ^{99m}Tc was added to this solution to simulate a target dissolution mixture. We experimented with various resin contents, ranging from 100 to 400 mg, various flow rates (0.2–0.6 mL/min), and water elution flow rates (0.5–5 mL/min). Further experiments were done using a purification system as described in Morley et al. (*21*) and implemented under real irradiation conditions of ^{100}Mo targets, dissolved as described above. One key modification was the addition of a syringe pump to control the loading rate of the target dissolution mixture on the AnaLig Tc02 resin.

To summarize the AnaLig purification process, the 2 M NaOH solution containing ^{99m}Tc and ^{100}Mo was passed through a solid-phase extraction cartridge containing 100 mg of AnaLig resin. The resin was loaded at a flow rate of 0.2 mL/min. At high pH, ^{100}Mo, along with small quantities of ^{99}Mo and radioactive niobium impurities, was recovered in the first waste vessel. The resin was rinsed with 2–3 mL of 2 M NaOH and then eluted with water.

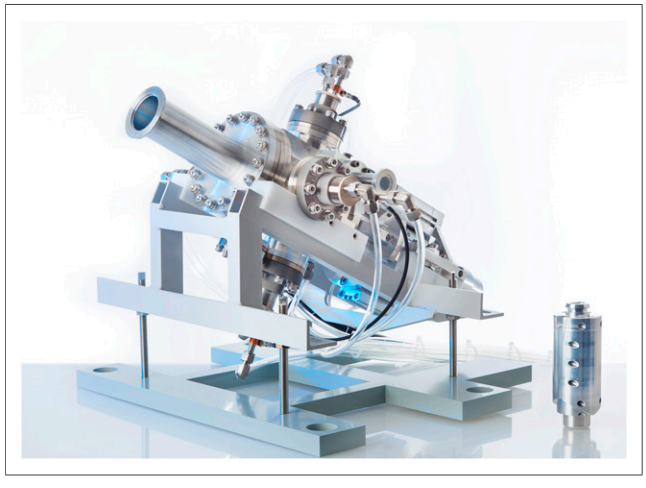

FIGURE 2. Photograph of high-current target station and target capsule (bottom right).

TABLE 1
Composition of Various Batches of ^{100}Mo

Batch	Isotopic composition (%)						
	^{92}Mo	^{94}Mo	^{95}Mo	^{96}Mo	^{97}Mo	^{98}Mo	^{100}Mo
99.01%	0.09	0.06	0.10	0.11	0.08	0.55	99.01
97.4%	0.005	0.005	0.005	0.005	0.01	2.58	97.39
99.8%	0.003	0.003	0.003	0.003	0.003	0.17	99.815

The ^{99m}Tc was recovered in 10 mL of water. The water/^{99m}Tc solution was neutralized over a cation exchange resin (On-Guard II H; Dionex) and trapped on a small Alumina A cartridge (Waters). The alumina cartridge was eluted with 0.9% saline solution, passed through a 0.22-μm filter and recovered in the product vial.

Measurement of Radionuclidic Purity

Samples for γ-ray spectroscopy were taken from the dissolved target solution before purification. Samples were counted 3 h after the end of beam and at 24 h, 3 d, 7 d, and 21–30 d after end of beam. For late samples, longer acquisitions were used (up to 24 h for the 21- to 30-d samples). All samples were measured on a high-resolution γ-ray spectrometer (Canberra) equipped with a high-purity germanium detector. The HyperLabs 2009 software (Hyperlabs Software Inc.) was used for data analysis. The γ-ray spectrometer was energy- and efficiency-calibrated using National Institute of Standards and Technology–traceable radioactive sources (Eckerd & Ziegler).

Quality Control and Kit Radiolabeling

The ^{99m}Tc-pertechnetate solution was tested for alumina with a colorimetric test kit (Biodex), compared with a test solution of 10 μg of aluminum per milliliter. The presence of residual ^{100}Mo was tested with a colorimetric assay, using a molybdenum assay kit (Quantofix Molybdenum; Macherey-Nagel).

The presence of hydrolyzed-reduced ^{99m}Tc was tested by thin-layer paper chromatography using Whatman paper developed in acetone. Kits for neutral (^{99m}Tc-exemetazime; GE Healthcare), cationic (^{99m}Tc-sestamibi; Covidien), and anionic (^{99m}Tc-medronate; Edmonton Radiopharmacy Centre) radiopharmaceuticals were reconstituted and tested according to the manufacturer's instructions.

Recycling of ^{100}Mo

The first waste solution containing ^{100}Mo in NaOH and radioactive impurities was decayed for 6 mo before reprocessing. The solution was purified by ion exchange chromatography using a Dowex 50W-X8 cation exchange column (50 × 2 cm diameter). The eluate containing molybdic acids ($MoO_3 \cdot n\ H_2O$) was evaporated to dryness and reduced to molybdenum metal in a tube furnace at 1,100°C under a hydrogen atmosphere (*22,23*).

RESULTS

Target Plate Preparation and Electron Microscopy

With EPD, fine molybdenum powder was rapidly deposited on the tantalum backing, forming a soft layer on top of the plate. Up to 1.5 g of molybdenum metal powder were deposited over a surface ranging from 15 to 18 cm^2 for the large-area targets. After high-temperature sintering, the deposited material formed a hard, adherent layer, which bonded with the tantalum backing (Fig. 3). The texture and bonding strength was dependent on the particle size of the ^{100}Mo metal powder—empirically we observed better results with finer (<10 μM) powder. The deposited layer could not be removed from the target backing by dropping or bending the tantalum plate. Scanning electron microscope images showed that the powder grains were adherent to each other, with residual gaps and voids (Fig. 4).

Target Irradiations

Several cold finger targets were irradiated to test the feasibility of the EPD/sintered targets. Two batches of ^{100}Mo were irradiated, containing 97.4% (Trace Sciences) and 99.01% (Isoflex) ^{100}Mo content, respectively. Irradiation conditions ranged from 20 to 50 μA peak proton current, for durations ranging from 22 to 377 min (total integrated current, 700–7,200 μA·min). The results are reported in Table 2. The total collected activity reflects measured ^{99m}Tc activity before purification, whereas the final product assay is the measured ^{99m}Tc pertechnetate after purification. Both values are decay-corrected to end-of-beam time. In some cases, we noticed that the target plate could be introduced in the holder without reaching optimal contact between the aluminum cooling finger and the target plate, leading to poor target performance due to inadequate thermal conductivity.

The large targets were irradiated at proton beam currents ranging from 100 to 240 μA, for durations ranging from 85 min to 6.9 h. These results are reported in Table 3. For these experiments, the total activity was assayed after target dissolution and before pertechnetate purification. As measured by the dose calibrator, the total ^{99m}Tc activity was likely overestimated by the presence of a small but significant quantity of higher energy isotopes present in the irradiated 99.01% ^{100}Mo targets.

Target Dissolution

For cold finger targets, the dissolution of the molybdenum target with H_2O_2 was an exothermic process, which required careful handling. The addition of NaOH to the molybdic solution was also exothermic. The target dissolution and evaporation process was achieved in 40 min.

The large targets were readily and completely dissolved within the capsule, with no trace of residual ^{100}Mo on the target at the end of the process. No burn marks were visible on the large-area targets after high-current irradiation.

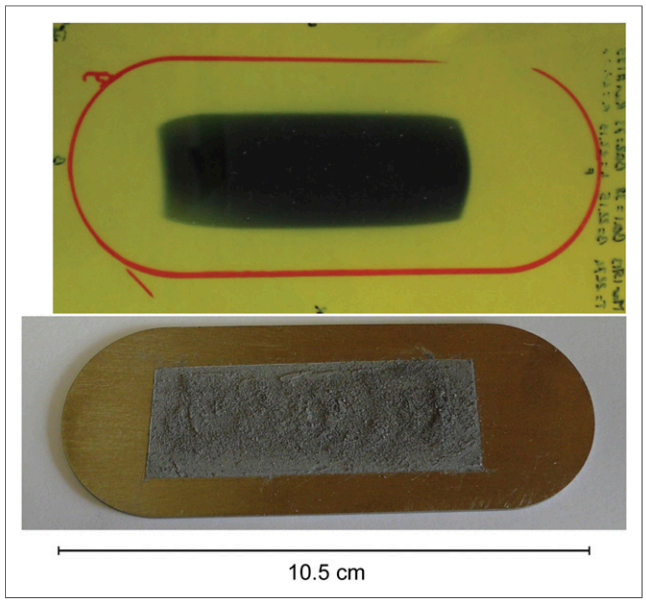

FIGURE 3. Picture of target plate for large target station, with ^{100}Mo layer prepared by EPD and high-temperature sintering (bottom). Corresponding beam shape is shown on film exposed to target plate (top).

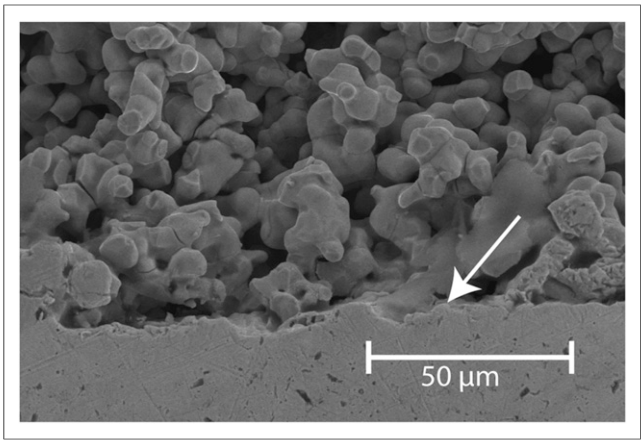

FIGURE 4. Scanning electron micrographs of target section. There is good bonding of molybdenum layer to tantalum target-backing plate (white arrow). Deposited material is porous as noted by voids in deposited target material.

Pertechnetate Purification

For the ABEC-2000 resin, the mean purification efficiency of ^{99m}Tc was 78.7%, with an SD of 9.5%. The content of ^{99m}Tc not trapped by the ABEC-2000 resin was 18.2% ± 9.3% (mean ± SD). Remaining losses were minimal (0.7% ± 0.9%, 2.1% ± 1.2%, and 0.3% ± 0.2% for the ABEC-2000 resin, alumina cartridge, and cation exchange resin, respectively).

With manual and eventually automated purification using the AnaLig Tc02 resin, optimal results were obtained using 100 mg of resin preconditioned with 5 mL of deionized water, loaded at a flow rate of 0.2 mL/min. The AnaLig Tc02 resin was readily eluted with water (2 mL/min).

For the cyclotron runs performed using the AnaLig Tc02 resin, the purification efficiency was 83.9% ± 1.7%, with 5.2% ± 1.5% losses in waste, some activity remaining trapped on the AnaLig resin (7.5% ± 1.8%), and minimal activity remaining on the alumina or cation exchange cartridges (3.0% ± 0.6% and 0.4% ± 0.1%).

Radionuclidic Purity Results

Radionuclide purity analyses were performed on batches of 99.01% and 97% ^{100}Mo irradiated at high currents, and the results are shown in the supplemental data. The technetium radionuclide contents showed that ^{99m}Tc constituted over 99.5% of all technetium radioisotopes produced. The content of ^{96g}Tc, ^{95g}Tc, ^{94m}Tc, and ^{94g}Tc was lower using the 97.4% ^{100}Mo target material, which had a lower content of $^{92–97}$Mo. The results agreed with extrapolations from experimental data (*24*) and showed lower amounts of long-lived impurities than predicted based on Empire III calculations (*19*). The quantity of ^{94m}Tc was higher than predicted based on theoretic models. The proportion of ^{96m}Tc could not be quantified because of its short half-life, low γ-emission rate, and overlap with other radioisotopes peaks. Because of chemical identity with ^{99m}Tc, other technetium radioisotopes could not be separated from the final ^{99m}Tc-pertechnetate solution. Radioisotopes other than technetium that were recovered in waste are reported in Supplemental Table 2.

Quality Control of Pertechnetate and Kit Radiolabeling

Three batches of cyclotron-produced ^{99m}Tc-pertechnetate produced using the cold finger targets were tested according to the quality control procedures used for generator-produced ^{99m}Tc-pertechnetate. The radiochemical purity of ^{99m}Tc-pertechnetate was 99.7% ± 0.5% (United States Pharmacopeia [USP] criteria > 95%). In all cases, the aluminum ion content was lower than 10 μg/mL. The radiochemical purity of ^{99m}Tc-sestamibi was 99.6% ± 0.7% (USP criteria > 90%). The radiochemical purity of ^{99m}Tc-medronate was 98.1% ± 3.2% (USP criteria > 90%). The radiochemical purity of ^{99m}Tc-exemetazime was 91.3% (USP criteria > 90%; n = 2). No traces of molybdenum were found in the pertechnetate solution.

Recycling of ^{100}Mo

The radioactive impurities in the waste included ^{99}Mo, ^{99m}Tc, and ^{95}Nb, with ^{95}Nb having the longest half-life (35 d). After 6 mo of decay, the waste solution contained significantly less than the exemption quantity of all radioisotopes. ^{100}Mo from the waste solution was recycled with an average yield of 85% (range, 80%–92%). High-temperature reduction under a hydrogen atmosphere yielded a light gray metallic powder that could be reused for deposition on tantalum target backings.

DISCUSSION

Our research effort was prompted by the need to find alternative solutions for medical isotope production after the Canadian government's decision to shut down isotope production at the Chalk River reactor in 2016 (*6*). The current supply is vulnerable and relies on a limited number of aging nuclear reactors.

The well-established use of ^{99m}Tc in nuclear medicine practice makes it unlikely to be replaced by another radioisotope over a short

TABLE 2
Production Yields with Small-Area Cold Finger Target

Run	^{100}Mo target	Irradiation time (min)	Integrated current (μA·min)	Total activity (MBq)	Saturated yield (GBq/μA)
1	97.4	22	700	3,709	2.81
2	97.4	60	1,800	3,202*	0.98*
3	99.01	58	1,134	3,425†	1.15†
4	99.01	205	3,600	19,415	3.39
5	99.01	377	7,200	39,270	3.97
6	99.01	36	1,250	4,372*	1.25*
7	99.01	124	2,400	13,417	2.17
8	99.01	94	1,800	10,201	3.22
9	99.01	95	1,800	10,549	3.33

*Some losses occurred because of overheating.
†Thinner target.

TABLE 3
Large Target Production Runs

Parameter	Run 1	Run 2	Run 3	Run 4
Target enrichment (%)	99.01	99.01	97.39	97.39
Energy (MeV)	18–11	18–12	18–12	18–12
Irradiation time (h)	1.5	1.32	6.43	6.9
Average current (μA)	85	159	188	223
Charge (μA·min)	7,775	13,555	74,895	83,223
^{99m}Tc activity (GBq)	55.5*	96.2*	333	348
Saturated yield (GBq/μA)	4.05*	4.0*	3.3	3.03

*Overestimated because of presence of high-energy peaks from other isotopes.

period of time (*25*). Given the kit chemistry of ^{99m}Tc (*26*), any replacement technology must be transparent to end users.

With an increasing number of medical cyclotrons installed for ^{18}F production for PET imaging, it was time to explore the practical feasibility of the direct production method using the ^{100}Mo(p,2n)^{99m}Tc reaction. Conveniently, the peak cross section for the ^{100}Mo(p,2n) ^{99m}Tc occurs at approximately 15 MeV (*17–19*), which is within the range of many existing medical cyclotrons used for PET radioisotope production.

Our team tackled several challenges to implement a simple, reliable method for routine production of ^{99m}Tc. This was made possible by prior work of Beaver and Hupf (*13*), Lagunas-Solar (*14,16*), and others (*15,17*), who had studied the feasibility of this approach.

The first challenge was the development of a target system that could be prepared using accessible laboratory equipment and small quantities of enriched target material. Molybdenum metal has a high melting point (>2,600°C) and is difficult to work with given its propensity for oxidation at lower temperatures (~440°C). As such, melting or sputtering the metal potentially leads to high losses.

We explored various methods for target production including electroplating (*27*) and sugar codeposition of molybdenum (*28*). These methods were not useful to produce high quantities of ^{99m}Tc. We developed an EPD method that makes thick, robust ^{100}Mo coatings for routine use. These targets were successfully used for high-current irradiations at up to 240 μA. The target plates faced the beam at either a 20° (cold finger target) or a 10° angle (large target) relative to the proton beam. These angles increased the effective thickness of the material by a factor of 2.9–5.7. Thus, the deposited ^{100}Mo layer was sufficiently thin to enable adequate thermal heat transfer from the cooled backing during irradiation. The porosity of the molybdenum layer facilitated the recovery of ^{99m}Tc.

Another challenge was the design of a target station that allowed the routine production of ^{99m}Tc. Our solution was to use a mechanical push-and-retrieve system that directly retrieved the target capsule to a hot cell. The target dissolution occurred directly inside the target capsule, allowing the safe handling of the targets.

The purification of ^{99m}Tc-pertechnetate from molybdenum at various specific activities was reviewed in a recent publication (*29*). Several methods are not applicable to cyclotron-produced ^{99m}Tc because of the quantity of nonradioactive molybdenum present in the target dissolution mixture. We tested several approaches, including the ABEC-2000 resin and the AnaLig resin, and found that these methods were suitable for the purification of ^{99m}Tc-pertechnetate from the irradiated ^{100}Mo target solution.

To reduce the cost of ^{100}Mo, we developed a recycling method for ^{100}Mo and achieved a recovery efficiency of up to 92%. This process can be optimized further to reduce ^{100}Mo losses.

The radionuclidic purity of ^{99m}Tc was analyzed using a high-resolution γ-ray spectrometer. The results highlighted the fact that the isotopic composition of the target material was more important than the absolute enrichment level. In particular, ^{94}Mo, ^{95}Mo, ^{96}Mo, and ^{97}Mo are significant contributors to the production of radionuclide impurities. We observed lower levels of long-lived impurities than theoretically predicted (*19,24*).

It is now possible to obtain batches of high-quality ^{100}Mo achieving 99.8% isotopic purity (Table 1), with $^{94–97}$Mo content below the detection limit, in sufficient quantities to meet clinical and commercial needs. The radionuclidic purity of cyclotron-produced ^{99m}Tc will change depending on the target material, irradiation conditions, and the time after production at which the ^{99m}Tc is used. No USP or European Pharmacopeia standards exist for cyclotron-produced ^{99m}Tc. We previously showed that the impact of these impurities on patient radiation dose was minimal when using batches of ^{100}Mo with low $^{94–97}$Mo content (*30*).

The specific activity of ^{99m}Tc was not measured in the current study but was previously reported (*18*). Both experimental and theoretical results suggest that similar ratios of ^{99m}Tc to ^{99g}Tc can be expected when comparing typical cyclotron irradiation parameters (e.g., 3–6 h) with a generator eluted at a 24-h frequency (*18,19*). We radiolabeled various radiopharmaceutical kits using cyclotron-produced ^{99m}Tc. All radiopharmaceuticals successfully passed routine quality control tests.

Our production system was able to reliably produce ^{99m}Tc in saturated yields exceeding 3 GBq/μA at a 18-MeV proton beam. In a single irradiation, we achieved the production of 347 GBq (9.4 Ci) of ^{99m}Tc in just over 6 h. The target dissolution and ^{99m}Tc purification were completed in approximately 75 min. We achieved average purification yields of 84%. Further optimization is possible to reduce the processing time and improve yields.

The precise production costs of cyclotron ^{99m}Tc were not compared with those of generator-produced ^{99m}Tc in this study. The cost estimates need to take into account overhead costs, equipment amortization, and implementation of good manufacturing practice–compliant production and various distribution models in addition to direct expenses. These factors will be important considerations for eventual market acceptance of this production method.

CONCLUSION

The production of large quantities of ^{99m}Tc is possible using a medical cyclotron. These results demonstrate that it is feasible to supply a large population base from a single cyclotron. The ^{99m}Tc produced by cyclotrons at 18 MeV can be obtained with high radionuclidic purity and is a potential alternative for routine clinical use. With some modifications of existing cyclotron infrastructure, this approach could be used to implement a highly decentralized medical isotope production model, eliminating the requirement for enriched uranium and radioactive waste associated with nuclear fission.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. This work was supported by the Natural Sciences and Engineering Research Council, the Canadian

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REFERENCES

1. Bartholomä MD, Louie AS, Valliant JF, Zubieta J. Technetium and gallium derived radiopharmaceuticals: comparing and contrasting the chemistry of two important radiometals for the molecular imaging era. *Chem Rev.* 2010;110:2903–2920.
2. Dilworth JR, Parrott SJ. The biomedical chemistry of technetium and rhenium. *Chem Soc Rev.* 1998;27:43–55.
3. Einstein AJ. Breaking America's dependence on imported molybdenum. *JACC Cardiovasc Imaging.* 2009;2:369–371.
4. Goodhand P, Drouin R, Mason T, Turcotte E. Report of the Expert Review Panel on Medical Isotope Production. 2009. http://www.nrcan.gc.ca/sites/www.nrcan.gc.ca/files/energy/pdf/eneene/sources/uranuc/pdf/panrep-rapexp-eng.pdf. Accessed April 1, 2014.
5. Pillai MR, Dash A, Knapp FF Jr. Sustained availability of ^{99m}Tc: possible paths forward. *J Nucl Med.* 2013;54:313–323.
6. Government of Canada. Government of Canada Response to the Report of the Expert Review Panel on Medical Isotope Production. https://www.nrcan.gc.ca/sites/www.nrcan.gc.ca/files/energy/pdf/eneene/sources/uranuc/pdf/isotopes-gc-re-eng.pdf. Accessed April 1, 2014.
7. The supply of medical radioisotopes: the path to reliability. OECD-NEA. 2011. https://www.oecd-nea.org/med-radio/reports/med-radio-reliability.pdf. Accessed March 21, 2014.
8. The Supply of Medical Radioisotopes: Market impacts of converting to low-enriched uranium targets for medical isotope production. OECD-NEA. 2012. http://www.oecd-nea.org/ndd/reports/2012/7129-leu.pdf. Accessed March 21, 2014.
9. Committee on Medical Isotope Production without highly enriched uranium. *Medical Isotope Production Without Highly Enriched Uranium.* Washington, DC: The National Academy of Sciences; 2009.
10. Ruth T. Accelerating production of medical isotopes. *Nature.* 2009;457:536–537.
11. Ryabchikov AI, Skuridin VS, Nesterov EV, Chibisov EV, Golovkov VM. Obtaining molybdenum-99 in the IRT-T research reactor using resonance neutrons. *Nucl Instrum Methods Phys Res. Sect B.* 2004;213:364–368.
12. Lambrecht RM, Sekine T, Vera Ruiz H. Alice predictions on the accelerator production of molybdenum-99. *Appl Radiat Isot.* 1999;51:177–182.
13. Beaver JE, Hupf HB. Production of 99m Tc on a medical cyclotron: a feasibility study. *J Nucl Med.* 1971;12:739–741.
14. Lagunas-Solar MC. *Accelerator Production of Tc-99m with Proton Beams and Enriched Mo-100 Targets*. International Atomic Energy Agency technical document 1065. Vienna, Austria: International Atomic Energy Agency; 1999.
15. Scholten B, Lambrecht RM, Cogneau M, Vera Ruiz H, Qaim SM. Excitation functions for the cyclotron production of Tc-99m and Mo-99. *Appl Radiat Isot.* 1999;51:69–80.
16. Lagunas-Solar MC, Kiefer PM, Carvacho OF, Lagunas CA, Cha YP. Cyclotron production of NCA ^{99m}Tc and ^{99}Mo: an alternative non-reactor supply source of instant ^{99m}Tc and ^{99}Mo—^{99m}Tc generators. *Int J Rad Appl Instrum [A].* 1991;42:643–657.
17. Takacs S, Szucs Z, Tarkanyi F, Hermanne A, Sonck M. Evaluation of proton induced reactions on Mo-100: new cross sections for production of Tc-99m and Mo-99. *J Radioanal Nucl Chem.* 2003;257:195–201.
18. Gagnon K, Benard F, Kovacs M, et al. Cyclotron production of ^{99m}Tc: experimental measurement of the ^{100}Mo(p,x)^{99}Mo, ^{99m}Tc and ^{99g}Tc excitation functions from 8 to 18 MeV. *Nucl Med Biol.* 2011;38:907–916.
19. Celler A, Hou X, Benard F, Ruth T. Theoretical modeling of yields for proton-induced reactions on natural and enriched molybdenum targets. *Phys Med Biol.* 2011;56:5469–5484.
20. Gutierrez CP, Mosley JR, Wallace TC. Electrophoretic deposition: a versatile coating method. *J Electrochem Soc.* 1962;109:923–927.
21. Morley TJ, Dodd M, Gagnon K, et al. An automated module for the separation and purification of cyclotron-produced 99mTcO4. *Nucl Med Biol.* 2012;39:551–559.
22. Tuominen SM. Preparation and sintering of fine molybdenum powder. *Powder Technol.* 1981;30:73–76.
23. Meyer HW, Baker JD, Ceckler WH, et al. inventors. Amax, Inc., assignee. Direct reduction of molybdenum oxide to substantially metallic molybdenum. US patent 4,045,216, 1977.
24. Lebeda O, van Lier EJ, Stursa J, Ralis J, Zyuzin A. Assessment of radionuclidic impurities in cyclotron produced ^{99m}Tc. *Nucl Med Biol.* 2012;39:1286–1291.
25. Srivastava SC. Is there life after technetium: what is the potential for developing new broad-based radionuclides? *Semin Nucl Med.* 1996;26:119–131.
26. Banerjee S, Pillai MR, Ramamoorthy N. Evolution of Tc-99m in diagnostic radiopharmaceuticals. *Semin Nucl Med.* 2001;31:260–277.
27. Morley TJ, Penner L, Schaffer P, et al. The deposition of smooth metallic molybdenum from aqueous electrolytes containing molybdate ions. *Electrochem Commun.* 2012;15:78–80.
28. Dmitriev S, Buklanov G, Starodub G, Shishkina T, Shishkin S. Production of high purity Tc-97 for environmental research. *Czech J Phys.* 1999;49:823–824.
29. Dash A, Knapp FF Jr, Pillai MR. ^{99}Mo/^{99m}Tc separation: an assessment of technology options. *Nucl Med Biol.* 2013;40:167–176.
30. Hou X, Celler A, Grimes J, Benard F, Ruth T. Theoretical dosimetry estimations for radioisotopes produced by proton-induced reactions on natural and enriched molybdenum targets. *Phys Med Biol.* 2012;57:1499–1515.

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