PRODUCING MEDICAL ISOTOPES USING X-RAYS*

M.S. de Jong#, CLS, Saskatoon, SK S7N 0X4, Canada

Abstract

In recent years, there have been frequent shortages of ^{99}Mo and its daughter isotope, ^{99m}Tc, which is the most widely used medical diagnostic radio-isotope. The Canadian Light Source is leading a project to demonstrate large-scale photo-neutron production of ^{99}Mo using a high-power 35 MeV electron linac as an alternative to production of ^{99}Mo from fission of highly enriched ^{235}U in research reactors. This talk will present the results that have been obtained to date and discuss the commercial potential for this alternative production scheme.

BACKGROUND

^{99m}Tc is the most common medical diagnostic radio-isotope, used in more than 80% of all diagnostic tests that use radio-isotopes. In Canada alone, more than 5000 medical tests use this isotope each day. The primary uses are for cardiac stress tests and bone scans. The ^{99m}Tc is derived as a daughter isotope from the decay of ^{99}Mo (see Fig. 1 for the decay scheme of ^{99}Mo).

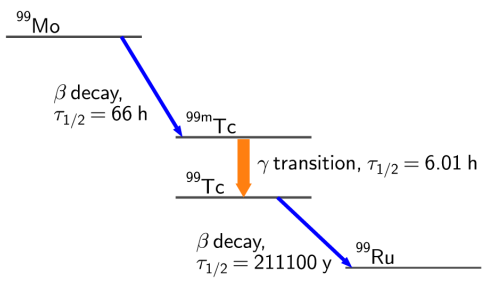

Figure 1: Decay scheme of ^{99}Mo.

The 66-hour half-life of ^{99}Mo allows sufficient time for world-wide distribution, and the 6-hour half-life of ^{99m}Tc reduces the radiation exposure to the patients. Diagnostic imaging with 99mTc uses SPECT (Single Photon Emission Computed Tomography) scanners which are relatively low cost and widely available.

The ^{99}Mo isotope is almost exclusively derived from fission of ^{235}U, where it is produced in approximately 6% of all fissions. The large-scale production of ^{99}Mo is done at several major research reactors world-wide, with the largest production at two aging reactors in Chalk River, Canada (NRU) and Petten, the Netherlands (HFR). Since the amount of ^{99}Mo produced reaches saturation within several days (e.g., a few times the 66 h half-life), the production is maximized using highly enriched ^{235}U (typically more than 90% enrichment).

In the past few years, there has been major shortages of ^{99}Mo arising because of planned, or unplanned, shut-downs of one or both of the major production reactors. Shortages occur in the hospitals within a couple of weeks of the production stoppage, placing great demands on the continued availability of these aging research reactors. At the same time, work on two dedicated isotope production reactors (the MAPLE project) at Chalk River was stopped because of high cost overruns and significant technical difficulties arising during commissioning.

THE CANADIAN PROGRAM

All of these difficulties prompted the Canadian government to review the issues with reactor production of these critical isotopes. The review highlighted three major issues:

- The aging research reactors (e.g., NRU first started in 1957) used for production needed replacements, with high capital costs and long construction and licensing times;
- The use of HEU (highly enriched uranium) for production while there are international efforts to eliminate HEU for all civilian applications; and
- The ^{99}Mo costs do not adequately reflect the capital costs of the reactors, nor the handling and disposal of the radio-active waste stream from the production.

In 2009, the Canadian government requested Expressions of Interest for alternative approaches to dealing with the isotope shortage. Following a review of the submissions, the government announced in 2010 that that NRU would stop producing ^{99}Mo in 2016. In addition, the government issued a call for proposals under the Non-reactor-based Isotope Supply Program (NISP) that had a total of $35M available to explore two alternative accelerator-based approaches to producing ^{99m}Tc: using conventional low-energy PET cyclotrons to directly produce ^{99m}Tc via the ^{100}Mo (p, 2n) ^{99}Tc reaction, or using electron linear accelerators to produce ^{99}Mo via the ^{100}Mo (γ, n) ^{99}Mo photo-neutron reaction. Project proposals were required to demonstrate a team with strong support from end-users (e.g., hospitals) and provide a business case for production without on-going federal government support. The ambitious goal was to ensure adequate alternative supplies of ^{99}Mo and ^{99m}Tc by 2016 when NRU production ceases. Four proposals were selected for funding, two supporting each approach to isotope production.

The Canadian Light Source (CLS) was the lead proponent on one of the two electron linac-based projects, with collaborators from the National Research Council (NRC) and major Canadian hospitals.

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#mark.dejong@lightsource.ca

ADVANTAGES OF ELECTRON LINACS FOR PRODUCTION OF ISOTOPES

At first glance, using electron linacs to make high-energy photons through bremsstrahlung radiation which then produces isotopes through a photo-nuclear reaction appears to be an inefficient means of production. It is a two-step process and electromagnetic interactions with the nucleus are usually significantly smaller than strong interactions with protons as the incident particle. As well, there are fewer possible reaction channels available, which may further restrict which isotopes can be produced.

However, for ^{99}Mo production at least, these possible limitations are not significant. In ^{100}Mo, like most heavy nuclei, there is a broad "giant dipole" resonance for photo-neutron reactions around 15 MeV photon energy which results in a significant enhancement of the reaction cross-section. As well, the radiation length of a high-energy photon (between 10 and 30 MeV) in ^{100}Mo is ~10mm, significantly longer than the range of a proton of the same energy. Consequently the effective target thickness is also much larger for photo-neutron reactions compared to proton-induced reactions. The reduced number of reaction channels limits the production of undesirable isotopes. For example, when using protons to directly produce ^{99}Tc from ^{100}Mo, there is the possibility of producing other Tc isotopes from other Mo stable isotopes that may be present in the enriched ^{100}Mo targets. Medical applications place strong limits on the amount of other radio-isotopes that may be present with the ^{99m}Tc. With the linac approach, there is no chance of producing any Tc isotopes directly, and photo-neutron reactions on other Mo isotopes usually results in stable Mo as well.

High-power electron linacs with output energy around 30 to 50 MeV have been available for many years, and the technology is well-known, reliable and not expensive. All these features are important for medical isotope production where high availability, low mean-time-to-repair and relative simplicity are important.

PROJECT SCOPE

The CLS project is a multi-disciplinary work covering all aspects of the production of suitable radio-pharmaceuticals that use ^{99m}Tc. The scope includes:

- ^{100}Mo target fabrication;
- Low-power testing (< 3kW) of the bremsstrahlung converter and target design to validate production yield estimates;
- Design and fabrication of high-power (>20 kW) converter and target assembly;
- Installation of a high-power 35 MeV industrial electron linac at CLS;
- Evaluation of the quality of the ^{99}Mo produced and the ^{99m}Tc separation process required for radio-pharmaceutical production; and
- Development of a suitable recycling process to recover the ^{100}Mo after irradiation and ^{99m}Tc separation for future targets.

ACHIEVEMENTS TO DATE

Target Manufacture and Recycling

Work on ^{100}Mo target manufacture was done by NRC's Industrial Materials Institute (IMI) in Boucherville. Initially solid natural molybdenum metal targets were evaluated but, since the extraction of 99mTc requires the targets to be dissolved to form a sodium molybdate solution, it was found that the rate of dissolution was too slow. Sintered powder targets were then tested, and found to have a much more suitable dissolution rate.

IMI also developed a process for extracting the molybdenum from a sodium molydate solution to reform molybdenum powder and then sintered targets with an overall recovery efficiency of more than 97%.

Low-Power Testing

Low-power tests for proof-of-concept evaluation of the ^{99}Mo production rates were performed by NRC's Institute for National Measurement Standards (INMS) on their Vickers 35 MeV linac. The initial tests, reported in reference [1], predated NISP funding and showed that production rates were within 20% of those predicted by Monte Carlo calculations.

A prototype automated radio-isotope separator (ARS-II developed by NorthStar Medical Radio-Isotopes LLC) was used to perform trial extractions of small amounts of ^{99m}Tc from the sodium molydate solution. The extraction efficiency was over 95% despite the low specific activity in the solution.

^{99m}Tc Quality

INMS performed a series of 12-hour irradiations of ^{100}Mo using the NRC linac. After each irradiation, which produced approximately 6 GBq (~160 mCi) of ^{99}Mo, the irradiated molybdenum disks were shipped to the Winnipeg Health Sciences Centre (HSC) where they were processed by the HSC Radio-pharmacy Research Group (RRG). Over twenty years ago, the RRG developed an automated solvent-solvent ^{99m}Tc extraction system for use with low specific activity ^{99}Mo produced by neutron capture on ^{98}Mo (an early method of ^{99}Mo production). The extraction system is equally suited to the low specific activity ^{99}Mo from electron linac production.

The molybdenum disks were dissolved and the ^{99m}Tc extracted daily for up to one week. The RRG performed all of their standard QA/QC checks on the ^{99}Mo and ^{99m}Tc. Several common standard ^{99m}Tc-tagged radio-pharmaceuticals (MDP, DTPA, MIBI, MAA) were produced and also placed through their standard QA/QC checks. The MDP and DTPA consistently passed all the tests, which included radio-chemical purity, pH, and 24-hour stability. The MIBI and MAA occasionally failed one or more of these tests, most likely because of the low amount of activity used for the tagging. The amount of

^{99}Mo activity delivered was typically the minimum amount that would be used for clinical diagnostic applications.

High-Power Linac Installation

In parallel with the work at NRC and HSC, CLS staff has worked on the design and fabrication of a high-power Ta converter for bremsstrahlung production and the ^{100}Mo target assembly (see Fig. 2) with the design goal of handling at least 20 kW of electron beam power at 35 MeV with a beam size of 5 mm diameter. Further design iterations, once some operating experience has been obtained with the initial design, will push the power handling to 40 kW.

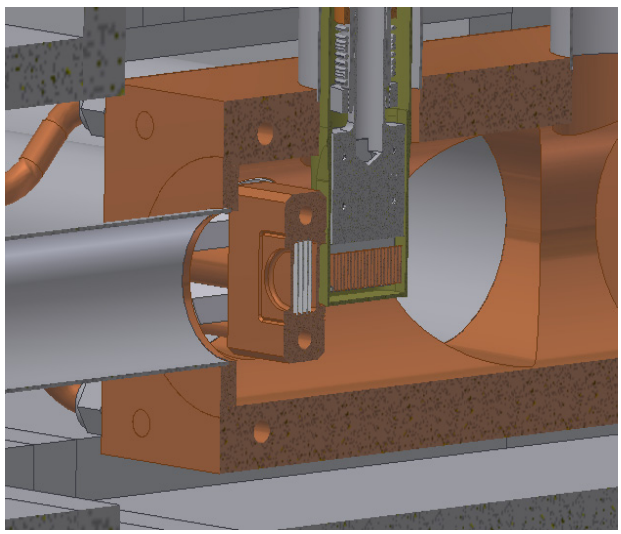

Figure 2: High-power target assembly showing the Ta converter and Mo target holder.

CLS also has worked on the facility design for a 35 MeV, 40 kW electron linac manufactured by Mevex Corp. The linac has been installed in an unused underground experimental hall (see Fig. 3 and 4), previously used for photo-nuclear experiments conducted with the 300 MeV electron linac that is now part of the main injector chain of the CLS storage ring.

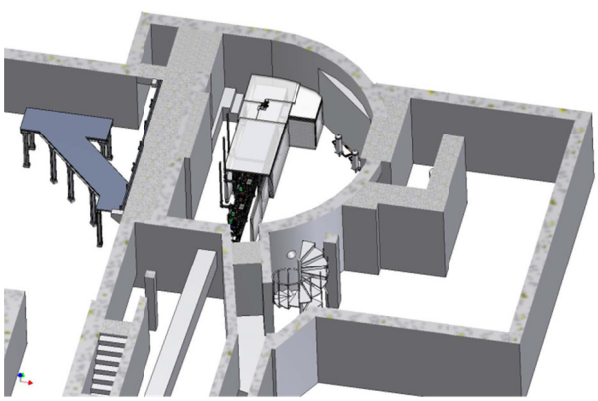

Figure 3: Layout of the CLS Medical Isotope linac.

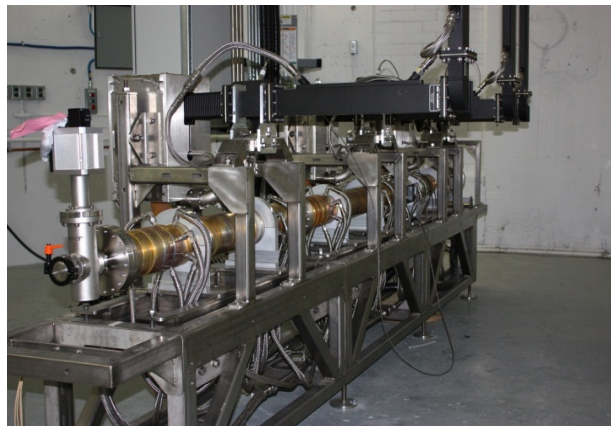

Figure 4: Mevex 35 MeV, 40 kW linac installed at CLS.

Based on the production rate measurements at NRC, the CLS medical isotope linac should be capable of producing up to 25 Ci (~1000 GBq) of ^{99}Mo per day at the full 40 kW power output. This is production rate is sufficiently high to support the demand from hospitals supporting a population base of 3 to 4 million people.

FUTURE WORK

The CLS isotope production linac will start be commissioned starting June 2012, and the first ^{100}Mo irradiations are planned for late summer 2012. These irradiations will also be evaluated by the Winnipeg HSC, and should be a realistic test of the quality and amount for normal use by a hospital.

Over the next year, CLS and Winnipeg HSC plan to obtain Health Canada approval for use of the linac-produced ^{99m}Tc for clinical use once the consistency of the production process is demonstrated. Beyond that time, CLS is looking for partners interested in establishing a small network of 3 to 5 linacs across Canada to meet the long-term Canadian needs, while working with other hospital radio-pharmacies to help with the transition to this new method of production.

ACKNOWLEDGMENT

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REFERENCES

[1] C. Ross et al., "Using the ^{100}Mo Photoneutron Reaction to Meet Canada's Requirement for ^{99m}Tc," Physics in Canada 66 (2010) 19.