Overcoming the $^{99m}$Tc Shortage: Are Options Being Overlooked?

Molybdenum-$99$ ($^{99}$Mo) ($\sim$66-h half-life) decays to $^{99m}$Tc ($\sim$6-h half-life), an isotope that is widely used for routine diagnostic applications in nuclear medicine. In the United States alone, it is estimated that $>$13 million $^{99m}$Tc diagnostic studies are performed annually. Separation of $^{99m}$Tc from the $^{99}$Mo parent requires repeated, efficient, and simple methods. Fission of $^{235}$U continues to be the source of high-specific-activity (HSA) fission $^{99}$Mo ($F$ $^{99}$Mo), which is isolated after chemical separation. Challenging logistics are required to coordinate the currently limited $^{99}$Mo reactor production sites in several countries. Processing chemistry for $F$ $^{99}$Mo is also complex and costly, and high levels of highly radioactive waste are generated. Realization of reliable, continued availability of $^{99m}$Tc has become more urgent because of repeated unexpected shutdowns of the current very limited number of aging reactors that are used for $F$ $^{99}$Mo production. Such repeated interruptions in $^{99m}$Tc availability demonstrate that alternative production strategies to provide $^{99m}$Tc on an international level must be critically evaluated.

The $^{99}$Mo shortage has been discussed in detail by the U.S. National Academy of Sciences and the Nuclear Science Advisory Committee of the Office of Nuclear Physics, U.S. Department of Energy (1). Canada has been a major supplier of $F$ $^{99}$Mo, and a panel of experts recently summarized the causes of insufficient $^{99}$Mo inventories in the “Expert Review Panel on Medical Radioisotope Production” (2). An annex to the “Nuclear Technology Review 2010,” published by the International Atomic Energy Agency (IAEA), summarized global initiatives undertaken to address the $F$ $^{99}$Mo shortage (3). A recent Google search for “molybdenum 99 shortage” resulted in more than a half million listings. The goal of this discussion is to review the expected relative benefits of alternative production and utilization of low-specific-activity (LSA) $^{99}$Mo on a broad scale to routinely provide $^{99m}$Tc.

Alternative HSA $^{99}$Mo and Direct $^{99m}$Tc Production Strategies

Any production strategy must carefully assess both practical and cost issues, as well as the time frames required before commercial distribution can be realized. Both initial capital and recurring costs must be evaluated, as well as costs associated with management and disposal of any long-lived radioactive waste. The current philosophy is that the per-dose price of $^{99m}$Tc should reflect every cost involved in the entire cycle of operation, including waste management, because country cross-border subsidies are not expected to be provided in the future (2,4,5).

Key alternative scenarios currently being evaluated for HSA $^{99}$Mo and $^{99m}$Tc production include the following technologies:

The aqueous homogeneous reactor (AHR). The AHR concept uses a critical assembly with a liquid $^{235}$U core. The fission-produced HSA $F$ $^{99}$Mo is obtained by processing the core solution at frequent intervals (6). A recent partnership between Covidien and Babcock & Wilcox is exploring the feasibility of this technology for routine commercial production of $F$ $^{99}$Mo (7).

Fission of $^{238}$U using linear accelerators. The use of high-power electron linear accelerators for photon fission of $^{238}$U targets has been widely discussed as another unique option for $^{99}$Mo production (8). This approach precludes any proliferation concern because of the proposed use of natural uranium. The economics of this approach were initially questioned in the Canadian Committee Report (2). This report suggested establishing 4 facilities with an estimated cost of $\geq500$ million CAN per facility. However, such a strategy would meet only the Canadian demand for $^{99}$Mo.

Direct cyclotron production of $^{99m}$Tc. Cyclotron-based direct production of $^{99m}$Tc is a feasible, attractive, and readily adaptable technology that offers an alternative for the large-scale production of clinical grade $^{99m}$Tc (9,10). $^{99m}$Tc can be produced by bombarding highly enriched $^{100}$Mo targets with intense proton beams with energies of 20–25 MeV. Many operating cyclotrons have proton beam currents (11) sufficiently high for production of several curies of $^{99m}$Tc per cycle. The specific activity of $^{99m}$Tc produced by the direct route is a concern that will require serious evaluation. Rapid decay of the short-lived $^{99m}$Tc would be expected to limit distribution to local or perhaps regional areas.

The principal challenges of these proposed untested technologies include high capital investments, expected prolonged timelines before market introduction, and regulatory challenges.

$^{99m}$Tc from LSA $^{99}$Mo

Direct reactor production of LSA $^{99}$Mo by irradiation of enriched $^{98}$Mo has not yet been adequately addressed. Many research reactors that could be used for network production of LSA $^{98}$Mo are available worldwide, as summarized in the IAEA database (12), in contrast to the limited number of reactors currently used for production of HSA $F$ $^{99}$Mo. A number of effective strategies are available for use of LSA $^{99}$Mo to obtain adequate specific
volume (i.e., concentration) of $^{99m}$Tc for routine clinical use. Approximately 251 research reactors currently operate worldwide (12); of these, approximately 134 have sufficient thermal neutron flux, target volume, and operational capabilities for routine production of LSA $^{99}$Mo. Fifty of these research reactors have thermal neutron flux $>1 \times 10^{14}$ neutrons/cm$^2$/sec, and the thermal flux of an additional 85 reactors ranges from $>1 \times 10^{12}$ to $1 \times 10^{14}$ neutrons/cm$^2$/sec. Seventy-eight of these reactors are already involved in radioisotope production, and these reactors have a good geographic distribution. Many of these reactors could be used for production of LSA $^{99}$Mo. Centrifuge technologies are readily available for the large-scale enrichment of $^{98}$Mo. The lower optimal thermal neutron flux limit required for production of $^{99}$Mo from irradiation of $^{98}$Mo depends on many factors, which include target volume requirements and the desired $^{99}$Mo product specific activity.

**LSA $^{99}$Mo Production for $^{99m}$Tc Clinical Use**

Because the $^{98}$Mo activation cross section is low (0.13 barn), the LSA $^{99}$Mo produced is generally unsuitable for fabrication of the traditional alumina-based column-type generators (the molybdenum mass is too high). However, several effective methods are available that would allow use of LSA $^{99}$Mo to obtain clinical grade $^{99m}$Tc. These include methyl ethyl ketone (MEK) extraction, postelution concentration of generator $^{99m}$Tc eluates, and use of high-capacity adsorbents or gel-type generators.

**MEK extraction of $^{99m}$Tc from $^{99}$Mo solution.** Use of MEK is a simple, established method to obtain $^{99m}$Tc-per-technetate of high radiochemical and radionuclidic purity from LSA $^{99}$Mo (13). In the late 1960s, a New Drug Application for such use of MEK-extracted $^{99m}$Tc. This method had been abandoned in developed countries with the introduction of F $^{99}$Mo and alumina-based column generator; however, it is still used in some developing regions. Reviving this technology could be an immediate step to help ameliorate future shortages of $^{99m}$Tc.

**Postelution concentration of $^{99m}$Tc from alumina-based generators.** Elution of the $^{99m}$Tc bolus requires significantly greater amounts of alumina to adequately bind the LSA $^{99}$Mo, as well as higher saline volumes. Although the bolus $^{99m}$Tc concentration (or specific volume, in millicuries per milliliter) is much lower and often too dilute for use with many “kits,” simple and effective postelution concentration technologies have been established that increase the $^{99m}$Tc specific volume. These methods have already been widely demonstrated and automated for use in the clinical arena for concentration of $^{188}$Re from the analogous $^{188}$W/$^{188}$Re generator (14, 15). These methods could be easily integrated with use of LSA $^{99m}$Tc alumina generators and implemented for central radiopharmacy use.

**New high-capacity adsorbents and “gel” type $^{99}$Mo/$^{99m}$Tc generators.** A polyzirconium compound with high molybdenum adsorption capacity has been reported (16). Recent studies also described preparation of nano zirconia and titania particles with higher molybdenum binding capacities (17). In addition, a new synthetic alumina material with very high capacity (binding as much as 400 mg of tungsten per gram of adsorbent) (18) is now being evaluated for use in the $^{99}$Mo/$^{99m}$Tc system. Use of this material would make it possible to fabricate generators that have much higher molybdenum binding than the alumina used to bind LSA $^{99}$Mo prepared in a network of research reactors. In addition to use of the gel-type generator, another option of broad interest is conversion of irradiated LSA $^{99}$Mo directly into a gel form, such as zirconium molybate, and column loading of the processed gel (19, 20). However, fabrication of the gel-type generators with reproducible and predictable performance is challenging. Further research is required to evaluate this technology as a viable option.

**Electrochemical-based $^{99}$Mo/$^{99m}$Tc generator system.** Electrochemical systems for separation of $^{99m}$Tc from LSA $^{99}$Mo solution have been developed (21). These systems involve a single electrolysis step using sodium molybdate solution and can be readily automated. Such a system would provide pharmaceutical quality $^{99m}$Tc.

Regulatory approval of $^{99m}$Tc as an approved pharmaceutical ingredient (API) obtained from any of these methods would, of course, be a prerequisite for clinical use. Automation of these systems would also be required.

**Advantages of LSA $^{99}$Mo**

The long-term availability of F $^{99}$Mo from the current limited and aging reactor network is of concern, and the potential production capabilities, costs, and regulatory issues associated with several proposed sophisticated new $^{99}$Mo and $^{99m}$Tc production strategies are unknown. For these reasons, use of the existing large research reactor network should be reassessed for direct production of $^{99}$Mo via neutron activation of $^{98}$Mo—an attractive and proven alternative to the use of F $^{99}$Mo. Radiopharmaceutical use of systems utilizing LSA $^{99}$Mo is more complex, represents a new paradigm, and would depend on the availability of the systems as APIs. But the well-established expertise and capabilities of centralized radiopharmacies would represent an important foundation for implementation of the best of these technologies. Regional strategies for availability of $^{99m}$Tc are important. What has worked best in developed countries and many world regions (i.e., F $^{99}$Mo) may require further careful assessment and may not be the best strategies to provide $^{99m}$Tc in the vast regions of the developing world.

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tor containing the hybrid pGB-CMVe promoter, the group was able to optically image T-cell effector function over time in response to tumor antigens in living mice. They concluded that this methodology “has the potential to accelerate the study of adoptive immunotherapy in preclinical cancer models.”

**Cancer Research**

**REVIEWS**

Review articles provide an important way to stay up to date on the latest topics and approaches and provide valuable summaries of pertinent literature. The Newsline editor recommends several reviews accessioned into the PubMed database in December. These include “Approaching MALDI molecular imaging for clinical proteomic research: current state and fields of application,” by Rauser et al. from the German Research Center for Environmental Health (Neuherberg, Germany) in the December issue of *Expert Review of Proteomics* (2010;7:927–941); “In vivo biodistribution of stem cells using molecular nuclear medicine imaging,” by Welling et al. from the Leiden University Medical Center (The Netherlands) on December 6 ahead of print in the *Journal of Cell Physiology*; “Nucleic acid aptamers for clinical diagnosis: cell detection and molecular imaging,” by Soontornworrarit and Wang from the University of Connecticut (Storrs) ahead of print in the December 15 issue of *Analytical and Bioanalytical Chemistry*; and “Current concepts and future directions in radioimmunotherapy,” by Lin and Iagaru in the December 1 issue of *Current Drug Discovery Technologies* (2010;7:253–262).

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**REFERENCES**


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