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

Molybdenum-99 (^{99}Mo) (~66-h half-life) decays to ^{99m}Tc (~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 >$500 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 1×10^{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-pertechnetate 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 molybdate, 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.

ACKNOWLEDGMENT

Research at the Oak Ridge National Laboratory is supported by the U.S. Department of Energy under contract DE-AC05-00OR22725 with UT-Battelle, LLC.

(Continued on page 28N)

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 Soontomworajit 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)

(continued from page 16N)

REFERENCES

1. Nuclear Science Advisory Committee Isotopes Subcommittee. *Isotopes for the Nation's Future—A Long Range Plan. Report for the Second of Two 2008 Charges to the Nuclear Science Subcommittee Advisory Committee on the Isotope Development and Production for Research and Application Program.* U.S. Department of Energy: Washington, DC; 2009. Available at: www.er.doe.gov/np/nsac/docs/NSACI_II_Report.pdf. Accessed on December 12, 2010.
2. *Report of the Expert Review Panel on Medical Isotope Production*. November 30, 2009. Available at: www.nrcan-rncan.gc.ca/eneene/sources/uranuc/pdf/panreprapexp-eng.pdf. Accessed on December 12, 2010.
3. International Atomic Energy Agency. *Nuclear Technology Review 2010: Production and Supply of Molybdenum-99 [annex 7].* Available at: www.iaea.org/About/Policy/GC/GC54/GC54InfDocuments/English/gc54inf-3-att7_en.pdf. Accessed on December 12, 2010.
4. Deconinck F, Ponsard B. "The Medical Isotope Crisis," Letter to the Community and Colleagues, March 16, 2009.
5. *The Supply of Medical Radioisotopes—An Economic Study of the Molybdenum-99 Supply Chain.* Nuclear Energy Agency, Organization for Economic Co-operation and Development, # NEA No. 696, 2010.
6. International Atomic Energy Agency. *Homogeneous Aqueous Solution Nuclear Reactors for the Production of Mo-99 and Other Short Lived Radioisotopes.* IAEA TECDOC Report 1601. Vienna, Austria: International Atomic Energy Agency; 2008.
7. Nuclear News. NNSA signs with GE Hitachi, B&W for Mo-99 development. January 28, 2010. Available at: www.news-medical.net/news/20100128/NNSA-helps-funding-development-of-domestic-radioisotope-supply.aspx. Accessed on December 12, 2010.
8. Ruth T. Accelerating production of medical radioisotopes. *Nature.* 2009;457:536–537.
9. 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.
10. Guerin B, Tremblay S, Rodrigue S, et al. Cyclotron production of ^{99m}Tc: an approach to the medical isotope crisis. *J Nucl Med.* 2010;51[4]:13N–16N.
11. International Atomic Energy Agency. *Cyclotron-Produced Radionuclides: Principles and Practice*. Technical Report Series 465. Vienna, Austria: International Atomic Energy Agency; 2008.
12. International Atomic Energy Agency. Operation Research Reactors in the World [database] Available at: www.naweb.iaea.org/napc/physics/research_reactors/database/RR%20Data%20Base/datasets/foreword_home.html. Accessed on December 20, 2010.
13. International Atomic Energy Agency. *Alternative Technologies for ^{99m}Tc Generators.* IAEA TECDOC Report 852. Vienna, Austria: International Atomic Energy Agency; 1995.
14. Knapp FF Jr, Beets AL, Guhlke S, et al. Development of the alumina-based tungsten-188/rhenium-188 generator and use of rhenium-188 labeled radiopharmaceuticals for cancer treatment. *Anticancer Res.* 1997;17:1783–1796.
15. Knapp FF Jr. Rhenium-188. A generator-derived radioisotope for cancer therapy. *Cancer Biother Radiopharm.* 1998;13:337–349.
16. Sarkar SK, Saraswathy P, Arjun G, Ramamoorthy N. High radioactive concentration of ^{99m}Tc from a zirconium [^{99}Mo]molybdate gel generator using an acidic alumina column for purification and concentration. *Nucl Med Commun.* 2004;25:609–614.
21. Chakravarty R, Dash A, Venkatesh M. A novel electrochemical technique for the production of clinical grade ^{99m}Tc using (n,γ) ^{99}Mo. *Nucl Med Biol.* 2010;37:21–28.

M.R.A. Pillai, PhD
Bhabha Atomic Research Centre
Mumbai, India
F.F. (Russ) Knapp, Jr., PhD
Oak Ridge National Laboratory
Oak Ridge, Tennessee