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Future Alternatives to Molybdenum-99 Production for Medical Imaging

Environmental Scan

Context

Up until recently, Canada produced approximately half the world's supply of molybdenum-99,[1] and the US imported approximately 50% to 80% of its supply from Canada.[2,3] In 2008, there were no facilities in the US manufacturing molybdenum-99.[1] Global efforts to reduce the proliferation of nuclear weapons and deter terrorism are believed, in part, to account for the lack of medical isotope production facilities.

Concerns about the long-term supply of medical isotopes have been further confounded by the decision in early 2008, by Atomic Energy of Canada Limited, to cancel the construction of the two MAPLE reactors. Once completed, these reactors would have been the world's first reactors dedicated exclusively to medical isotope production and could have supplied the entire global demand for molybdenum-99.[1] Approximately $300 million was spent over a period of 15 years on their construction.[4]

The recent lack of reliable supplies of technetium-99m, the medical isotope produced from molybdenum-99, has focused international attention on the lack of global production facilities. The repeated shutdown of Canada's Chalk River nuclear reactor that produces molybdenum-99, and the subsequent cancellation and delay of diagnostic testing throughout Canada and the US, has given industry the impetus to seek alternative solutions in medical imaging.

Objectives

The purpose of this report is to identify new and emerging technologies that may play a role in providing either solutions to the supply issue of molybdenum-99 or alternate technologies that circumvent the need for nuclear reactor-based molybdenum-99 over the next five to 15 years.

Findings

Solutions to the disruption in the supply of medical isotopes fall into three broad categories: the building of new, or the modification of existing, nuclear reactors and accelerators to produce medical isotopes; the development of alternative isotopes that do not rely on existing nuclear reactor infrastructures; and a reliance on new and emerging medical imaging devices that bypass the need for technetium-99m, the most commonly used radioisotope in medicine. Table 1 below summaries these technologies and their product lifecycle status.

The building of new, or the utilization of existing, nuclear reactors and accelerators

On April 28, 2009, MDS Nordion, Canada's radioisotope production facility, and TRIUMF, Canada's national laboratory for particle and nuclear physics, announced a collaboration to study the feasibility of producing a viable and reliable supply of photo-fission-produced molybdenum-99.[5] Technetium-99m, the radiopharmaceutical used in more than 80% of diagnostic applications, derives from molybdenum-99.[6] The technology that is the focus of this partnership is photo-fission accelerator technology as opposed to nuclear reactor technology.[5] The technique processes molybdenum-99 by exposing uranium to high-intensity light beams that are generated by an accelerator. The process requires uranium-238, a less fissile uranium isotope than that used by reactors.[7]

Table 1: Summary of Medical Imaging Technologies and Their Status		
Alternative	**Technology Description**	**Status (Investigational[1] / Emerging[2] / Available)**
Nuclear reactor/accelerator	Revive existing	Available
	Photo-fission accelerator	Investigational
	Aqueous homogeneous	Investigational
	Neutron beam	Investigational
	Neutron reactor	Investigational
Molecular imaging	PET/CT	Available
	PET/MRI, SPECT/CT, PEM, D-SPECT	Emerging
	SPECT/MRI	Investigational
	Photoacoustic	Emerging
	CT/MRI/3-D, image-guided cell therapy	Investigational
Radiopharmaceutical tracer solutions	SPECT tracers: I-123 MIBG, I-123 BMIPP	Emerging
	PET tracer: BMS747158	Emerging
	SPECT tracer: RAFT-RGD, radioiodinated compounds	Investigational
	SPECT tracer: Tl-201 tracer. Replaces Tc-99 tetrofosmin (Myoview) and Tc-99m sestamibi for cardiac perfusion imaging	Available
	PET tracer: F-18 fluorine. Replaces Tc-99m MDP as bone-imaging agent	Available

CT = computed tomography; CT/MRI/3-D = computed tomography combined with magnetic resonance imaging and 3-D imaging; D-SPECT = dynamic single photon emission computed tomography; I-123 MIBG = Iodine-123 metaiodobenzylguanidine; I-123 BMIPP = Iodine-123 p-iodophenyl-3-(R,S)-methylpentadecanoic acid; MDP = methylene diphosphonate; MRI = magnetic resonance imaging; PEM = positron emission mammography; PET = positron emission tomography; PET/CT = positron emission tomography combined with computed tomography; PET/MRI = positron emission tomography combined with magnetic resonance imaging; RAFT-RGD = regioselectively addressable functionalized template–arginine-glycine-aspartic acid; SPECT = single-photon emission computed tomography; SPECT/CT = single-photon emission computed tomography combined with computed tomography.

[1]An investigational technology is one that is either at the conceptual stage, anticipated, or in early stages of development, through to a technology that is undergoing bench or laboratory testing.

[2]An emerging technology is one that is not yet adopted by the health care system, usually in phase II or III clinical trials or pre-launch. The time horizon is zero to five years before introduction.

This accelerator-based method would eliminate the security risks associated with making the isotopes with weapons-grade uranium, the process used at the Chalk River nuclear reactor. In addition, the photo-fission accelerator technique can be turned on or off at will, and it is comparatively inexpensive to decommission. However, an accelerator-based production facility would require substantially more electrical power than a reactor-based facility.[1] The time frame for when this production source is likely to be operational has not yet been determined.

At the beginning of 2008, TRIUMF set up a task force to look at alternative molybdenum-99 production methods. Two other accelerator-driven processes were reviewed: the neutron-capture process and the photo-neutron process. However, it was the photo-fission option that stood out as being the most commercially viable.[1]

Inspired by the shortages and supply options of isotopes, Advanced Medical Isotope Corporation (AMIC), a US company, was established in 2006 to fulfill the US's domestic supply of medical isotopes. Using modified production practices, AMIC is working toward launching compact generator systems and developing and

implementing proprietary devices to produce short-lived as well as longer-lived isotopes. The corporation entered into agreements with Idaho State University, the University of Missouri at Columbia, the State University of New York at Buffalo, and the University of Utah to produce isotopes.

Over the next two to three years, AMIC plans to produce 13 isotopes in regional facilities across the country. AMIC has identified the following 13 isotopes as being the most important for commercial and research purposes: actinium 225, carbon 11, cobalt 57, copper 64, fluorine 18, gallium 68, indium 111, iodine 123, iodine 124, iodine 131, technetium 99, rubidium 82, and thallium 201.[2]

In 2009, AMIC and the US Department of Energy partnered on a two-year project with the Kharkov Institute of Physics and Technology in the Ukraine to develop and market compact systems technology for producing medical isotopes. The new production method is based on technology being developed by the Kharkov Institute. The method generates an intense neutron beam at high fluence rate under controlled conditions, with an advanced target design for efficient production of neutron-rich medical isotopes.[8]

In January 2009, Babcock & Wilcox, an energy technology supplier, signed an agreement with Covidien, a health care products company, to develop solution-based reactor technology for the manufacture of molybdenum-99. Production will use aqueous homogenous reactor technology utilizing low-enriched uranium.[9] This facility could potentially supply 50% of the US market and could be operational by 2012.[10]

SNM, an international scientific and medical organization, recently set up an Isotope Availability Task Force to look at potential solutions for creating a domestic supply of medical isotopes in the US. The task force examined the possibility of reviving domestic production of molybdenum-99 at facilities like the University of Missouri Research Reactor Center in Columbia, Missouri. Production of molybdenum-99 at this site could begin in 2012 and could potentially meet approximately 50% of the current market need.[10] It is believed that the Annular Core Research Reactor at Sandia National Laboratories in Albuquerque, New Mexico, was considered as another possibility, although the US Department of Energy would have to modify the reactor's current designation.[10]

In 2008, URENCO, an international energy and technology group, and the University of Delft in the Netherlands collaborated to patent a new technique to produce technetium-99m. This new method of producing molybdenum-99 from naturally occurring molybdenum-98, the most common molybdenum isotope, does not require a high neutron influx reactor.[11]

Molecular Imaging Solutions

SPECT and PET hybrids and other molecular imaging solutions

Imaging techniques are key tools for understanding living systems at a molecular and physiological level. The *New England Journal of Medicine* selected medical imaging as one of the 11 most important innovations of the past 1,000 years.[12] Advances in medical imaging technologies have allowed physicians to detect, diagnose, and manage diseases earlier and more accurately.

The most common molecular imaging tools include molecular magnetic resonance imaging (MRI), magnetic resonance spectroscopy, optical bioluminescence imaging, optical florescence imaging, targeted ultrasound, single-photon emission computed tomography (SPECT), and positron emission tomography (PET).[13] However, it is SPECT and PET that are the most commonly used molecular imaging modalities.[1]

SPECT combined with computed tomography (SPECT/CT) and PET combined with CT (PET/CT) operate on the same basic design principles by providing images of the structure and function of tissue and organs that reflect biochemical processes and blood flow. The major attribute of PET and SPECT, which distinguishes them from MRI and X-ray CT methods, is the high sensitivity with which they can detect metabolic activity and trace the concentration of specific proteins in the body.[14] CT and MRI, on the other hand, provide images of the structure of tissue and organs based on rich anatomical detail.

Recent advances in technology have combined PET and SPECT with CT. The benefit of these combined modalities is faster acquisition times with increased performance in resolution and sensitivity. This allows clinicians to more accurately diagnose disease, provide better therapy planning, and prevent unneeded surgeries and other invasive procedures.

The development of hybrid imagers originated with PET/CT. Whereas PET-alone evolved slowly as an imaging tool relative to other imaging modalities, PET/CT has become the preferred technology for PET imaging. PET/CT scanners have been so successful that none of the major manufacturers currently offers stand-alone PET scanners for commercial sale.[15] In 2005, PET/CT comprised 95% of total PET billings in the US.[16]

Canada, unlike the US and other countries, has not experienced universal clinical acceptance of PET. This is believed to be because of PET's high capital and operating costs and a perceived need to more thoroughly evaluate its suitability for particular clinical applications.[16] The new hybrid PET/CT, on the other hand, is gaining faster acceptance in Canada than stand-alone PET.

Although PET was first to widely exploit the hybrid capabilities of CT, SPECT/CT has evolved in its shadow to offer the same advantages. The most important application of PET and PET/CT is in oncology;[16] this is because whole body imaging is used to identify primary cancer sources and scan for metastatic disease. In comparison, SPECT is more focused on organ function.[16] Although some SPECT procedures employ whole body scanning, such as bone scans, these are not as specific as the organ scans. Also, SPECT/CT has a unique application with thyroid, parathyroid, neuroendocrine, and prostate gland cancers because these cancers can not be detected by PET tracers.[17]

The most important application of SPECT and SPECT/CT is in cardiology. Approximately, 60% of SPECT/CT procedures are performed in this field. However, orthopedics, oncology, and infection imaging are emerging areas that can benefit from SPECT/CT.[17]
Potential future applications of SPECT/CT imaging include estimation of patient radiation dosimetry for radiation therapy planning; hepatic infusion chemotherapy, after beta-emitter therapy, for quantitation to develop a measurement similar to the standardized uptake value in PET; and guided biopsy.[18]

With constant upgrades in multislice CT technology, the diagnostic applications of SPECT/CT are likely to increase. However, because the main benefit of SPECT/CT would be attenuation correction and anatomic image fusion, except for cardiology, the development of 64- and even 256-detector row CT is unlikely to affect SPECT/CT in most applications.[18] This may be advantageous to SPECT/CT because it will help keep the costs down.

According to the International Atomic Energy Agency, the future value of SPECT/CT in terms of clinical impact on patient care and cost-effectiveness, as compared with PET/CT, may improve with the development of better instruments, newer computer-based procedures for image analysis and display, and new technetium-99m-labelled agents for visualizing biologically significant events.[19] SPECT still constitutes the majority of nuclear radiologists' workload and, as such, the potential market for SPECT/CT could be larger than that for PET/CT. SPECT and SPECT/CT are less expensive options from an equipment and pharmaceutical perspective.[17]

Despite the success of hybrid nuclear imaging, there are some drawbacks to the use of CT as a complementary anatomical imaging modality. Firstly, CT adds radiation dose to the overall examination. Secondly, CT provides relatively poor soft tissue contrast in the absence of oral and intravenous iodinated contrast.[15] MRI, on the other hand, is not impacted by these limitations, and it can provide more progressive functional techniques, such as diffusion and perfusion imaging as well as spectroscopy.[15]

PET/MRI is a novel non-invasive imaging technique that was catalyzed by the clinical success of PET/CT and SPECT/CT. PET/MRI combines the soft-tissue contrast, high specificity, and structural detail of MRI together with PET's sensitivity in assessing physiological and metabolic state.[16] It is speculated that technological evolutions of PET/MRI may replace PET/CT as the molecular multimodality imaging platform of choice for neurologic and central nervous system

indications. In the area of small-animal research, where high soft tissue contrast is required, and the scan time as well as radiation dose are critical factors, the combination of PET and MRI would be beneficial compared with PET/CT.[20]

In the clinical setting, PET/MRI is intended to improve health care by increasing our understanding of the causes, effects, and development of disease processes such as cancer, where it is believed to have a significant impact,[21] and Alzheimer disease, schizophrenia, and metabolic disorders such as osteoporosis and atherosclerosis.[22] It could also advance diagnosis and help monitor treatment, particularly related to cancer and bone disease. In addition, PET/MRI could help verify the efficacy of certain drugs by enabling clinicians to observe how drugs travel through the body.

PET/MRI offers the potential to provide more structural detail than CT scans,[23] especially when imaging soft tissue. And MRI does not expose the patient to ionizing radiation.[23]

Recent advances in gamma ray detector technology have paved the way toward the development of fully magnetic-field-insensitive high-performance PET detectors.[20]

The first PET/MRI images were acquired on a dedicated brain imaging prototype system. The technology was supported with industrial backing from Siemens, which debuted its first non-commercial PET/MRI brain imager in 2006. There is still commercial interest in producing PET/MRI devices, but at present none is available as a clinical product.[21] There is a belief that investment in these technologies will be justified by their improved throughput, patient compliance, and diagnostic accuracy.[21]

Thus, although the technology required to combine PET with MRI is readily available, it will continue to develop and to affect clinical practice within the next decade.[21]

Because of advancements in solid-state gamma camera technology, SPECT/MRI is also on the horizon, but this too is in its early stages of clinical development.[21]
D-SPECT is a novel SPECT system for nuclear cardiology. D-SPECT technology produces cross-sectional images of the heart using advanced solid-state detectors.[24] The potential advantage of D-SPECT in comparison with conventional dual-headed SPECT cameras is that it could provide better energy resolution and higher sensitivity,[25] thereby decreasing radiation dose or imaging time and opening the door to the development of entirely new tracers.[25]

Positron emission mammography (PEM), is an organ-specific high-resolution PET scanner that is not affected by either breast density or a woman's hormonal status, two factors that limit the effectiveness of standard mammography and MRI at detecting cancer.[26] PEM technology uses two planar detectors integrated into a conventional mammography system that enables the co-registration of a mammographic and emission fluorine-18-2-fluorodeoxyglucose (FDG) image.[26] The ability to use PEM technology to biopsy lesions has also been investigated and appears feasible. This technology is in its infancy, but preliminary reports are promising for the detection of ductal carcinoma in situ (DCIS). No imaging device to date has been able to accurately image DCIS unless it happens to be associated with pleomorphic calcifications seen on mammography. This is an important future component of the technology if it is to be useful clinically. In addition, further refinements, including combining PEM with tomographic acquisition (using detectors that rotate about the breast), have the potential to improve detection compared with the technology that is based on stationary detectors. Whereas further refinements to the technology are needed, it is believed that its potential to detect early breast cancer is significant.[27]

Photoacoustic imaging

Photoacoustic imaging (also known as "optoacoustic" or "thermoacoustic imaging") is a hybrid imaging modality that is believed to be a fast-growing biomedical imaging technology.

A photoacoustic image is formed by irradiating tissue with pulses of nanosecond laser light that induces the transient thermoelastic expansion of the tissue. A wideband ultrasonic wave is emitted that can be detected by an ultrasonic receiver. These waves are then converted into high-resolution 3-D images of

tissue structure. Because the waves contain tissue-specific information about absorption, the technique allows non-invasive in vivo imaging based on absorption contrasts.[28]

Photoacoustic imaging has already become an important tool for studying small-animal models and providing unique insights into disease pathogenesis, drug development, and effects of therapy.[29] A recent animal study demonstrates how a photoacoustic system was used to image the cardiovascular dynamics of mice. Because of the rapid heart rates of mice, cardiovascular imaging requires high frame rate imaging modalities. Currently, commonly used small animal imaging techniques such as micro-PET and micro-CT do not permit imaging frame rates sufficient for the cardiovascular visualization of mice.[30]
It is believed that photoacoustic imaging may play a role in the future of mammography as a mass screening alternative to current gold standards.[31,32] It is also predicted that photoacoustic imaging may be useful in the following clinical areas: melanoma detection using photoacoustic microscopy, photoacoustic endoscopy, simultaneous functional and molecular photoacoustic tomography, photoacoustic tomography of gene expression, Doppler photoacoustic tomography for flow measurement, photoacoustic tomography of metabolic rate of oxygen, photoacoustic mapping of sentinel lymph nodes, multiscale photoacoustic imaging in vivo with common signal origins, photoacoustic and thermoacoustic tomography of the brain, and low-background thermoacoustic molecular imaging.[32]

One of the advantages of photoacoustic imaging is the strong correlation between optical absorption and hemoglobin concentration and/or oxygenation. Oxygenation of the blood is believed to be indicative of the speed with which a tumour grows. If photoacoustics is able to offer information about oxygenation, it is believed it may also be able to offer information that may help inform a physician's choice of treatment.[31]

Siemens Corporate Research is currently working with the Beckman Laser Institute to develop a novel software imaging platform for a hand-held laser and broadband diffuse optical spectroscopy probe. This device could be used for breast imaging. The probe would work in a similar way to how an ultrasound transducer works, but with light instead of sound. This technology is approximately five years away from clinical production.[33]

Also in development is an automated microscope, a device that combines imaging in the near infrared part of the spectrum with hematoxylin and eosin staining. The microscope's image-processing functions will be driven by a software platform that is currently in development. The new microscope could potentially automate the detection and classification of cancer cells with a high level of confidence, making early detection more effective.[33]

Other hybrid imaging technologies

Canada's Lawson Health Research Unit is currently investigating the plausibility of combining prostate cancer images using CT, MRI, 3-D ultrasound, and nuclear medicine techniques to create a single technological platform to predict the location of cancer within the prostate. This research has the potential to advance patient care in prostate cancer diagnosis. The principle behind the research may also have applications for many other types of cancer.[34]

The European Institute for Biomedical Imaging Research (EIBIR), founded in 2006, is working on a project called "ENCITE" — European Network for Cell Imaging and Tracking Expertise. This project is focused on in vivo image guidance for cell therapy and the development and testing of new MRI imaging methods and biomarkers. Currently, there is no single imaging modality that meets the requirements of cell therapy. It is predicted that these technologies will eventually be used for the treatment of cancer, cardiovascular diseases, and diabetes.[35] The EIBIR is also involved in the HAMAM project — European Highly Accurate Breast Cancer Diagnosis through Integration of Biological Knowledge, Novel Imaging Modalities, and Modelling.

The future of radiopharmaceutical tracers

There is ongoing interest in developing more easily available and cheaper isotopes. Both PET

and SPECT imagers require tracers that emit small amounts of radiation throughout the body that make it possible to visualize disease and treatment processes. It is believed by some that the future of medical imaging lies in the development of new tracers.[36]

Whereas alternatives to technetium-99m, SPECT's most widely used tracer, are sought because of continued disruptions in its supply, alternatives to FDG, PET's most widely used tracer, are in demand because FDG is expensive and difficult to process.

Two new I-123-labelled tracer agents, metaiodobenzylguanidine (I-123 MIBG) for imaging the sympathetic nervous system of the heart and p-iodophenyl-3-(R,S)-methylpentadecanoic acid (I-123 BMIPP) for imaging fatty acid metabolism and for use in emergency departments as an evaluation tool for patients with episodes of chest pain, have recently completed clinical trials. The latter tracer, I-123 BMIPP, is marketed as Zemira and is believed to be the only tracer that can directly link symptoms to true cardiac tissue ischemia.[37] The University of Ottawa's Heart Institute is working on tracer development. MDS Nordion has helped fund a new lab to focus on early stage characterization of tracers.

There is also a PET F-18-labelled perfusion tracer, BMS747158. This is a mitochondrial complex 1 inhibitor, which has a very high extraction fraction by the myocardium and may allow the use of exercise stress, which has not been possible with existing PET perfusion tracers.[38]

A recent study characterized this tracer in a rat model of permanent and transient coronary occlusion using small-animal PET. The study found that the kinetic parameters may allow for assessment of flow using exercise–rest protocols similar to those used in combination with exercise and rest perfusion SPECT.[24]

Regioselectively addressable functionalized template–arginine-glycine-aspartic acid (RAFT-RGD) is another new tracer that is believed to have potential for targeting and imaging.[39] A recent animal study has evaluated the potential of 99mTc-labelled RAFT-RGD (99mTc-RAFT-RGD) for the non-invasive in vivo SPECT molecular imaging of neoangiogenesis.[40]

Another new tracer agent for SPECT imaging of the noradrenaline and peripheral benzodiazepine receptors is also in development. This project involves radioiodinated compounds for SPECT imaging of neurological receptors that are implicated in a range of neurological disorders such as clinical depression, Parkinson disease, Alzheimer disease, anxiety, and stroke. The success of this project may lead to imaging agents with greater selectivity for the peripheral benzodiazepine receptor.[41]

Knowledge Gaps

Results of this report are based on a limited literature search. Results include articles published between 2005 and May 2009 and are limited to English-language publications. As such, the comprehensiveness of this report cannot be confirmed. In addition, although the technologies identified in this report have potential for future adoption, it is difficult to determine which products will have any real place in the future. There are a number of determinants that may influence their commercial viability. For example, there is no guarantee that projects at the investigational stage of a product's lifecycle will see it through to successful launch — the MAPLE reactors are a case in point. In addition, there is no certainty that a technology that makes it to launch will command mainstream clinical acceptance; especially if the technology is expensive, is not reimbursable, and is aimed at replacing established modalities where there is already significant capital, infrastructural, and technological investment. Also, unanticipated technological developments may render these technologies obsolete.

Conclusion

There are a number of accelerator and nuclear-based technologies that may play a potential role in providing solutions to the disruption in the production of molybdenum-99. There are also a variety of new and emerging technologies that could possibly bypass the need for nuclear reactor-based medical isotopes. PET/CT has already been successful here, and its full potential may not have been entirely realized.

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