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Future Alternatives to Molybdenum-99 Production for Medical Imaging, 2010

Environmental Scan

Context

The shutdown of Atomic Energy of Canada Limited's (AECL) Chalk River nuclear reactor in May 2009, and the subsequent ongoing supply disruption of technetium 99 (^{99m}Tc), the isotope used in approximately 80% of all nuclear medicine procedures,[1] forced the medical community to seek alternative diagnostic and therapeutic imaging solutions. The extended isotope supply disruption was further confounded by the temporary shutdown, in August 2009, of an isotope reactor in The Netherlands.

The impact on Canadian patients and the medical community has been considerable: according to a recent national survey, approximately 22% fewer cardiac, lung, and bone diagnostic tests were performed in October 2009, when the Chalk River reactor was off-line, compared to October 2008, when the reactor was working. As well, medical facilities have had to find new ways to prioritize patients, reschedule or cancel some imaging appointments, and use alternative tests to diagnose some conditions.[2]

In July 2010, Canada's nuclear regulator, the Canadian Nuclear Safety Commission, authorized the Chalk River facility to resume production after more than a year of suspended operations.[3] At the end of August, 2010, the Chalk River reactor resumed production of isotopes.[4]

While the current isotope supply disruption is expected to be alleviated once the Chalk River reactor is working, the reactor is scheduled to be permanently decommissioned in 2016. Subsequently, alternative medium- and long-term isotope solutions are needed. Concerns about the long-term supply of medical isotopes have been intensified by the decision in early 2008, by AECL, to cancel the construction of the two Multipurpose Applied Physics Lattice Experiment or MAPLE reactors. Once completed, these reactors would have been the world's first reactors dedicated exclusively to medical isotope production and were predicted to be capable of supplying the entire global demand for molybdenum-99 (^{99}Mo);[5] ^{99m}Tc is generated from ^{99}Mo. According to Robert Atcher, chair of the American-based Society of Nuclear Medicine's Domestic Isotope Availability Task Force, current problems faced by the United States (US) molecular imaging community are due in part to the cancellation of the MAPLE reactor project.[6]

Objectives

This report is an update to an environmental scan published by CADTH in August, 2009 (*Future Alternatives to Molybdenum-99 Production for Medical Imaging*). 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 ^{99}Mo or alternate technologies that circumvent the need for nuclear reactor-based ^{99}Mo over the next five to 15 years.

Results of this report are based on a limited literature search of articles published between 2005 and July 2010 that are written in English. The comprehensiveness of this report cannot, therefore, be confirmed.

In some cases, the technologies listed in this report are not new or emerging; rather, interest in them may have been revitalized as a result of the isotope supply disruption, recent technological innovations may have made them more viable, or there may have been a recent expansion in their clinical applications.

Findings

Solutions to the disruption in the supply of medical isotopes fall into three broad categories:

- Building new, or modifying existing, nuclear reactors and accelerators to produce medical isotopes
- Producing new and emerging medical imaging devices that bypass or minimize the need for reactor-produced ^{99m}Tc
- Developing alternative isotopes that do not rely on existing nuclear reactor infrastructures.

Table 1 summarizes these technologies and their product life-cycle status.

Although the technologies identified in this report have the potential for future adoption, it is difficult to determine which products will have any real place in the future. The technical feasibility of many of the alternative production methods is still being evaluated, and 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 life cycle will see it through to successful launch. 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.

The Building of New (or the Modification of Existing) Nuclear Reactors/Accelerators

Canadian activity

Alternate methods of isotope production are currently being investigated in Canada. In 2009, the Government of Canada appointed an independent Expert Review Panel on Medical Isotope Production to assess more reliable ways of supplying isotopes. In November 2009, the Panel published its findings.[7] The Panel made a number of recommendations that include the building of a multi-purpose research reactor, setting up new cyclotron-based ^{99m}Tc production programs, researching linear accelerator-based ^{99}Mo transmutation technology, and the creation of a dedicated isotope facility.[7]

The Government of Canada asserted its commitment to secure a reliable supply of medical isotopes with the announcement in June 2010 of an investment of $48 million over two years for research, development, and application of medical isotopes. The funding is to support the development of non-federal supply options that will replace the Chalk River source when the facility is decommissioned in 2016. While the Canadian government did not endorse building a new reactor — the key recommendation of the panel's report— it did pledge to invest in non–reactor-based production techniques.[8]

These non–reactor-based alternatives will include cyclotron-based production of ^{99m}Tc, and linear accelerator-based production of ^{99m}Tc via the transmutation of molybdenum-100 (^{100}Mo). ^{100}Mo is a naturally occurring radioactive isotope. A key advantage to using cyclotron-produced isotopes is that Canada already has a skeletal infrastructure in place — there are 10 operating cyclotrons in Canada's pubic health system, and two more are anticipated.[9] Also, cyclotrons are accelerators that are smaller and less expensive than nuclear reactors. According to a report by the European Industrial Association for Nuclear Medicine and Molecular Healthcare, the demand for ^{99}Mo will remain critical, at least for the next decade, as the techniques and equipment relying on ^{99m}Tc are still used in the vast majority of nuclear medicine procedures. It is therefore believed that investment in accelerator-based isotope production for nuclear medicine imaging is important.[10]

In June 2010, the Canadian government issued a call for project proposals to expand medical isotope supply chain options in Canada. The deadline for submitting project proposals was July 26, 2010.

Table 1: Summary of Medical Imaging Technologies and Their Status		
Alternative	**Technology Description**	**Status (Investigational*/ Emerging†/Available)**
Nuclear reactor/accelerator	Revive existing	Available
	Convert HEU to LEU	Available
	Photofission accelerator	Investigational
	Aqueous homogeneous	Investigational
	Neutron beam	Investigational
	Neutron reactor	Investigational
Molecular imaging	PET/CT, SPECT/CT, resolution recovery software, CMRI	Available
	PET/MRI, PEM, D-SPECT, HD PET, TOF/PET, DbPET/CT, hyperpolarization MRI, CEST, photoacoustic, optical	Emerging
	CT/MRI/3-D, image-guided cell therapy, SPECT/MRI, DbCT, VECT, DSCT	Investigational
Radiotracer	SPECT tracers: ^{123}I-MIBG, ^{123}I- BMIPP	Emerging
	PET tracer: BMS747158, ^{82}Rubidium, ^{11}C AFM, ^{18}F-FLT, ^{18}F-FET, LM1195, ^{18}F-FBnTP, ^{18}F-Fallypride, ^{18}F-MAU, FET, ^{18}F-MISO	Emerging
	PET tracer: ^{68}Gallium to replace ^{99m}Tc for pulmonary embolism, chronic obstructive pulmonary disease, lung cancer, cardiac imaging, LMI1195, florbetaben, ^{18}F-Av-45, ^{89}Zirconium, Anti-^{18}F-FACBC, FES, ^{18}F-FEAU, ^{18}F-FHBG	Investigational
	SPECT tracer: RAFT-RGD, radioiodinated compounds	Investigational
	SPECT tracer: ^{201}Tl tracer; replaces ^{99m}Tc tetrofosmin (Myoview) and ^{99m}Tc sestamibi for cardiac perfusion imaging	Available
	PET tracer: ^{18}F-fluorine; replaces ^{99m}Tc MDP as bone-imaging agent, ^{18}F-DOPA, ^{18}F-choline, ^{18}F-fluorine	Available

Anti-^{18}F-FACBC = anti-1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid; Av-45 = [18F] amyloid detection ligand florpiramine; ^{11}C AFM = [11C]2-[2-(dimethylaminomethyl) phenylthio]-5-fluoromethylphenylamine; CEST = chemical exchange saturation transfer; CMRI = cardiac magnetic resonance imaging; CT = computed tomography; CT/MRI/3-D = computed tomography combined with magnetic resonance imaging and 3-D imaging; DbCT = dedicated breast computed tomography; DbPET/CT = dedicated breast positron emission tomography computed tomography; DSCT = dual-source computed tomography; D-SPECT = dynamic single photon emission computed tomography; ^{18}F-DOPA = fluorine-18-L-dihydroxyphenylalanine; ^{18}F-FES = ^{18}F-16 alpha-fluoroestradiol; ^{18}F-FET = ^{18}F-fluoroethyl-L-tyrosine; ^{18}F-FEAU = [18F] F-fluoro-5-ethyl-1-beta-D-arabinofuranosyluracil; ^{18}F-FBnTP = [18F] fluorobenzyl-triphenylphosphonium; ^{18}F-FHBG = 9-(4-[18F]fluoro-3-hydroxymethylbutyl) guanine; ^{18}F-FLT = [18F]-fluoro-L-thymidine; ^{18}F-FMAU = 1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl)thymine; ^{18}F-MISO = [18F] fluoromisonidazole; HD PET = high definition positron emission tomography; HEU = highly enriched uranium; ^{123}I-BMIPP = beta-methyl-p-[123 Iodine]-iodophenyl-pentadecanoic acid; ^{123}I-MIBG = [123 Iodine] metaiodobenzylguanidine; LEU = low enriched uranium; 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; TOF PET = time of flight positron emission tomography; VECT = versatile emission computed tomography.

*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.

†An emerging technology is one that is not yet adopted by the health care system, usually in phase 2 or 3 clinical trials or pre-launch. The time horizon is zero to five years before introduction.

Funding for these priorities will be targeted at activities that relate to high-priority areas necessary to address commercial-scale potential of the technologies including: target and converter design and optimization; cooling capacity; target processing and achievable yield; generator design and optimization; ^{100}Mo costs, availability, and recycling; overall process optimization, including yield optimization; and work to address regulatory requirements.[11]

Industry and research institutes have already been mobilized to seek alternative molecular imaging solutions and numerous projects have been launched. In June 2010, TRIUMF, Canada's National Laboratory for Particle and Nuclear Physics, announced construction plans on an Advanced Rare Isotope Laboratory (ARIEL) that will be built in Vancouver. Commercial production of isotopes, from this new advanced electron linear accelerator, is expected to start in 2014. This is a joint venture between a consortium of Canadian universities and the provincial government of British Columbia, with the support of the federal government.[12]

In May 2010, the Université de Sherbrooke in Quebec and the University of Alberta's Department of Oncology in Edmonton announced that they are studying methods to produce ^{99m}Tc in decentralized cyclotrons.[13] The cyclotrons used in these investigations are manufactured by a Canadian company, Advanced Cyclotron Systems.[14] A study conducted by the universities' investigators compared the scintigraphic images and distribution patterns of both cyclotron and generator-produced ^{99m}Tc, in addition to prepared isotopes used in molecular imaging of the thyroid, bone, and heart of healthy rats. Both cyclotron and generator-produced ^{99m}Tc were shown to share equivalent radioisotopical, chemical, and biological characteristics.[15]

In March 2010, TRIUMF received $222 million in government funding for its core operating budget for five years. The funding will be used to enhance TRIUMF's strategic activities, which include researching superconductor radio-frequency technology for next-generation accelerators.[16] TRIUMF was also awarded $1.3 million by the Natural Sciences and Engineering Research Council of Canada and the Canadian Institutes of Health Research in October 2009 to investigate cyclotron technologies for producing ^{99m}Tc and several alternative isotopes.[17]

Last year, TRIUMF and MDS Nordion, Canada's medical radioisotope production facility, announced a collaboration to study the feasibility of producing photofission-produced ^{99}Mo in a linear accelerator. MDS Nordion and TRIUMF have already collaborated on the production of other medical isotopes using cyclotron accelerators.[18]

In June 2009, MDS Nordion announced a collaboration with the Karpov Institute of Physical Chemistry in Russia to study the feasibility of the Karpov Institute providing MDS Nordion with a supply of reactor-based ^{99}Mo isotopes.[19]

Also in June 2009, the Canadian government committed $22 million for infrastructural upgrades to McMaster University's nuclear reactor, Canada's only nuclear reactor outside of Chalk River capable of producing medical isotopes. The funding will be used to upgrade McMaster's physical infrastructure, allowing for the expansion of the isotope research and production capacity, and the training of staff in the nuclear industry and health care sectors.[20]

United States activity

Efforts to address the supply disruption of medical isotopes in the US are also gaining momentum and have been mobilized by congressional action and advice from a governmental advisory panel. As Canada is the main source of supply of ^{99}Mo to the US,[21] the US has experienced similar supply issues as Canada. The production of a domestic supply is currently not feasible in the US, as its Department of Energy isotope program does not have any working facilities that can produce long-lived isotopes.[22] 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 in the US.

In 2009, the US Committee on Medical Isotope Production Without Highly Enriched Uranium produced a report requested by the US Congress to examine the feasibility of eliminating the use of highly enriched uranium (HEU) in reactor fuel, reactor targets, and

medical isotope production facilities. The Committee found that, while there currently are not sufficient amounts of medical isotopes available for low enriched uranium (LEU) targets to meet US domestic demand, the technical capability is possible and adequate quantities can be produced from LEU targets in the future.[23]

Also in 2009, the US House of Representatives proposed the American Medical Isotopes Production Act. The main purpose of this legislation is to promote the production of domestic supplies of ^{99}Mo using LEU. The US Senate is currently considering this legislation. If enacted, this bill is intended to reduce the US dependence on foreign sources of medical isotopes. The bill would also provide the US Department of Energy with US$163 million over five years to fund ^{99}Mo production options.[24] The money would be used to support private or research sector projects.

Most reactors in the world that produce ^{99}Mo utilize HEU, which can also be used in the construction of nuclear weapons. Under this legislation, the US would not import isotopes from nuclear reactors that produce ^{99}Mo using HEU, but instead would produce isotopes with LEU. The US would have up to 11 years after enactment of the Act to develop alternative, LEU-based medical isotopes before HEU exports would be ended.

Canada is supportive of converting nuclear fuel from HEU to LEU. The Chalk River reactor switched to LEU fuel in 1991-1992.[21] However, the Chalk River reactor still produces isotopes using HEU targets (obtained from the US).[7] While the Canadian government supports non-proliferation efforts, the Chalk River facility is unlikely to convert to LEU given that the reactor is approaching the end of its life cycle and technical challenges associated with yields using LEU targets have not been resolved.[7]

In June 2010, Advanced Medical Isotope Corporation (AMIC), a US company established in 2006 to fulfill the US domestic supply of medical isotopes, announced that it had signed an exclusive global licence for patented technology for a sub-critical, accelerator-driven system.[25] This technology would generate thermal neutrons using an electron accelerator to produce ^{99}Mo from uranium and would have a similar infrastructure as that of a commercial cyclotron facility. A number of strategically located units in North America and other continents could potentially supply 50% of the projected domestic demand for ^{99}Mo (and other fission isotopes). AMIC claimed it could start producing ^{99}Mo within two to four years.[26]

In June 2010, MiPod Nuclear Inc., a medical isotope production company, announced the commercialization of ^{99}Mo production technology. This process uses depleted uranium as the target medium, which is irradiated by a neutron generator in a proprietary chamber design that uses electrolytic separation technology. MiPod anticipates the commercial production of ^{99}Mo within 18 months. This technology would allow ^{99}Mo to be produced in regional production centers.[27]

In January 2010, Babcock & Wilcox, an energy technology supplier, received US$9 million in funding from the US National Nuclear Security Administration for the development of an aqueous homogeneous reactor technology utilizing LEU technology.[28] Babock & Wilcox signed an agreement with Covidien in 2009 to investigate this technology. The program has the potential to supply 50% of the US market and could be operational by 2012.[29]

In January 2010, the US National Nuclear Security Administration also awarded US$4.5 million in funding to GE Hitachi Nuclear Energy to develop an ^{99}Mo production method by placing molybdenum targets in commercial nuclear power reactors using a new technology that does not require HEU. The funding will be used to conduct research and development to ensure that the technology will work on a commercial scale. The funding will also be used to determine the infrastructure and logistics needed to support commercial operations.[30]

Although it has not been confirmed, the US is hoping to upgrade the University of Missouri Research Reactor or MURR.[31] It would be converted from an HEU facility into an LEU facility. The University of Missouri Research Reactor could produce about 50% of the US demand for ^{99m}Tc. Funding of approximately US$40 million would be needed to convert and license the facility.[32]

International activity

In February 2010, Covidien announced a collaboration with the Institute of Atomic Energy in Poland to irradiate targets at the Maria research reactor near Warsaw to produce ^{99}Mo. According to Covidien, the Polish reactor could produce a commercial supply of ^{99m}Tc by the end of 2010.[33] Health Canada and the US Food and Drug Administration (FDA) have approved the use of the research reactor in Poland as a site to irradiate HEU targets for ^{99}Mo.[34]

Ion Beam Applications, a Belgian cyclotron producer, is working on a proton-driven fission neutron source for the production of ^{99}Mo. The proposed Accelerator Driven Optimized Nuclear Irradiation System (ADONIS) will produce ^{99}Mo in a cyclotron. The ADONIS proposal is based on a cyclotron-driven sub-critical intense neutron source that generates thermal neutron fluxes equivalent to those produced by reactor-produced ^{99}Mo. The ADONIS system could potentially supply over 50% of the world demand for ^{99}Mo.[35]

In October 2009, The Netherlands announced plans to build a new nuclear reactor to produce medical isotopes. The new Pallas reactor will replace the aging High Flux reactor in Petten that is being used to produce medical isotopes.[36]

Belgium's multipurpose facility, MYRRHA, an accelerator-driven subcritical system, could also produce large quantities of ^{99}Mo.[37] MYRRHA is expected to be operational when Belgium's current research reactor, BR2, is decommissioned in 2022.[38]

The Jules Horowitz multipurpose research reactor in France, which is expected to be operational by 2015, can produce ^{99}Mo. This reactor will replace France's aging OSIRIS reactor.[39]

In August 2009, the OPAL reactor in Australia started distributing ^{99}Mo by the irradiation of LEU targets to a global market. Health Canada and the FDA have fast-tracked the reactor's approval as licensed supplier of LEU-derived ^{99}Mo.[40]

The FRM II neutron source reactor at the Technical University of Munich in Germany is seeking funding to upgrade the facility to make ^{99}Mo. The proposed changes could potentially allow the FRM II to produce almost enough ^{99}Mo to cover all of Europe's needs.[41]

New and Emerging Molecular Imaging Devices

SPECT and PET hybrids and other molecular imaging alternatives

Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are the most commonly used molecular imaging modalities in nuclear medicine.[5] The major attribute of PET and SPECT — which distinguishes them from magnetic resonance imaging (MRI), magnetic resonance spectroscopy, optical bioluminescence imaging, optical fluorescence imaging, and targeted ultrasound methods — is the high sensitivity with which they can detect metabolic activity and trace the concentration of specific proteins in the body.[42] The independent Canadian Expert Review Panel on Medical Isotope Production, appointed by the Government of Canada, made specific recommendations regarding the use of newer SPECT software and hardware technologies, and recommended an increased investment in PET scanners.[7]

Recent advances in technology have combined PET and SPECT with computed tomography (CT). The benefit of these combined modalities is increased performance in resolution and sensitivity. At least 35 SPECT/CT scanners[43] and approximately 29 PET/CT scanners[9] are currently used in Canada.

PET/CT has become the preferred technology for PET imaging; none of the major manufacturers currently offer stand-alone PET scanners for commercial sale.[44] Canada has not embraced PET as readily as the US and other countries. 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.[45] PET/CT, however, is gaining faster acceptance in Canada than stand-alone PET. Canadian health authorities have been more proactive in expanding coverage for alternative PET imaging during the isotope supply disruption. For

example, up until July 2009, in Ontario, PET was only accessible via three routes: clinical trials for specific cancers through the Ontario Clinical Oncology Group, via individually approved access through the Ontario PET Registry program, or through special access. Ontario has now made PET scanning a publicly insured health service available to cancer and cardiac patients in conditions where PET scans have proven to be clinically effective. There are approximately 28 centres performing publicly funded PET/CT scans in seven Canadian provinces.[9]

The most popular application of PET and PET/CT is in oncology,[45] as whole body imaging is used to identify primary cancer sources and scan for metastatic disease. Until recently, SPECT/CT has had a unique application with thyroid, parathyroid, neuroendocrine, and prostate gland cancers because these cancers typically cannot be detected by PET tracers.[46] However, advancements in PET technologies continue to overcome these barriers and expand PET's diagnostic applications.

The most popular application of SPECT and SPECT/CT is in cardiology. However, orthopedics, oncology, and infection imaging are areas that are benefiting from SPECT/CT.[46] 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 quantification to develop a measurement similar to the standardized uptake value in PET; and guided biopsy.[47]

Advances in PET technology, particularly in the area of PET detector and PET reconstruction algorithms, continue to expand the clinical diagnostic horizons of PET.

High definition PET/CT (HD PET/CT) is an example of a new PET technology that optimizes the elements of image uniformity, resolution, and contrast. HD PET/CT images the body's physiological functions and automatically corrects distortions that occur during scanning. HD PET/CT performs scans in approximately 10 minutes, taking less than half of the time of traditional PET/CT studies. It is believed that HD PET/CT allows physicians to identify very small lesions through its enhanced clarity, improved resolution, and better uniformity.[48]

Time-of-flight PET (TOF/PET) is another advancement in PET technology that has expanded its clinical and preclinical applications. Although first developed in the early 1980s, recent advances in photomultiplier tubes, electronics, and scintillators have renewed interest in this technology.[49] Unlike conventional PET, TOF/PET measures the precise time difference it takes for X-rays to reach PET detectors. This added information enables the reconstruction algorithm to arrive at an image with less image noise and fewer iterations — improving image quality and lesion detectability, particularly in heavy patients.[50]

PET/MRI is a novel hybrid imaging technique 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 the physiological and metabolic state.[45] 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 clinical setting, PET/MRI is intended to improve health care by increasing clinical understanding of the causes, effects, and development of disease processes such as cancer,[51] Alzheimer disease, schizophrenia, and metabolic disorders such as osteoporosis and atherosclerosis.[52] PET/MRI could potentially 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.

Although the technology required to combine PET with MRI is readily available, it will likely continue to develop over the next decade before it will affect clinical practice.[51] 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.[51]

Just as advances in PET technology have expanded its clinical diagnostic horizons, new SPECT technological improvements continue to expand the gamut of its applications. These improvements include advances in attenuation correction; shorter acquisition times; and new

camera and processing technologies, which have been shown to limit radiation exposure, improve laboratory efficiency, and expand SPECT imaging capabilities.

Improvements in solid-state detectors have led to the development of a new generation of gamma cameras. Solid-state technology is designed to provide greater spatial and energy resolution, and improved count sensitivity and image contrast, compared with conventional detectors. This added efficiency allows SPECT to perform scans using either shorter acquisition time or reduced ^{99m}Tc doses. A study comparing new solid-state technology with conventional SPECT in 168 myocardial perfusion patients was published in 2009. The diagnostic performance of the solid-state SPECT was found to be comparable to that of conventional SPECT on a per-patient basis. Superior image quality was achieved with significantly shorter acquisition times with the solid-state SPECT over conventional SPECT.[53]

Dynamic SPECT (D-SPECT) is a novel solid state detector system used in cardiology to provide better energy resolution and higher sensitivity.[54] D-SPECT has attracted recent attention on two fronts. Firstly, the isotope crisis has made the lower isotope dose requirements of D-SPECT very attractive, as it presents an opportunity to conserve scarce supplies of ^{99m}Tc. Secondly, the long-term effects of radiation exposure has become an increasing health concern. A recent study of over 900,000 patients aged 18 to 64 years found that myocardial perfusion imaging with SPECT or PET contributed to the greatest radiation exposure of any cardiac imaging procedure.[55] In June 2010, two new trials were initiated to demonstrate that D-SPECT uses significantly lower doses of ^{99m}Tc compared with conventional cardiac imaging. These trials are being conducted at Columbia University in New York and at Cardiovascular Imaging Technologies in Kansas City.[56]

Another innovation that conserves ^{99m}Tc supplies is imaging reconstruction software. Used in SPECT, reconstruction software allows 3-D reconstruction algorithms acquisition to be processed with resolution recovery and noise reduction techniques.[57] Iterations of this resolution recovery software have the potential to enable a reduction of patient dose by half or reduction of acquisition time, while maintaining image quality as compared with conventional reconstruction methods that do not use depth-dependent resolution recovery.[58]

Positron emission mammography (PEM) is a dedicated PET breast imaging technology. It 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.[59] 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-fluoro-2-deoxy-D-glucose image (^{18}F-FDG).[59] The ability to use PEM technology to biopsy lesions has also been investigated and appears feasible.[60] This technology is in its infancy, but preliminary reports are promising for the detection of ductal carcinoma in situ. No imaging device to date has been able to accurately image ductal carcinoma in situ unless it happens to be associated with pleomorphic calcifications seen on mammography. In addition, further refinements, including combining PEM with tomographic acquisition (using detectors that rotate around 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.[61]

Other specific breast imaging devices are being investigated. Dedicated breast PET/CT (DbPET/CT) is a current example that involves the acquisition of 3-D images of the uncompressed breast by either the rotation of two or more planar heads around the breast or by complete rotation of the breast with detectors. Images are produced with isotropic spatial resolution and can show the size, extent, and location of biopsy-confirmed breast cancer.[62]

Another dedicated breast imaging technology currently being investigated is dedicated breast CT (DbCT) scanning. This technology provides images of the uncompressed breast using cone beam geometry. Cross-sectional images of the breast are captured while the CT scanner and detectors rotate around the entire breast. These images are converted into a single 3-D image. As dedicated breast CT scanning

technology becomes more sophisticated, it may have a place as an alternative screening modality to mammography for breast cancer.[63]

Versatile Emission Computed Tomography (VECT) is a new diagnostic imaging modality being investigated that combines PET and SPECT into a single device. The technique involves the simultaneous performance of a PET and SPECT scan that is intended to show functional details smaller than half a millimetre. It is currently being used for the imaging of small animals to test new isotopes and pharmaceuticals for cancer, cardiac disorders, and brain diseases.[64] VECT only uses SPECT isotopes, such as ^{99m}Tc, and requires smaller quantities than other devices for the same result.

MRI

Magnetic resonance imaging (MRI) is a molecular imaging modality that provides soft tissue contrast and resolution in the submillimetre range. However, its sensitivity for identifying imaging probes is approximately 10^6 times lower than PET.[65] Nonetheless, technological innovation in MRI, especially regarding improved sensitivity, are moving MRI beyond anatomic imaging and into the domain of functional imaging.

Hyperpolarization MRI is an example of an emerging technique that is intended to enhance the sensitivity of MRI. During the hyperpolarization process, many targeted nuclei are excited, which improves the sensitivity of images.[66] In conventional MRI, only a small fraction of nuclei is excited and is not enough to generate a detectable signal. Hyperpolarization in MRI allows the real time metabolic tracking and detection of biomarkers, which could potentially reduce the examination time frame from nearly an hour to seconds.[67]

There are five distinct hyperpolarization methods: dynamic nuclear polarization (DNP), parahydrogen-induced polarization–parahydrogen and synthesis allow dramatically enhanced nuclear alignment (PHIP-PASADENA), xenon/helium polarization transfer, Brute Force, and 1H hyperpolarized water.[68] Hyperpolarization with MRI has shown clinical promise in measuring pulmonary structure, function, and metabolism.[69] It also has the potential to become a valuable tool for the early detection of cancer[70] and neurological disorders.[68]

Recently, it has been demonstrated that magnetic resonance contrast may be altered by a new mechanism based on chemical exchange saturation transfer (CEST). CEST agents are an emerging class of negative MRI contrast agents that have unique MRI properties which facilitate activatable contrast. These compounds contain pools of exchangeable protons that can be selectively saturated using radiofrequency irradiation. CEST contrast can originate from the exchange of endogenous amide, hydroxyl protons, or from exchangeable sites on exogenous CEST agents.[71] CEST is intended as an alternative to relaxivity-based contrast mechanisms for MRI. It is believed that this emerging class of MRI contrast agents is likely to grow in importance as they offer new opportunities for imaging metabolism using endogenous biomolecules and exogenous agents.[72] As CEST is characterized by problems relating to concentration and sensitivity, its newer development, paramagnetic chemical exchange saturation transfer (PARACEST), addresses these by allowing specific metabolites such as glucose to be evaluated noninvasively in vivo, in all organs. PARACEST can also be used to measure pH, temperature, lactate, and the concentration of various metabolites.[73] Preclinical data has shown that molecular MRI, including CEST, offers promise for improving the quality of diagnosis for oncologic, cardiovascular, and neurological diseases.[74]

Cardiac MRI (CMRI) is a recently emerged technology that is already being practiced in Canada.[75] It is intended to enable accurate and reproducible quantification of measurements of global and regional ventricular function, blood flow, perfusion at rest and stress, as well as myocardial injury (MI).[76] A study involving 72 patients compared CMRI and SPECT for the detection of unrecognized MI in patients with end-stage renal disease. The authors reported that CMRI with myocardial delayed enhancement can depict unrecognized MI in patients with end-stage renal disease with better sensitivity than SPECT.

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.[78]

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.[79]

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.[80] 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.[81]

It is believed that photoacoustic imaging may play a role in the future of mammography as a mass screening alternative to current gold standards.[82,83] It is also predicted that photoacoustic imaging may be useful in detecting melanomas, gastrointestinal and other cancers, imaging of blood flow, imaging of the metabolic rate of oxygen, and mapping of sentinel lymph nodes.[83]

Optical imaging

Optical imaging is a molecular imaging procedure in which light-emitting molecules that are designed to attach to specific cells or molecules are injected into the bloodstream and then exposed by an optical imaging device. Optical imaging uses light emitted through fluorescence or bioluminescence.[65] Optical imaging has been used primarily for research in small-animal models. There are, however, several areas in which optical imaging, especially fluorescence imaging, can be used in a clinical setting.[84]

Fluorescence imaging can be performed using quantum dots, dyes, and proteins. In all cases, the image acquisition requires the excitation of the agent with an external light source at the appropriate wavelength, followed by the detection of the resulting photon emissions from the decal of the excited states.[85] This technique allows imaging of many different metabolic pathways, but the requirement of an external light source limits the depth of the detectable signal. The main advantage of optical imaging is the lack of radiation burden, which theoretically allows unlimited continuous or repeated imaging.

Fluorescence imaging using quantum dots is believed to be a promising optical imaging modality. Quantum dots are nanoparticles that possess unique optical and electronic properties. They are bright, photostable, and nontoxic optical probes. They are characterized by a wide absorption band and a narrow emission band, which lends to extensive multiplexing capabilities.[86] Quantum dots-based technology may help in the early detection of primary tumours such as ovarian, breast, prostate, and pancreatic cancer, as well as regional lymph nodes and distant metastases.[87]

Another novel optical imaging technique is Cerenkov luminescence imaging (CLI). This technique does not require external illumination, as light is produced from the radioactivity. This process brings light to nuclides that could not previously be visualized. In a small-animal study, researchers evaluated several tracers for potential use with CLI. The researchers used CLI and PET imaging to visualize tumour-bearing mice. The results show that CLI visualizes radiotracer uptake in vivo, and can be observed from a range of positron beta- and alpha-emitting radionuclides using standard optical imaging devices. The resulting decrease of light over time correlates with the radioactive decay of the injected tracer. The study investigators believe this technique could lead to the faster and more cost-effective development of tracers for the diagnosis and treatment of cancer and other conditions.[88]

Other hybrid imaging technologies

Dual-source computed tomography (DSCT) is a new, non-invasive multidetector scanner that is intended to provide diagnostic information comparable to traditional SPECT for myocardial perfusion. A DSCT scanner is able to assess myocardial perfusion and coronary anatomy simultaneously. Currently, a phase I/II study is underway to compare DSCT and SPECT scans.[89] A small study was published in 2009 involving 35 subjects in which DSCT coronary angiography for the diagnosis of coronary artery disease was compared with SPECT and conventional angiography. The authors reported that DSCT and SPECT provide mutually complementary information on coronary artery disease. CT angiography was noted for its ability to rule out functionally relevant coronary artery disease but had a poor ability to predict ischemia. DSCT was reported to provide high-quality diagnostic images without needing to control heartbeat, and had a high precision rate in identifying obstructive stenosis.[90] 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.[91] The EIBIR is also involved in the European HAMAM project — Highly Accurate Breast Cancer Diagnosis through Integration of Biological Knowledge, Novel Imaging Modalities, and Modelling.

The Development of Alternative Isotopes

There is ongoing interest in developing more easily available and cheaper isotopes. Both PET and SPECT imaging requires 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.[92]

Alternatives to ^{99m}Tc, SPECT's most widely used tracer, are sought partly because of the continued disruptions in its supply, but also because of the planned decommissioning of the Chalk River isotope reactor in 2016 and global efforts to move away from nuclear reactor production of isotopes.[93]

Alternatives to FDG, PET's most widely used tracer, are also in demand because FDG, an analogue for imaging glucose metabolism, is expensive, not suitable for all patients, difficult to process, and many molecular targets cannot be measured or assessed with FDG. As well, although FDG provides high specificity and sensitivity in numerous cancers, it is not an ideal tracer for imaging specific conditions. Subsequently, there has been a series of new ^{18}F-labelled tracers that are in development.

SPECT radiotracers

Two new ^{123}I-labelled tracer agents have recently completed clinical trials: Iodine-123 metaiodobenzylguanidine (^{123}I-MIBG) for imaging the sympathetic nervous system of the heart and Iodine-123 p-iodophenyl-3-(R,S)-methylpentadecanoic acid (^{123}I-BMIPP) for imaging fatty acid metabolism and for use in emergency departments as an evaluation tool for patients with episodes of chest pain. The former has the ability to assess the nerves of the heart at a cellular level, which cannot be achieved using standard tests such as echocardiography.[94] The latter tracer, ^{123}I-BMIPP, is marketed as Zemira and is believed to be the only tracer that can directly link symptoms to true cardiac tissue ischemia.[95]

Regioselectively addressable functionalized template–arginine-glycine-aspartic acid (RAFT-RGD) is another new tracer that is believed to have potential for targeting and imaging.[96] A recent animal study has evaluated the potential of ^{99m}Tc-labelled RAFT-RGD for the non-invasive in vivo SPECT molecular imaging of neoangiogenesis.[97]

Another new tracer agent for imaging of the noradrenaline and peripheral benzodiazepine receptors is also in development. Researchers at the University of Glasgow in Scotland are developing 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.[98]

Iodine-123 (^{123}I) is an established SPECT imaging agent. It was originally used for imaging the brain,[99] kidney,[100] and thyroid.[101] More recently, its diagnostic capabilities are being assessed for myocardial imaging,[102] cerebral blood flow,[103] and neurological disease such as Parkinson disease and dementia.[104] Since serotonin dysfunction has been linked to a variety of psychiatric diseases, it is also being studied to image serotonin transporters for various psychiatric disorders.[105,106]

Indium-111 (^{111}I) is a metallic radionuclide that requires chelation chemistry for radiolabelling to an antibody. It is another well-established SPECT imaging agent that can be used to identify local, as well as diffused, myocardial damage[107] and tumour detection.[108] More recently, it is being used to image infected or inflamed areas.[109]

PET radiotracers

A number of problems limit the clinical diffusion of alternative PET tracers. These problems relate to the need for an on-site cyclotron (due to the short-lived isotopes), problems in gaining approvals for using non-registered tracers, and high costs associated with their processing and distribution.[110] Included here is a list of emerging PET tracers that have been broken down into four clinical categories: heart imagers, neurological imagers, cancer metabolism and functional imagers, and infection imagers.

Heart radiotracers

Gallium-68 (^{68}Ga) is a tracer that can be produced in a generator. It is believed to play a potential role in the management of numerous clinical conditions, including melanoma,[86] and the assessment of infections and inflammations such as osteomyelitis.[111] Researchers at the University of British Columbia's Department of Pharmaceutical Sciences were recently awarded $874,000 from Canadian Institutes of Health Research and Natural Sciences and the Engineering Research Council of Canada to develop alternative isotopes. Professor Urs Hafeli, the lead investigator, is focusing on two ^{68}Ga projects. The first involves replacing macroaggregated albumin, a blood product tagged with ^{99m}Tc, with a microsphere tagged with ^{68}Ga. It is to be used to identify pulmonary embolism, chronic obstructive pulmonary disease, and lung cancer. The second project involves replacing red blood cells tagged with ^{99m}Tc with a biocompatible polymer tagged with ^{68}Ga. The ^{68}Ga is to be used for cardiac blood pooling imaging for diagnosis of heart function. This new procedure is intended to eliminate the handling of blood and blood components, and will remove the risk of adverse interactions between isotopes and chemotherapeutic drugs. Preliminary clinical trials are expected to end in 2012.[112]

Rubidium-82 (^{82}Rb) is a potassium analogue tracer that can be used for myocardial perfusion imaging. It is currently being investigated at the University of Ottawa Heart Institute, where it is produced in a small generator. ^{82}Rb is useful in distinguishing normal from abnormal myocardium in patients with suspected MI.[113] Recent advances in PET and PET/CT technology have increased the sensitivity of ^{82}Rb for cardiac imaging in comparison to SPECT imaging.[114] In 2009, Health Canada approved its reimbursement through a small number of heart studies at the request of physicians, or through clinical trial.[115] It is also being tested in animals as a measurement of renal cortical blood flow.[116]

LMI1195 is a newly developed PET imaging agent labelled with the ^{18}F-benzylguanidine analogue. It is being used for the identification and evaluation of patients at risk of heart failure or sudden cardiac death. LMI1195 is transported into the heart via the norepinephrine transporter.[117] Preliminary data from a phase I study shows that LMI1195 has the potential to deliver high-quality, well defined images of the cardiac autonomic nervous system.[118]

^{18}F-FBnTP, [18F] fluorobenzyl-triphenylphosphonium, is a novel myocardial perfusion PET tracer that is being studied in animals. It is taken up rapidly by the myocardium and has a high contrast that is believed to be superior to ^{99m}Tc. It also targets mitochondria and has shown promise for myocardial perfusion imaging.[119]

Neurological radiotracers

C-11 AFM or [11C]2-[2-(dimethylaminomethyl) phenylthio]-5-fluoromethylphenylamine (^{11}C AFM) is an emerging PET imaging agent for serotonin transporters. The serotonin transporter is the target of the selective serotonin reuptake inhibitors — medication widely used to treat depression. ^{11}C AFM is intended to accurately measure the effects of antidepressants on the serotonin transporters. In 2008, the first human study to assess the imaging qualities of ^{11}C AFM in five healthy subjects was published. The study investigators found that ^{11}C AFM provides higher specific binding signals and is a superior tracer than C-11 DASB, the current standard ligand as a seratonin transporter agent.[120]

Florbetaben is an investigational imaging agent that provides visualization of beta-amyloid, a naturally occurring protein that builds up in the brain. Beta-amyloid is believed to be a precursor to Alzheimer disease. Monitoring the movement and spread of beta-amyloid through imaging may provide important information about the progression of the disease and its impact on a cellular and molecular level.[121] Results of a phase II, multi-center study showed florbetaben and PET images with a high specificity of over 90%. In the study, 81 patients believed to have Alzheimer disease, and 69 healthy subjects aged 55 and older, were imaged to test the agent's potential for diagnosing Alzheimer disease. Patients were tested both visually and quantitatively by normalizing to an amyloid-free reference region in the brain and analyzing the segmented data. Both methods proved to be highly accurate in diagnosing the disease.[122]

^{18}F (florpiramine) is another promising tracer aimed at supporting the diagnosis of Alzheimer disease by detecting significant amyloid loads in imaged brains.[123]

^{18}F-fallypride is a selective dopamine D2/D3 receptor antagonist. It is currently being studied in patients with schizophrenia, to determine the amount and distribution of the D2/D3 dopamine receptors.[124]

Fluorine-18-L-dihydroxyphenylalanine (^{18}F- FDOPA) is a PET neuroimaging tracer used primarily for helping in differential diagnosis of movement disorders, measuring efficacy of new therapies, elucidating the benefits and complications of surgical interventions, and assessing the utility of neuroprotective strategies.[125] It has been assessed for early detection of Parkinson disease,[126] and is being evaluated for the detection of brain tumours.[125]

Cancer metabolism and functional imaging radiotracers

^{18}F-fluoro-L-thymidine (^{18}F-FLT) is a novel PET tracer that accumulates in cells with high thymidine kinase-1 activity, reflecting areas of cell proliferation. Since ^{18}F-FLT is absorbed well by cancer cells, it can determine if chemotherapy is working — often very early in the course of chemotherapy treatment. Numerous small studies have reported on ^{18}F-FLT's performance as a measure of tumour proliferation in squamous cell carcinoma,[127] lung cancer,[128] colorectal cancer,[129] and brain cancer.[130]

1-(2'-deoxy-2'-fluoro-beta-D-arabinofuranosyl) thymine (^{18}F-FMAU) is a thymidine analogue that is incorporated into DNA once it has been phosphorylated by thymidine kinase. In 2005, the first human study of ^{18}F-FMAU was conducted as a pilot in patients to determine its biodistribution and suitability for imaging DNA synthesis in tumours using PET. The study found that tumours in the brain, prostate, thorax, and bone were clearly visualized with F-MAU. Yet, visualization in the upper abdomen was limited by the physiological uptake by the liver and kidneys.[131]

Zirconium-89 (^{89}Zr) is a PET nuclide that has properties for imaging of intact monoclonal antibodies (mAbs) using immuno-PET. ^{89}Zr is ideally suited to be conjugated with mAbs as a positron emitter. A feasibility study evaluated the diagnostic imaging capabilities of immuno-PET with ^{89}Zr-labelled-chimeric(c) mAb U36 in 20 patients with head and neck cancer who were at high risk of having neck lymph node metastases. The study found that immuno-PET with ^{89}Zr-cmAb U36 performed as well as CT/MRI for detection of primary head and neck tumour lymph node metastases.[132]

^{18}F-fluoroethyl-L-tyrosine (^{18}F-FET) is another PET tracer that has demonstrated clinical success in detecting brain tumours.[133]

^{18}F-choline is a choline analogue that is structurally similar to natural choline. A new study involving 96 patients suggests integrated ^{18}F-choline PET/CT technology offers a significant advantage in the detection of both local and distant recurrences after radical prostatectomy in patients with increasing prostate-specific antigen levels.[134] It is also believed to improve the diagnostic accuracy of endocrine tumours.[135] Several European companies have shown recent interest in the commercial potential of ^{18}F-choline.[110]

Anti-1-amino-3-[18F]fluorocyclobutane-1-carboxylic acid (Anti-^{18}F-FACBC) is another new PET imaging agent intended to improve the diagnosis of recurrent prostate cancer and determine the best possible course of treatment for patients. The tracer consists of a fluorine-based radioisotope paired with a synthetic amino acid analogue. In a study involving 83 patients suspected of recurrent prostate carcinoma who received PET/CT imaging with anti-^{18}F-FACBC, cancer was positively identified in the prostate with 74% accuracy.[136] Metastatic cancer was detected with 96% accuracy.[136] Small tumours with lymph nodes that other imaging agents could not detect were discovered using anti-^{18}F-FACBC.[136]

^{18}F-16 alpha-fluoroestradiol (^{18}F-FES) is an investigational PET imaging agent consisting of an analogue form of an estrogen known as estradiol. It has been studied to help predict which patients with recurrent or metastatic breast cancer will respond to hormone therapy[137] and for the diagnosis of endometrial tumours. ^{18}F-FES is intended to help predict the outcome of treatment and enable clinicians to discontinue therapies that are not beneficial.

^{18}F-fluorine is a PET tracer used for imaging of bone metastases. While ^{18}F-fluorine show uptake in normal bone, it is much more visible in bone invaded by metastases. With the higher sensitivity and resolution of PET, its sensitivity and specificity for bone metastases are believed to be greater than that of ^{99m}Tc-methylene diphosphonate.[139] ^{18}F-fluorine has also been used for the evaluation of skeletal trauma in cases of suspected child abuse.[140] In 2009, Health Canada approved its reimbursement for bone scanning through clinical trials.[115]

^{18}F –fluorine is reported to be an accurate technique for the evaluation of chronic musculoskeletal infections.[149]

^{18}F-EF5 is an investigational PET tracer used for imaging hypoxia. It has shown promise for the detection of hypoxia with head and neck cancer,[141] and its diagnostic imaging capabilities are also being investigated for the detection of locally advanced or recurrent cervical cancer.[142]

^{18}F-fluoromisonidazole (^{18}F-MISO) is another hypoxia-specific imaging agent. ^{18}F-MISO has been validated as a non-invasive assay of tumour hypoxia. Hypoxia is known to play a role in tumour progression and treatment resistance.[143] Various studies have been conducted with ^{18}F-MISO to assess tissue hypoxia in tumours.[144-146]

Infection radiotracers

^{18}F-fluoro-5-ethyl-1-beta-D-arabinofuranosyluracil (^{18}F-FEAU) and 9-(4-[18F]fluoro-3-hydroxymethylbutyl) guanine (^{18}F-FHBG) are newer PET imaging tracers that are currently being investigated for herpes simplex virus thymidine kinase gene expression. Early studies indicate that the high uptake rate of ^{18}F-FEAU[147] and ^{18}F-FHBG,[148] together with their high selectivity, make these tracers potential candidates as PET tracers for herpes simplex virus thymidine kinase gene expression.

^{18}F-FMAU is an established tracer to monitor cellular proliferation and herpes simplex virus type 1 thymidine kinase reporter gene expression with PET.[147]

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 ^{99}Mo. There are also a variety of new and emerging isotopes and 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. As well, even though a technology may be commercially viable, there is no guarantee that it will command clinical acceptance. Determinants such as cost, ease of use, facilities for the production and transportation

of isotopes, training requirements, and the attitude of physicians toward innovation are factors that can influence the diffusion of new technologies. This is further intensified if the technology is aimed at replacing established modalities where there is already significant capital, infrastructural, and technological investment.

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