

By Greg Freiherr

PET and SPECT prepare to climb atop a radiopharmaceutical wave

A renaissance is in the offing for molecular imaging. It is arising from a coming together of new radiopharmaceuticals and expanded clinical applications for ones already in hand, as well as rapidly advancing scanner technology. PET will lead with a raft of new agents now making their way through clinical studies, just as the modality promises advantages that include the potential for exposing patients to less radiation, as well as a broad and underutilized installed base of PET scanners. SPECT will add to the mix with radiotracers that expand the use of this modality and scanner technologies that have the potential to remarkably improve image resolution.

PET NOW AND TOMORROW

Clinical PET was built on fluorodeoxyglucose (FDG). Its uptake by for cancer has made FDG the go-to- agent when staging and monitoring patients battling lymphoma and lung cancer. And PET's range is continuing to expand.

The August issue of the *Journal of Nuclear Medicine* (August 2013, Vol. 54:8, pp. 1244-1250) reported that FDG PET is more sensitive, has a better negative predictive value, and is more accurate than bone marrow biopsy in patients with diffuse large B-cell lymphoma. Similarly, the July issue of the *Journal of Thoracic Oncology* published research finding that FDG PET improves staging accuracy and intrathoracic disease identification, which can lead to improved clinical outcomes for patients with limited-stage small-cell lung cancer (LS-SCLC).

With this kind of potential, it's not surprising that bullish predictions for the radiotracer marketplace are surfacing. The business research firm MarketsandMarkets predicts an annual growth rate of nearly 8% from 2012 to 2017, estimating the global market by then to be \$5.5 billion, a \$1.7 billion increase over global radiopharmaceutical sales in 2012.

Transparency Market Research is even more bullish. A report released last summer predicted a compound annual growth rate in radiopharmaceutical sales of 18.3% beginning in 2013 and running through 2018 as annual sales are forecast to quadruple over the period from \$3.8 billion to more than \$12 billion in 2018.

Market research firm Bio-Tech Systems breaks down the markets for SPECT and PET radiopharmaceuticals, predicting that new clinical indications and rising reimbursement for cardiac studies could boost PET radiopharmaceutical

sales in the U.S. to more than \$4 billion by 2018 from its current \$400 million mark.

While PET agents show most of the promise for future growth, established agents — particularly ones based on technetium-99m — represent most of the current sales. These sales are expected to grow further, according to MarketsandMarkets, as procedure volumes increase, primarily in North America, Europe, Japan, South Korea and Asia-Pacific nations.

Bio-Tech Systems predicts a doubling by 2018 of the current \$800 million level of purchases of SPECT radiopharmaceuticals by U.S. customers. The research firm predicts that in five years annual sales will be at \$1.68 billion, a prediction based on the expectation that new radiopharmaceuticals will be added and that the installed base of PET and SPECT scanners is sufficient to support continued growth for both modalities.

The primary threat to such bullish predictions comes from supply chain problems, specifically the supply of molybdenum-99, the precursor to technetium-99m. Within two years Canada plans to shut down its National Research Universal reactor, which is today a major source of molybdenum-99 and whose unplanned shutdown in 2009 and 2010 snarled the use of SPECT around the globe.

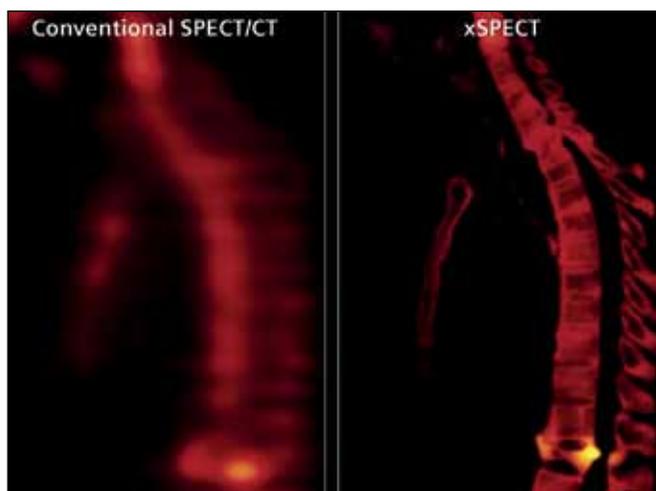
Other hurdles that have slowed molecular imaging throughout its history are regulatory constraints, the dependence of radiopharmaceuticals on continuing advances in scanners, the high cost of these machines, and the distribution and use problems associated with the short half-lives of the radioisotopes.

NEW AGENTS ON THE HORIZON

While FDG is very good, it is far from perfect. Exemplifying FDG shortcomings is a 2011 report from the German Institute for Quality and Efficiency in Health Care who released a study (https://www.iqwig.de/download/D06-01F_Execu

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Advances in scanner technology offer unprecedented clarity in fused SPECT and CT images, as demonstrated in this comparison of conventional SPECT/CT and Siemens' new xSPECT. Siemens unveiled xSPECT last spring. Image courtesy of Siemens Healthcare.

tive_Summary_PET_and_PET_CT_in_melanoma.pdf) stating there is no compelling evidence that PET/CT is a reliable aid in diagnosing melanoma or in monitoring melanoma patients in remission. FDG falls similarly short when assessing patients for renal cell or prostate cancers.

FDG PET is expanding its utility in lung cancer and lymphoma, however, just as the market readies for the arrival of neurological agents designed to help in the diagnosis of Alzheimer's disease

Beta-amyloid imaging as a diagnostic indicator of Alzheimer promises to have a huge effect on clinical medicine. The first such commercial radiopharmaceutical, Amyvid (florbetapir F-18), received clearance from the U.S. Food and Drug Administration (FDA) in April 2012 and has since been approved by the European Commission for sale in the European Union. Amyvid indicates the density of beta-amyloid plaque in the brains of adult patients, which serves as an indicator of Alzheimer's disease when evaluation patients with cognitive impairment.

As with the density of amyloid plaque, the amount and location of tau tangles in the brain has been pegged as an early sign of the Alzheimer's disease. In spring 2013, Lilly acquired from Siemens Healthcare two investigational PET biotracers designed to image the neurofibrillary tangles in the brain that have come to be associated with Alzheimer's. Lilly's goal is to groom these biotracers as the means for identifying at risk patients.

Similar agents are in development. One is florbetaben, an investigational PET amyloid agent in development at Piramal Imaging. Another is NAV4694, which is being developed by Navidea Biopharmaceuticals. Like Amyvid, florbetaben binds to beta amyloid.

Not only are such agents of potentially great importance as diagnostics, they may be helpful in gauging the effect of experimental therapies. Last spring the Japanese pharmaceutical firm Eisai entered into a research collaboration with GE Healthcare to use GE's experimental F-18 flutemetamol as a means for measuring the effect of Eisai's investigational compound E2609. Esai is developing an inhibitor of a beta-site amyloid precursor protein-cleaving enzyme (BACE) for the potential treatment of Alzheimer's disease. Like Amyvid,

F-18 flutemetamol visualizes amyloid plaques in the brain. A negative scan would argue against the presence of Alzheimer's disease in patients with reduced cognitive function.

CARDIAC PET: THE NEW FRONTIER

As good as these agents may be, it will probably be cardiologic agents that most propel the future of PET. Yet the current state of PET heart imaging barely hints at this.

The comparatively few PET heart studies done today in comparison to oncologic studies involve rubidium-82, a myocardial perfusion agent that is expensive and, recently, tainted by radiation overexposure that led to a temporary recall of the Bracco-made product and an FDA Black Box warning in the package insert.

The next generation of PET perfusion agents promises to minimize radiation dose while helping mainstream interpreters routinely make difficult diagnostic calls.

Leading this generation are fluorinated positron emitters, which have an edge over rubidium in the diagnosis and monitoring of cardiovascular disease. One is Lantheus Medical Imaging's Flurpiridaz F-18. Now in Phase III testing, this myocardial perfusion agent passed a milestone in summer when the company completed enrollment for its first of two Phase-3 studies. These two trials will involve approximately 1,400 patients with known or suspected coronary artery disease (CAD) and will be conducted at sites in North America and Europe. Both studies have received a Special Protocol Assessment from the FDA.



Lantheus' newly released LEU Technelite generator offers an alternative source for generating technetium-99m, promising to mitigate the risk of supply disruptions of this radioisotope, which supports the majority of oncologic and cardiac SPECT. Photo courtesy of Lantheus Medical Imaging.

Corporate start up FluoroPharma is developing several new PET agents. One, a fluorinated myocardial perfusion agent called BFPET, has shown potential utility in the assessment of patients suspected of chronic CAD. The company plans to position the agent as a competitor to thallium and technetium-based SPECT agents, as

well as rubidium-82 in PET.

A second agent, CardioPET, could be useful to gauge the myocardial uptake of the heart's primary source of energy, fatty acids. Through the visualization – or even quantification – of this agent, physicians might measure perfusion initially, then use data collected later on to determine tissue viability, thus providing the basis to diagnose acute coronary syndrome and CAD. Both CardioPET and BFPET are still in clinical trials.

Even more speculative is VasoPET, the third fluorine based agent in development by FluoroPharma. So far it has shown promise but only in preclinical testing. This agent homes in specifically on vulnerable plaques, promising the means to assess the degree of risk patients may be at for stroke or heart attack.

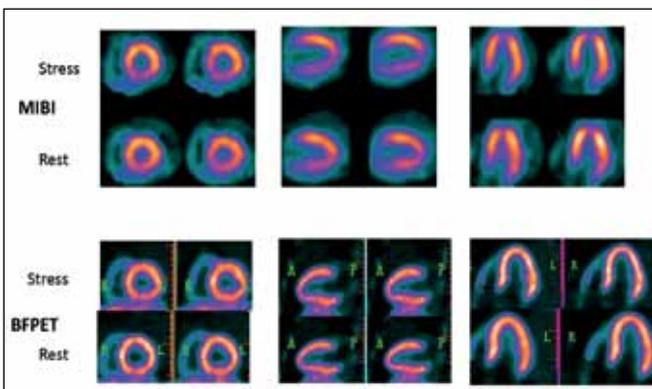


Improvements in PET scanner technology, such as motion management techniques built into Siemens' new Biograph mCT Flow, promise increased resolution. Spotting small lesions is essential to accurately staging lung cancer. Photo courtesy of Siemens Healthcare.

WORKING ON SPECT

The promise of new SPECT agents is exemplified by GE Healthcare's DaTscan (ioflupane I-123 injection), which the company is developing for use in the diagnosis of adult patients suspected of dementia with Lewy bodies (DLB). Data reported at the 2013 American Academy of Neurology (AAN) meeting regarding a randomized study of DaTscan showed that the agent improved diagnostic confidence. The multicenter study involving 170 subjects (114 suspected of DLB; 56 controls) involved 23 centers in six European countries. At eight and 24 weeks into follow-up, physicians interpreting DaTscan data reported being significantly more confident in their diagnoses compared with physicians who assessed control patients.

Last spring, GE commercialized its AdreView (iobenguane I-123), an iodine based agent that allows the assessment of nerve function in the heart as a gauge for mortality risk. Specifically AdreView addresses cardiac nerve activity to assist in the evaluation of patients suffering from heart failure and substantially decreased left ventricular ejection fraction (LVEF). Increased nerve function is associated with heart failure and a decline in LV function leading ultimately to heart failure.



FluoroPharma's experimental fluorine-18 based BFPET demonstrates higher resolution in the evaluation of myocardial perfusion than the technetium-based SPECT agent sestamibi. Top two rows of images MIBI Bottom two rows BFPET. Images courtesy of 301 Hospital in Beijing, China

Promise sometimes give way to problems as developers attempt to navigate the clinical testing of their fledgling products. And, to be clinically successful, they must produce consistent and reproducible results regardless of a practitioner's skill level. Helping considerably on that score is a new generation of PET and SPECT equipment, the forerunners of which appeared in the Siemens booth at the Society of Nuclear Medicine and Molecular Imaging (SNMMI) meeting last spring. These systems promise to make complex studies easier and, in the case of SPECT, allow quantification on a scale similar to what can be achieved with PET.

A new technology, dubbed xSPECT by Siemens Healthcare, is the core of the company's recently commercialized Symbia Intevo SPECT/CT. xSPECT integrates the CT and SPECT data sets, substantially boosting resolution levels and removing artifacts, while allowing quantitative analysis.

Also groundbreaking but for other reasons, is the second in Siemens' one-two punch delivered at SNMMI, the Biograph mCT Flow PET/CT system. The new Siemens product is the first to offer continuous motion scans instead of ones that depend on step-and-shoot acquisitions. Continuous flow speeds the exam, offering the physician the opportunity to dwell over one or another body area for greater resolution.

Advances in both modalities are primarily in two categories, improved resolution and shorter scan times. These translate directly into lower doses of radiopharmaceuticals, whose reduced radiation burden will make the modalities more attractive to users. Beyond the reach of hardware improvements and expanded utility, however, is the vulnerability of SPECT agents to technetium shortages.

ENSURING THE SUPPLY OF TECHNETIUM

Failed production at the handful of reactors around the world that make the technetium generator molybdenum have periodically crippled the nuclear medicine community. The most recent crisis was in 2009 when a radiation leak at Canada's Chalk River reactor put it out of commission for more than a year. Now the Canadian government plans to shut down the Chalk River reactor in 2016. Alternatives must be developed soon if technetium based agents are to remain in routine use.

Lantheus began shipping one solution early this year, namely its LEU TechneLite generator, a technetium generator based on molybdenum-99 produced from low-enriched uranium. The generator contains at least 95 percent non-HEU (highly enriched uranium) sourced molybdenum-99.

Shine Medical, a start-up that evolved from research at the nearby University of Wisconsin-Madison, is developing a process for manufacturing large quantities of molybdenum-99m using low-enriched uranium. Early testing of the process at Los Alamos National Laboratory has been promising. Shine Medical's goal is to build a plant employing as many as 100 staff. They will draw their molybdenum 99m from a particle accelerator rather than a nuclear reactor.

Infrastructure improvements that mitigate supply problems associated with SPECT radiopharmaceuticals, in the context of advances in scanner technology across both SPECT and PET and PET expansion into cardiology and neurology suggest a golden age in molecular imaging, one that may have unprecedented impact on the management of patients and personalization of medicine. For this to happen, many pieces must fall into place. Encouragingly, many already have.