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INFORMA

Lectura recomendada



- ✓ **Letter from the Editors: Positron Emission Tomography Radiopharmaceuticals—Current Status** Leonard M. Freeman, M. Donald Blaufox
- ✓ **Guest Editorial: New PET Radiopharmaceuticals as Molecular Imaging Probes** Shankar Vallabhajosula
- ✓ **A Broad Overview of Positron Emission Tomography Radiopharmaceuticals and Clinical Applications: What Is New?** Shankar Vallabhajosula, Lilja Solnes, Brigitte Vallabhajosula
- ✓ **The Next Generation of Positron Emission Tomography Radiopharmaceuticals in Oncology** Samuel L. Rice, Celeste A. Roney, Pierre Daumar, Jason S. Lewis
- ✓ **Positron Emission Tomography Radiopharmaceuticals for Imaging Brain Beta-Amyloid** Shankar Vallabhajosula
- ✓ **Florbetapir F-18: A Histopathologically Validated Beta-Amyloid Positron Emission Tomography Imaging Agent** John Lister-James, Michael J. Pontecorvo, Chris Clark, Abhinay D. Joshi, Mark A. Mintun, Wei Zhang, Nathaniel Lim, Zhiping Zhuang, Geoff Golding, Seok Rye Choi, Tyler E. Benedum, Paul Kennedy, Franz Hefti, Alan P. Carpenter, Hank F. Kung, Daniel M. Skovronsky
- ✓ **The Next Generation of Cardiac Positron Emission Tomography Imaging Agents: Discovery of Flurpiridaz F-18 for Detection of Coronary Disease** Ming Yu, Stephan G. Nekolla, Markus Schwaiger, Simon P. Robinson
- ✓ **68Ga-labeled DOTA-Peptides and 68Ga-labeled Radiopharmaceuticals for Positron Emission Tomography: Current Status of Research, Clinical Applications, and Future Perspectives.** Wouter A.P. Breeman, Erik de Blois, Ho Sze Chan, Mark Konijnenberg, Dik J. Kwekkeboom, Eric P. Krenning.



Letter from the Editors: Positron Emission Tomography Radiopharmaceuticals—Current Status

Leonard M. Freeman, MD, M. Donald Blafox, MD, PhD

The Editors are greatly indebted to Dr. Shankar Vallabhajosula for his work as the Guest Editor of this issue of the *Seminars in Nuclear Medicine*. Dr. Vallabhajosula has a special relationship with the Editors and the Department of Nuclear Medicine at the Albert Einstein College of Medicine. His first published article originated from the laboratory of Dr. Lakshman Chervu, who was the Director of the Radiochemistry Laboratory in Nuclear Medicine at the Albert Einstein College of Medicine from 1971 to 1988. Even at this stage in his career, Shankar was already a valuable and productive contributor to the field of nuclear medicine. This early article was a report entitled “Quality Control of Technetium Labelled Lung Imaging Agents,” which he coauthored with Dr. Chervu and one of us (Dr. Blafox) in 1977.¹ Several years later, Dr. Vallabhajosula was again second author on an article originating from the Radiochemistry Laboratory at Einstein.² Dr. Vallabhajosula's career continued with increasing productivity and contributions as he moved on to become Director of the Radiochemistry Laboratory at New York Presbyterian Hospital–Weill Cornell Medical College. This issue shows the depth and breadth of his knowledge, where in addition to serving as Guest Editor, a time consuming task to begin with, he also wrote several of the articles. These articles each have the promise to become classics in the field of nuclear medicine.

The accompanying Guest Editorial³ outlines quite nicely the rationale for the selection of the contributors to this issue. One of the ongoing shortcomings of nuclear medicine, in spite of its tremendous power, is the general lack of specificity of many of the diagnostic agents that we use. Positron emission tomography (PET) imaging has become a dominant force in medical and molecular imaging, but the agent upon which we depend primarily, ¹⁸F-fluorodeoxyglucose, is not specific for any special disease, but rather shows abnormalities in a broad spectrum of diseases. This general lack of specificity impairs the amount of information we can provide the referring physician. In single-photon emission computed tomography (SPECT) imaging, a significant number of specific agents have been introduced such as ¹¹¹In-DOTA-octreotide, but much work remains to be done. It is clear from viewing this issue that the next decade will see the introduction of a large number of very significant and specific diagnostic agents in the field in nuclear medicine, both in SPECT imaging and in PET. This will greatly enhance our diagnostic accuracy and further build upon the valuable information that we can provide to the referring physician.

In addition, because of the increasing specificity of these agents, there is the promise of a new field, “theranostics.” This will make it possible to use the same agent both for diagnostic imaging and, subsequently, for therapy of the disease



disclosed; and, finally, as a means of follow-up of the efficacy of therapy. The field of theranostics has become so important that the editors are planning an issue devoted specifically to this area in 2012.

A review of this seminar will surely leave the reader with an increased appreciation of the enormous potential that nuclear medicine offers in diagnostic and therapeutic medicine.

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Guest Editorial: New PET Radiopharmaceuticals as Molecular Imaging Probes

[Shankar Vallabhajosula, Ph.D. \(Guest Editor\)](#)

Despite the availability of hundreds of positron-emission tomography (PET) radiotracers and successful documentation of their clinical usefulness, [^{18}F]fluorodeoxyglucose (FDG) is currently the most widely used radiopharmaceutical. The field of molecular imaging is anxiously awaiting the introduction of new-generation of PET radiopharmaceuticals for routine clinical use. The editors of *Seminars in Nuclear Medicine* have wisely chosen the most appropriate time to dedicate this July issue to provide a broad overview of new PET radiopharmaceuticals. It has been a privilege and an honor to be a guest editor for this special volume and assemble 6 major manuscripts from senior investigators in academic research as well as in pharmaceutical industry.

Like any other drug or pharmaceutical, the Food and Drug Administration (FDA) approval of a PET radiopharmaceutical typically involves submission of a New Drug Application (NDA) by a manufacturer or a company that clearly documents 2 major aspects of the drug: (1) manufacturing of PET drug; and (2) safety and effectiveness of a drug with specific indications for its clinical use. The safety and effectiveness of all PET radiopharmaceuticals must also be performed in multicenter phase I, II, and III clinical trials using PET radiopharmaceuticals manufactured under current good manufacturing practices (cGMPs), as required by the FDA new regulatory guidance issued in December 2009.

In the first article, Drs Vallabhajosula and colleagues¹ from Weill Cornell Medical College provide a summary of various PET drugs (generic and proprietary agents) of clinical interest and describe various issues involved in obtaining an approval NDA by FDA. The nonproprietary or generic PET radiopharmaceuticals, such as [^{18}F]FDOPA, [^{18}F]FLT, and several others have never been evaluated in multicenter clinical trials with use of a specific manufacturing process or quality control criteria. Therefore, to obtain FDA approval for a clinical indication, the National Cancer Institute (NCI), Society of Nuclear Medicine Clinical Trials Network (SNM-CTN), and American College of Radiology Imaging Network (ACRIN) have been conducting multicenter clinical trials with several nonproprietary PET drugs. Although ACRIN started multicenter clinical trials with [^{18}F]FMISO and ^{64}Cu -ATSM, the clinical trials with [^{18}F]FLT sponsored by SNM-CTN have not even started yet. The routine clinical use with these generic agents may not happen soon. In contrast, pharmaceutical companies developed several new proprietary PET drugs, which are in different phases of clinical trials and potentially available for routine clinical use soon.



Dr Lewis and colleagues² from Memorial Sloan-Kettering Cancer Center provide a brief of summary, including labeling methods, biological targets, and the most recent preclinical or clinical data, of some of the next-generation of PET radiopharmaceuticals. Generic agents like [18F]FDHT, [11C]choline, [18F]fluorocholine, and 68Ga-DOTATOC continue to play a significant role in research protocols as imaging biomarkers in the assessment of antitumor response after therapy. Among the proprietary PET drugs, multicenter clinical trials are in various stages of clinical evaluation with 3 new agents¹; [18F]FACBC (fluciclovine) for imaging prostate cancer and brain tumors; 4-[18F]fluoro glutamic acid (TIM-1, also known as [18F]-BAY 85-8050) to image intermediary tumor metabolism of breast cancer and melanoma; 18F-AH111585 (fluciclatide), an RGD peptide to image tumor angiogenesis of solid tumors. ImmunoPET based on 124I or positron-emitting radiometals (64Cu or 89Zr) may play a significant role in the tumor detection and to monitor response after immunotherapy and/or radioimmunotherapy. Successful completion of phase 3 trials and potential approval of NDA for 124I-cG250 (Redectane) for targeting an epitope of carbonic anhydrase IX antigen expressed in clear cell renal cell carcinoma is a perfect example of the role of immunoPET technique in patient management.¹

A number of peptide receptors have been demonstrated to be overexpressed with greater incidence and/or density in various neuroendocrine tumors (NETs). Because most NETs express somatostatin (SST) receptors, 111In-DOTA-octreotide (OctreoScan) has been successfully used for almost 2 decades as a routine diagnostic single-photon emission computed tomography radiopharmaceutical to image NETs. Breeman and colleagues³ from Erasmus MC, Rotterdam provide a summary of 68Ga-labeled DOTA-peptides and 68Ga-labeled radiopharmaceuticals for PET. The peptides DOTA-TOC and DOTA-NOC have been developed recently and are becoming the gold standard for peptide-based 68Ga-PET. Preclinical data suggest that these radiotracers are superior to existing radiolabeled SS analogs, having a greater affinity for SSTR2 but, most important, also for SSTR5. Preliminary clinical evaluation with 68Ga-DOTA-TOC and 68Ga-DOTA-NOC demonstrated rapid renal clearance and accumulate rapidly in the tumors providing higher contrast imaging. With the availability of commercial 68Ga generator, SSTR-PET has the potential to become a major molecular imaging biomarker in early detection of NETs, and selection of suitable candidates for therapy based on 90Y- and/or 177Lu-labeled SST analogs.

Almost 20 years ago, the FDA approved Cardiogen-82 (Rubidium Rb 82 Generator) for myocardial perfusion imaging studies based on PET. Subsequently in the year 2000, the FDA also approved [13N]-ammonia-PET for the assessment of myocardial perfusion. Both these PET radiopharmaceuticals, however, have their own disadvantages for routine clinical use and the field of nuclear cardiology uses single-photon emission computed tomography radiopharmaceuticals mainly for the assessment of myocardial perfusion



imaging studies. Dr Robinson and colleagues⁴ from Lantheus Medical Imaging and Poliklinik der Technischen Universität, Munich, describe the discovery of the next generation of cardiac PET imaging agent, BMS747158 (flurpiridaz F-18) for the detection of coronary disease. It exhibits rapid uptake in the myocardium, prolonged retention, and superior extraction versus flow profiles compared with ²⁰¹Tl and ^{99m}Tc sestamibi. On the basis of preclinical studies, it has been observed that a high and flow-independent first-pass extraction fraction promises linearity between tracer uptake and myocardial blood flow. Phase 1 and 2 studies have been completed with Flurpiridaz F-18, and Phase 3 studies are being planned starting early 2011.

Alzheimer's disease (AD) is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations. In the last decade, the diagnosis of AD, along with the prediction of who will develop dementia, has been assisted by magnetic resonance imaging and FDG-PET. Because AD is defined histologically by the presence of extracellular β -amyloid (A β) plaques and intraneuronal neurofibrillary tangles in cerebral cortex, several investigators have developed several positron emitting radiotracers with specific binding to brain A β plaques. Dr Vallabhajosula⁵ provides an extensive summary of amyloid biology and chemistry of A β -specific ¹¹C and ¹⁸F PET radiopharmaceuticals. Among these radiotracers, [¹¹C]-PiB is the most studied A β binding PET radiopharmaceutical in the world. Because ¹¹C is not ideal for commercialization, several ¹⁸F labeled tracers have been developed. At this time, ¹⁸F-AV-45 (florbetapir) completed phase III clinical studies, whereas ¹⁸F-AV-1 (florbetaben) and [¹⁸F]3'-F-PiB (flutemetamol), are in phase II and III clinical trials. Dr Lister-James and colleagues⁶ from Avid Radiopharmaceuticals summarize the chemistry, pharmacology, and clinical experience with florbetapir F-18. The results of clinical studies with this agent demonstrate a clear correlation between in vivo pet imaging using Florbetapir F-18 and postmortem histopathological quantitation of A β in the brain. An NDA for florbetapir F-18 Injection (Amyvid) is under review by the FDA at the time of preparation of this manuscript.

Clinical trials have clearly documented that PET radiopharmaceuticals capable of assessing A β content in vivo in the brains of AD subjects and subjects with mild cognitive impairment will be important as diagnostic agents to detect in vivo amyloid brain pathology. A β imaging can have a significant role in identifying patients at risk for AD, who would be suitable candidates for anti-A β therapies particularly drugs that would target A β production and aggregation. In addition PET amyloid imaging will also help test the amyloid cascade hypothesis of AD and as an aid to assess the efficacy of anti-amyloid therapeutics currently under development in clinical trials.



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A Broad Overview of Positron Emission Tomography Radiopharmaceuticals and Clinical Applications: What Is New?

Shankar Vallabhajosula, PhD, Lilja Solnes, MD, Brigitte Vallabhajosula, PhD

Positron emission tomography (PET)/computed tomography (CT) is a rapidly expanding imaging modality, thanks to the availability of compact medical cyclotrons and automated chemistry synthesis modules for the production of PET radiopharmaceuticals. Despite the availability of many radiotracers, [^{18}F]fluorodeoxyglucose (FDG) is currently the most widely used radiopharmaceutical in PET, and the field of molecular imaging is anxiously awaiting the introduction of new PET radiopharmaceuticals for routine clinical use. During the last five years, several proprietary PET radiopharmaceuticals have been developed by major companies, and these new agents are in different stages of clinical evaluation. These new PET drugs are designed for imaging brain beta amyloid, myocardial perfusion, amino acid transport, angiogenesis, and tumor antigen expression. In addition, the National Cancer Institute, Society of Nuclear Medicine Clinical Trials Network, and the American College of Radiology Imaging Network have been conducting multicenter clinical trials with several nonproprietary PET drugs such as sodium [^{18}F]fluoride, [^{18}F]fluorothymidine, [^{18}F]fluoromisonidazole, and ^{64}Cu -labeled diacetyl-bis (*N*4-methylthiosemicarbazone. All new PET radiopharmaceuticals, like any other drugs, must be manufactured under current good manufacturing practices as required by the Food and Drug Administration before clinical evaluation (phases I, II, and III) and submission of new drug application. This review briefly describes the chemistry, mechanisms(s) of localization, and clinical application of both proprietary and nonproprietary new PET drugs under multicenter clinical evaluation.



The Next Generation of Positron Emission Tomography Radiopharmaceuticals in Oncology

Samuel L. Rice, MD, Celeste A. Roney, PhD, Pierre Daumar, PhD, Jason S. Lewis, PhD

Although ^{18}F -fluorodeoxyglucose (^{18}F -FDG) is still the most widely used positron emission tomography (PET) radiotracer, there are a few well-known limitations to its use. The last decade has seen the development of new PET probes for in vivo visualization of specific molecular targets, along with important technical advances in the production of positron-emitting radionuclides and their related labeling methods. As such, a broad range of new PET tracers are in preclinical development or have recently entered clinical trials. The topics covered in this review include labeling methods, biological targets, and the most recent preclinical or clinical data of some of the next generation of PET radiopharmaceuticals. This review, which is by no means exhaustive, has been separated into sections related to the PET radionuclide used for radiolabeling: fluorine-18, for the labeling of agents such as FACBC, FDHT, choline, and Galacto-RGD; carbon-11, for the labeling of choline; gallium-68, for the labeling of peptides such as DOTATOC and bombesin analogs; and the long-lived radionuclides iodine-124 and zirconium-89 for the labeling of monoclonal antibodies cG250, and J591 and trastuzumab, respectively.



Positron Emission Tomography Radiopharmaceuticals for Imaging Brain Beta-Amyloid

Shankar Vallabhajosula, PhD

Alzheimer's disease (AD) is defined histologically by the presence of extracellular β -amyloid ($A\beta$) plaques and intraneuronal neurofibrillary tangles in the cerebral cortex. The diagnosis of dementia, along with the prediction of who will develop dementia, has been assisted by magnetic resonance imaging and positron emission tomography (PET) by using [^{18}F]fluorodeoxyglucose (FDG). These techniques, however, are not specific for AD. Based on the chemistry of histologic staining dyes, several $A\beta$ -specific positron-emitting radiotracers have been developed to image neuropathology of AD. Among these, [^{11}C]PiB is the most studied $A\beta$ -binding PET radiopharmaceutical in the world. The histologic and biochemical specificity of PiB binding across different regions of the AD brain was demonstrated by showing a direct correlation between $A\beta$ -containing amyloid plaques and in vivo [^{11}C]PiB retention measured by PET imaging. Because ^{11}C is not ideal for commercialization, several ^{18}F -labeled tracers have been developed. At this time, [^{18}F]3'-F-PiB (Flutemetamol), ^{18}F -AV-45 (Florbetapir), and ^{18}F -AV-1 (Florbetaben) are undergoing extensive phase II and III clinical trials. This article provides a brief review of the amyloid biology and chemistry of $A\beta$ -specific ^{11}C and ^{18}F -PET radiopharmaceuticals. Clinical trials have clearly documented that PET radiopharmaceuticals capable of assessing $A\beta$ content in vivo in the brains of AD subjects and subjects with mild cognitive impairment will be important as diagnostic agents to detect in vivo amyloid brain pathology. In addition, PET amyloid imaging will also help test the amyloid cascade hypothesis of AD and as an aid to assess the efficacy of anti-amyloid therapeutics currently under development in clinical trials.



Florbetapir F-18: A Histopathologically Validated Beta-Amyloid Positron Emission Tomography Imaging Agent

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Florbetapir F-18 is a molecular imaging agent combining high affinity for β -amyloid, pharmacokinetic properties that allow positron emission tomography (PET) imaging within a convenient time after dose administration, and the wide availability of the radionuclide fluorine-18. Florbetapir F-18 is prepared by nucleophilic radiofluorination in approximately 60 minutes with a decay-corrected yield of 20%-40% and with a specific activity typically exceeding 100 Ci/mmol. The florbetapir F-18 dissociation constant (K_d) for binding to β -amyloid in brain tissue from Alzheimer's disease (AD) patients was 3.7 ± 0.3 nmol/L, and the maximum binding capacity (B_{max}) was 8800 ± 1600 fmol/mg protein. Autoradiography studies have shown that florbetapir F-18 selectively binds to β -amyloid aggregates in AD patient brain tissue, and the binding intensity is correlated with the density of β -amyloid quantified by standard neuropathologic techniques. Studies in animals revealed no safety concerns and rapid and transient normal brain uptake (6.8% injected dose/g at 2 minutes and 1.9% injected dose/g at 60 minutes in the mouse). Florbetapir F-18 has been well-tolerated in studies of more than 2000 human subjects. Biodistribution studies in humans revealed predominantly hepatobiliary excretion. The whole body effective dose was 7 mSv from a dose of 370 MBq. The pharmacokinetic of florbetapir F-18 make it possible to obtain a PET image with a brief (10 minutes) acquisition time within a convenient time window of 30-90 minutes after dose administration. Clinical studies have demonstrated a clear correlation between in vivo PET imaging with florbetapir F-18 and postmortem histopathologic quantitation of β -amyloid in the brain



The Next Generation of Cardiac Positron Emission Tomography Imaging Agents: Discovery of Flurpiridaz F-18 for Detection of Coronary Disease

Ming Yu, MD, PhD*, Stephan G. Nekolla, PhD†, Markus Schwaiger, MD†, Simon P. Robinson, PhD*

Myocardial perfusion imaging (MPI) with thallium 201 (^{201}Tl) or $^{99\text{m}}\text{Tc}$ based imaging agents has become a major tool for noninvasive identification of coronary artery disease (CAD). However, single photon emission computed tomography (SPECT) imaging with the current agents is vulnerable to artifacts associated with soft tissue attenuation, proximal gastrointestinal activity, image quality, and suboptimal sensitivity and is limited by the degree of first-pass myocardial extraction. The development of ^{18}F -based flurpiridaz F-18 takes advantage of positron emission tomography (PET) to overcome many of the imaging issues and structural design to achieve an ideal MPI agent profile. Flurpiridaz F-18 was designed to bind to mitochondrial complex I with high affinity and demonstrates high heart uptake in multiple species with clear delineation of perfusion deficits. It exhibits rapid uptake in the myocardium, prolonged retention, and superior extraction versus flow profiles compared with ^{201}Tl and $^{99\text{m}}\text{Tc}$ -sestamibi. A first in man study has established the safety and dosimetry of flurpiridaz F-18 and confirmed high sustained cardiac uptake. Subsequent studies performed in CAD patients established the dose and timing needed to detect perfusion deficits when the agent is administered under rest and stress conditions. This review compares the current preclinical and clinical data with an ideal MPI agent profile. The assessment indicates flurpiridaz F-18 represents a new generation of PET MPI agents and demonstrates significantly improved molecular and imaging characteristics.



68Ga-labeled DOTA-Peptides and 68Ga-labeled Radiopharmaceuticals for Positron Emission Tomography: Current Status of Research, Clinical Applications, and Future Perspectives

Wouter A.P. Breeman, PhD, Erik de Blois, MSc, Ho Sze Chan, MSc, Mark Konijnenberg, PhD, Dik J. Kwekkeboom, MD, PhD, Eric P. Krenning, MD, PhD

In this review we give an overview of current knowledge of 68Ga-labeled pharmaceuticals, with focus on imaging receptor-mediated processes. A major advantage of a 68Ge/68Ga generator is its continuous source of 68Ga, independently from an on-site cyclotron. The increase in knowledge of purification and concentration of the eluate and the complex ligand chemistry has led to 68Ga-labeled pharmaceuticals with major clinical impact. 68Ga-labeled pharmaceuticals have the potential to cover all today's clinical options with 99mTc, with the concordant higher resolution of positron emission tomography (PET) in comparison with single photon emission computed tomography. 68Ga-labeled analogs of octreotide, such as DOTATOC, DOTANOC, and DOTA-TATE, are in clinical application in nuclear medicine, and these analogs are now the most frequently applied of all 68Ga-labeled pharmaceuticals. All the above-mentioned items in favor of successful application of 68Ga-labeled radiopharmaceuticals for imaging in patients are strong arguments for the development of a 68Ge/68Ga generator with Marketing Authorization and thus to provide pharmaceutical grade eluate. Moreover, now not one United States Food and Drug Administration–approved or European Medicines Agency–approved 68Ga-radiopharmaceutical is available. As soon as these are achieved, a whole new radiopharmacy providing PET radiopharmaceuticals might develop.



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