Dopamine Transporter (DaT) SPECT Imaging

$^{123}$I-ioflupane (N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl) nortropane), is a single photon emission computed tomography (SPECT) molecular imaging agent for imaging the dopamine transporter (DaT) (Figure 1). It was recently approved by the U.S. Food and Drug Administration (FDA) and is available in the U.S. market. This agent was approved in Europe in 2000, and several hundred thousand patients have been scanned. It has proven to be safe, reliable and very sensitive for detection of degeneration of nigrostriatal nerve cells in the differential diagnosis of movement disorders such as Parkinson’s disease (PD) and dementia. Although clinical diagnosis is straightforward in many patients, it may be difficult in others—especially in early disease—and structural imaging with computed tomography or magnetic resonance imaging usually is of little help.

$^{123}$I-ioflupane is a cocaine analogue with high affinity and relatively good selectivity for DaT. DaT concentration is highest in striatum (putamen and caudate nucleus) where the dopamine transporters are located on the presynaptic side of dopaminergic synapses (Figure 2). They transport dopamine out of the synaptic cleft, back into presynaptic axons for either re-use or degradation.

Degeneration of these presynaptic neurons results in lower striatal DaT density. Parkinsonian symptoms typically become apparent only after at least 50 percent of nigrostriatal nerve terminals are lost. Thus, DaT imaging is excellent for early detection of nigrostriatal dopaminergic degeneration. Also, the degree of reduction in DaT binding is related to disease severity.

In PD and related parkinsonian syndromes such as multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), there is presynaptic dopaminergic degeneration and therefore decreased DaT binding. Although the pattern of DaT binding tends to be somewhat different, there is a large overlap in DaT imaging findings among these syndromes, and $^{123}$I-ioflupane imaging is unable to discriminate among them. In essential tremor, psychogenic parkinsonism and neuroleptic drug-induced parkinsonism, however, there is no presynaptic dopaminergic degeneration and DaT SPECT is normal.

$^{123}$I-ioflupane SPECT can also be used to differentiate dementia with Lewy bodies (DLB) from other dementias. This can be important clinically, because DLB patients

### Indications for $^{123}$I-ioflupane imaging
- Detection of loss of functional dopaminergic neuron terminals in the striatum of patients with clinically uncertain parkinsonian syndromes
- Differentiation of essential tremor, psychogenic parkinsonism, or neuroleptic induced parkinsonism from presynaptic parkinsonian syndromes (Parkinson’s disease, multiple-system atrophy, corticobasal degeneration, progressive supranuclear palsy)
- Early detection of Parkinson’s disease
- Assessment of disease severity and progression
- Differentiation of dementia with Lewy bodies from other dementias

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respond better to therapy with acetylcholinesterase inhibitors but may suffer severe side effects if given neuroleptic drugs and have worse prognosis. In DLB, DaT binding is reduced, whereas in most other dementias (with the exception of dementia associated with PD), DaT binding is normal.

Technical Aspects

Typically 185 MBq (5 mCi) of $^{123}I$-ioflupane is injected intravenously. To reduce exposure of the thyroid to free $^{123}I$, the thyroid can be blocked at least one hour before tracer injection, although even without blocking, the radiation dose to the thyroid would be low. The only contraindications are pregnancy, the inability to cooperate with SPECT brain imaging, or a known hypersensitivity to the active substance or to any of its excipients (which is rare). Iodine allergy is not a contraindication. Breastfeeding should be interrupted for at least 24 hours after injection.

Figure 1: $^{123}I$-ioflupane structure

Figure 2: Dopaminergic synapse in the striatum

Figure 3: $^{123}I$-ioflupane images: normal subject and various stages of Parkinson’s disease

Anti-parkinsonian medications usually do not significantly interfere and therefore do not need to be discontinued. Of course, cocaine and related substances, such as methylphenidate, fentanyl, or ketamine, may interfere with DaT binding and should be discontinued (see Booij et al. Eur J Nucl Med Mol Imaging 2008;35:424-38 for an extensive list of interfering medications). Three to six hours after injection, SPECT images are acquired on a dual (or more) head gamma camera. On a dual head camera, this typically takes 30-45 minutes. A detailed procedure guideline is downloadable from the Society of Nuclear Medicine Web site (“Practice Management”>“Procedure Guidelines”>“Neurology”).

Image Interpretation

Images should be reoriented to a standard plane to avoid the false appearance of asymmetry due to head tilt. Images should be checked for asymmetry and a decrease of the target to background ratio. In a normal scan, the striatum is clearly visible as right and left symmetric, comma-shaped regions, with both caudate and putamen showing a high intensity compared to background (Figure 3). With increasing age, a slight decline in target to background ratio is expected (typically some 5-8 percent per decade).

In early PD there is usually an asymmetrical pattern of reduced DaT binding starting in the dorsal putamen contralateral to the clinically most symptomatic body side, gradually progressing anteriorly and ipsilaterally as the disease becomes more severe. Activity in the caudate nucleus is relatively preserved in early disease but will also decline with advancing disease. In the atypical parkinsonian syndromes (MSA, PSP), there usually will be a more symmetrical decrease in DaT binding and relatively more involvement of the caudate nucleus; however, there is too much overlap to reliably differentiate between PD and these other conditions. In DLB, DaT binding is reduced, typically with bilateral loss of DaT binding, mainly in the putamen but also in the caudate and generally with less asymmetry than in PD.

Many specialized centers also use semiquantitative image assessment in which specific binding ratios are calculated, e.g., the ratio of striatal to occipital activity. These can be compared to values of a normal reference population. Because semiquantification is influenced by many factors (e.g., camera, scanning protocol, reconstruction algorithms, semiquantification method, etc.) there is no universal cutoff value for normal vs. abnormal. Each site needs to establish its own normal reference range. Although semiquantification may have some advantages, especially for research purposes or in case of very subtle changes, it usually is not necessary.
because the decrease in DaT binding is clearly visible even in the early stages of disease.

**Conclusion**

Dopamine transporter imaging with $^{123}$I-ioflupane has recently been FDA approved. It is a robust and simple technique that can sensitively detect or rule out degeneration of presynaptic striatal dopaminergic nerve cells. It can differentiate presynaptic parkinsonian syndromes (PD, MSA, PSP) from essential tremor, drug-induced parkinsonism and psychogenic parkinsonism, but it cannot differentiate between these presynaptic parkinsonian syndromes. $^{123}$I-ioflupane SPECT can also be used to differentiate dementia with Lewy bodies from other types of dementia, such as Alzheimer’s disease.

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curricula and a white paper on molecular imaging training for scientists was published. The task force submitted formal suggestions to the Residency Review Committee in both 2007 and 2008 for the expansion of the nuclear medicine residency curriculum that included increased emphasis on 13 “advanced practice” topics. Although these suggestions have not yet been incorporated in the residency curriculum, SNM is now offering a training course on this material.

A new series of educational lectures in molecular imaging debuts in 2012 in a monthly webinar format. The curriculum is designed primarily for nuclear medicine and radiology residents in order to provide a firm foundation in the basic principles of molecular imaging. The course is primarily designed for nuclear medicine and radiology residents, but is also helpful for physicians, scientists, technologists and other professionals who want a better understanding of molecular imaging. This series of webinars is designed to educate participants on the basic principles of molecular imaging, including methods employing radioisotopes, optical imaging agents and magnetic resonance.

At the conclusion of the program, participants will be able to:

- Review the basic science of molecular imaging, including molecular and cellular chemistry, biochemistry, biology, imaging physics and instrumentation.
- Apply key concepts to effectively communicate and interact with experts in molecular imaging.
- Discuss the current and future roles of advanced molecular imaging techniques and agents for clinical imaging of disease.

The following topics will be offered monthly (and on-demand) with CME and VOICE credit: Molecular and Cellular Biology Overview, Cell Trafficking, Animal Imaging and Instrumentation, Magnetic Resonance Imaging and Spectroscopy, Molecular Imaging of the Heart, Optical Imaging, Techniques and Agents, Apoptosis, Angiogenesis, Proliferation, Reporter Genes, Amyloid Imaging, Hypoxia, and Molecular Imaging with Ultrasound Technology.

Through training mechanisms such as this course, SNM hopes to help grow and evolve the field of molecular imaging.

Heather Jacene, MD

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**SNM Brings Molecular Imaging to the Public on Times Square Jumbotron**

On December 23, SNM debuted a 15-second message on the CBS jumbotron screen in New York City’s Times Square to raise public awareness of molecular imaging. The video will run once an hour for three months, including the holiday season and the New Year’s Eve celebration, which alone attracted an estimated one million people.

The CBS “Super Screen” is 26 feet tall and 20 feet across and is strategically positioned at 42nd St. between 7th and 8th Avenues in the heart of the Times Square Plaza. It is estimated that 1.6 million people pass through Times Square each day.

The video focuses on how molecular imaging can provide earlier diagnosis and directs people to SNM’s new patient website, discovermi.org, for more information.
SNM and AACR Announce Joint Conference

Achieving the ultimate goal of curing cancer will require the collaborative efforts of cancer researchers and the molecular imaging community at all levels—basic, translational, and clinical. SNM and the American Association for Cancer Research (AACR) are thrilled to announce a joint effort to present the SNM–AACR conference on State-of-the-Art Molecular Imaging in Cancer Biology and Therapy, to be held February 27 through March 2, 2013, at the Manchester Grand Hyatt in San Diego, Calif.

With our Program Committee, including Christopher Contag, Kim Kelly, Hisataka Kobayashi, Steve Larson, Jason Lewis, Martin Pomper, and Zena Werb, we have designed a three day conference to bring together imaging scientists with biologists specializing in basic, translational, and clinical cancer research to discuss the latest developments in the field of imaging and its applications in cancer biology. The goal of this conference is to provide a forum for the collaborative exchange of information and to provide background for imagers on cancer biology, while educating cancer biologists on how we can advance cancer research with the latest imaging research and ways in which it can be used toward diagnosing and monitoring treatment of cancer. The speakers will be expert molecular imaging scientists, medical oncologists, chemical engineers, basic cancer biologists, and systems biologists.

The primary focus of the conference will be on areas in cancer biology that interface with molecular imaging technologies and/or imaging agent development. Sessions will emphasize the role of imaging in visualizing cancer stem cells, the tumor microenvironment, stroma, premetastatic conditions, cancer metabolism, and immune cell migration. Other topics include innovative cancer therapies guided by imaging in real time for the improvement of patient outcomes.

We aim to encourage discussion by following scientific talks with panel discussions addressing some of the more controversial topics. We will present opportunities for participation from junior scientists by offering mentoring breakfasts and short talks selected from the highest-rated abstracts. We will also feature preconference educational workshops on selected topics and both these sessions and the conference will offer continuing medical education credit.

We are confident that this conference will prove to be a fruitful union between state-of-the-art molecular imaging and cancer research, two important branches of science that together will enhance the ability to fight cancer by combining new discoveries in the diagnosis, staging, and treatment of patients with cancer.

Carolyn J. Anderson, PhD
David Piwnica-Worms, MD, PhD
Conference Co-chairs, SNM–AACR Joint Conference on State-of-the-Art Molecular Imaging in Cancer Biology and Therapy

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**References**

Each month, the CMIIT Editorial Board selects the top molecular imaging research papers from all papers indexed by PubMed. Below are recent papers on molecular imaging research. The links below go to these references, including their abstracts and links to the full paper on PubMed.

Clinical Molecular Imaging with Radiotracers: Current Status.
Graham MM. Med Princ Pract. 2011 Nov 30. [Epub ahead of print]

Dual-Labeling Strategies for Nuclear and Fluorescence Molecular Imaging: A Review and Analysis.

In vivo imaging of ligand receptor binding with Gaussia luciferase complementation.
Nat Med. 2011 Dec 4. doi: 10.1038/nm.2590. [Epub ahead of print]

Leveraging the power of ultrasound for therapeutic design and optimization.
Caskey CF, Hu X, Ferrara KW.
Upcoming CMIIT Meetings and Awards

The SNM Center for Molecular Imaging Innovation and Translation (CMIIT) has an exciting line-up of meetings this spring following the Mid-Winter Meeting and Dementia Summit. On March 20-21, 2012, Johns Hopkins University (JHU), the University of Virginia and CMIIT are hosting a preclinical imaging workshop on the JHU campus in Baltimore, Md. The workshop is targeted towards physicians, scientists (including postdoctoral fellows and graduate students) and scientific laboratory professionals interested in using molecular imaging for in vivo biomedical applications. Individuals of all experience levels are welcome to participate and all participants will learn the fundamentals of various small animal imaging modalities. A limited number of individuals can also register to attend a half-day session of hands-on training and demonstrations. To see the complete program or for more information about attending the workshop, please visit www.snm.org/pci2012.

In April, CMIIT will sponsor the third “Multimodality Cardiovascular Molecular Imaging Symposium” on April 19–21, 2012, at the Natcher Auditorium on the National Institutes of Health campus in Bethesda, Md. This 2 ½ day symposium will bring together individuals from multiple scientific disciplines with an emphasis on interaction among speakers and registrants to stimulate further growth in the field. Sessions will review the current state of the art in cardiovascular imaging, from novel probes for evaluation and treatment of cardiovascular disease to evaluation of stem cell therapy. Challenges of translation of molecular imaging and therapy also will be addressed. These lectures will provide an overview of the potential of molecular imaging for improving understanding and management of critical cardiovascular pathophysiological processes, such as atherosclerosis, angiogenesis, cardiomyopathies, ischemia and infarction. For additional information, visit www.snm.org/cvmi2012.

Finally, applications are currently being accepted for CMIIT’s Laboratory Professional Award, which is designed to recognize novel and high-impact tools, techniques, and practices in molecular imaging developed by non-PhD laboratory professionals. Its purpose is to promote the innovative efforts and exemplary accomplishments by individuals in the laboratory who may not have the opportunity to receive recognition in other arenas. Publication of the work is not a requirement and larger bodies of work may be better suited for submission for CMIIT’s Young Investigator Award, especially if the emphasis is upon research results as opposed to the development of new tools and techniques. Applications will be accepted online until March 31, 2012, at www.snm.org/miawards.

Carolyn J. Anderson, PhD

SNM House of Delegates Passes Name Change Amendment

In January 2012 at the SNM Mid-Winter Meeting, the SNM House of Delegates (HOD)—consisting of the leadership of the councils, centers, chapters and technologist section that make up the society—supported by greater than a two-thirds majority a proposed amendment to the SNM bylaws that would change the society’s name to the “Society of Nuclear Medicine and Molecular Imaging.”

The process of determining whether a name change is in the best interest for the society began last year. In May 2011, The Journal of Nuclear Medicine (JNM) published an article discussing the potential name change and asking for member feedback. Almost 75 percent of the feedback received in response to the article was in favor of the name change. It was clear that the majority of those who responded felt that the name change was accurate and necessary in order to continue the growth of the field and the society membership. An article in the November issue of JNM discussed the feedback and included the proposed changes to the bylaws. A point and counterpoint debate on the topic was published in the December JNM to illustrate both points of view.

Over the past five years—in particular through the Bench to Bedside campaign—SNM has made a concerted effort to embrace other modalities that, like nuclear medicine, image physiology at a cellular and molecular level to diagnose, treat, and monitor therapy of disease. Our field and professional organization have the potential to grow for the ultimate benefit of patients by welcoming professionals who utilize these emerging technologies while continuing to focus on our core area, nuclear medicine. The name “Society of Nuclear Medicine and Molecular Imaging” retains our rich history and identity while recognizing the growing diversity in our field, imaging and nonimaging, nuclear and nonnuclear, molecular and nonmolecular. Retaining the term “nuclear medicine” also recognizes the therapeutic, medicinal aspects of our specialty.

The last step towards finalizing the name change required by our letters of incorporation is for members to vote on this change at our annual business meeting. The vote will take place on Monday, June 11, at the SNM Business Meeting, held between 8:00-10:00 am, during the society’s Annual Meeting in Miami, Fla. We strongly encourage all members to attend the meeting in order to actively participate in this historic and very important vote. For more information, please visit www.snm.org/namechange.
DaTscan: A New Tracer for Parkinsonian Syndromes

Molecular imaging brings exciting changes to our field with the horizon full of new agents. With many Phase II and Phase III trials showing promising results, we find ourselves busy learning about new tracers that are or will be available to us in the fields of oncology, cardiology and neurology. For example, a significant development has been the creation of β-amyloid radiopharmaceuticals that can detect Alzheimer’s disease and differentiate between other dementias, such as frontotemporal dementia.

On January 17, 2011, GE Healthcare announced the Food and Drug Administration’s (FDA) approval of ioflupane iodine-123 injection (DaTscan). It is the first FDA-approved radiopharmaceutical imaging agent to help evaluate patients with suspected parkinsonian syndromes, such as Parkinson’s disease (PD). This single photon emission computed tomography (SPECT) agent has been available in Europe since 2000 and has been used in nearly 300,000 patients. GE Healthcare announced the availability of the tracer in more than 80 hospitals across the United States during the summer of 2011.

123I-ioflupane is a cocaine analogue and is a Drug Enforcement Administration (DEA) Schedule II controlled substance. Therefore, special procedures are required for physician licensure and clinic registration, as well as for secure storage, handling, destruction and record-keeping practices.

123I-ioflupane has a high affinity and relatively good selectivity for the dopamine transporter (DaT) and can be used in the differential diagnosis of specific movement disorders and dementias. It can detect DaT loss in early stages of PD and can differentiate parkinsonian syndromes from essential tremor, neuroleptic-induced parkinsonism and psychogenic parkinsonism. Another important indication is the differentiation of dementia with Lewy bodies from other dementias. In dementia with Lewy bodies, DaT binding is reduced, whereas in most other dementias including Alzheimer’s disease, DaT binding is normal.

Typically 5 mCi (185 MBq) of 123I-FP-CIT is injected intravenously. It is cleared rapidly from the blood. The effective dose is 3.94 mSv in an adult. Thyroid blocking is recommended to minimize uptake of radioiodine. Three to six hours after injection, SPECT images are acquired using a dual (or more) headed camera with high-resolution collimators and set to a photopeak of 159 keV with a ± 10 percent energy window. On a dual headed camera, imaging typically takes 30-45 minutes. The patient should be in a comfortable position and the head and shoulders secured to avoid movement during acquisition.

DaTscan images are interpreted visually, based upon the appearance of the striatum (caudate and putamen). It is valuable for early diagnosis of PD; the degree of reduction in DaT binding is related to the clinical stage and severity. In a normal scan, the striatum is clearly visible as symmetric, comma-shaped regions, with both the caudate and putamen showing a high intensity compared to the background. In early Parkinson’s disease, there is usually an asymmetrical pattern of reduced DaT binding, starting in the putamen contralateral to the clinically most symptomatic side. As the disease progresses, decreased tracer binding gradually progresses anteriorly as well as toward the other side. In dementia with Lewy bodies, DaT binding is reduced, typically with bilateral loss of binding, mainly in putamen but also in caudate and generally with less asymmetry than in PD. While some clinicians have reservations about how widely DaTscan may be used and in what clinical situations it will be most effective in differential diagnosis, it is showing promising results and has high potential for movement disorder patients.

As a molecular imaging community, we are in an exciting time of development and growth, with a bright future!
Lifelong active brains have fewer deposits of Alzheimer’s protein
http://www.medicalnewstoday.com/articles/240656.php
A new study using PET scans to examine the brains of healthy older people finds those who have been mentally stimulated all their lives, doing things like reading, writing, and playing games and puzzles, have fewer deposits of beta-amyloid, a destructive protein that is a hallmark of Alzheimer’s disease. The researchers suggest their findings will encourage scientists to think differently about how mental stimulation affects the biology of the brain.

Addiction linked to increased dopamine D3 levels
Canadian researchers used innovative techniques in their research of mental illness, leading to an exciting new discovery. Investigators at the Centre for Addiction and Mental Health (CAMH) identified a potential treatment target for methamphetamine addicts while using a chemical probe developed by the facility.

PET tracer 4DST beats FDG for imaging cancer proliferation
A Japanese study highlights the benefits of a new PET radiotracer for imaging the proliferation of cancer cells in non-small cell lung cancer (NSCLC), as compared with PET’s workhorse radiopharmaceutical, FDG. The new tracer may also help noninvasively reveal the DNA synthesis of NSCLC cells.

Label-free pulsed laser-driven imaging tool tracks nanotubes in cells, blood
Carbon nanotubes have potential applications in drug delivery to treat diseases and in imaging for cancer research, but up until now there has been no technique to see both metallic and semiconducting nanotubes in living cells and the bloodstream, according to Ji-Xin Cheng, associate professor of biomedical engineering and chemistry at Purdue University (West Lafayette, IN).

Radiology: PET could serve as surrogate marker for head, neck cancer outcomes
http://www.molecularimaging.net/index.php?option=com_articles&view=article&id=30909&division=mi
FDG PET could be used as a noninvasive surrogate marker for tumor growth and viability in treatment of head and neck cancer, based on a rodent model study published in the December issue of Radiology.
SNM 2012 Annual Meeting

Recognized by thousands of professional attendees as the premier educational and networking event in molecular imaging and nuclear medicine, the 2012 Annual Meeting will feature outstanding scientific and educational presentations covering cutting-edge topics in molecular imaging including:

- Cerenkov, Intraoperative, and Photoacoustic imaging
- Radiopharmaceutical development and applications
- Multimodal breast, cardiovascular, and prostate imaging
- Animal preparation in preclinical imaging
- Hybrid nuclear/MR technologies
- PET/MR potential applications
- Radionuclide production and distribution
- Molecular imaging of liver function
- Radiopharmaceutical development and the IND process
- Late phase development of molecular imaging agents
- Neuroreceptor imaging
- New agents for prostate cancer
- F-DOPA in clinical research

Plus, key FDA sponsored sessions, featured topics from SNM’s translational molecular imaging curriculum, and an categorical seminar: “Molecular Imaging in Europe and Asia, New Lessons from the Old World.”

Make your plans early. Register now.

www.snm.org/am2012

SNM 2012 Annual Meeting
June 9-13, 2012
Miami Beach Convention Center
Miami Beach, FL